# Clinical Practice Guideline on Systemic Lupus Erythematosus

**NOTE:**

More than 5 years have passed since the publication of this Clinical Practice Guideline, and **its validity has not been reviewed**.

Therefore, **it is unclear whether its recommendations remain valid**; they should therefore be treated with caution and applied in accordance with **clinical judgement and the individual circumstances of each patient**.

**CLINICAL PRACTICE GUIDELINES IN THE SPANISH NHS**
MINISTRY OF HEALTH, SOCIAL SERVICES AND EQUALITY

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD
RED ESPAÑOLA DE AGENCIAS DE EVALUACIÓN DE TECNOLOGÍAS Y PRESTACIONES DEL SISTEMA NACIONAL DE SALUD
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Gobierno de Canarias

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This CPG is an aid for decision making in health care. It is not mandatory, and it is not a substitute for the clinical judgement of heathcare personnel.

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# Presentation

Documenting the variability of clinical practice, analysing the causes and adopting strategies aimed at eliminating it, have proved to be initiatives that foster effective and safe patient-centred decision-making by health practitioners. Noteworthy among the strategies is the development of Clinical Practice Guidelines (CPGs), a "series of recommendations based on a systematic review of evidence and on the assessment of risks and benefits of different alternatives, in order to optimise patients' healthcare".

Consolidating the development of CPGs, coordinated by GuiaSalud, within the framework of the Spanish Network of Agencies for Health Technology Assessment and NHS benefits is one of the priorities of the Ministry of Health, Social Services and Equality.

This CPG on Systemic Lupus Erythematosus (SLE) is framed within this context.

SLE is a systemic autoimmune disease whose clinical manifestations, course and prognosis are very heterogeneous and require the involvement of a large number of specialists in the healthcare process. It is one of the most frequent autoimmune diseases, with an estimated prevalence in our country of 9 out of every 10,000 inhabitants.

This CPG on SLE responds to clinical questions concerning this disease, to its diagnosis and the management of the clinical manifestations, both general and specific by organ. It also addresses sexual and reproductive health and the comorbidities that patients with this disease suffer from, trying to reduce variability in clinical practice.

Its main target are professionals involved in the healthcare of SLE patients and the objective is to provide them with the appropriate tools to approach and treat this pathology, and facilitate coordination between the Primary and Hospital Healthcare.

This CPG is the result of considerable effort made by a group of health professionals who belong to different specialities and representatives of several Scientific Associations involved in this disease.

We, at the Directorate General of Public Health, Quality and Innovation, would like to thank all these people for the work carried out and we hope that it will help professionals and patients in decision making, improving treatments appropriateness and the quality of life of the population affected by SLE.

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Spanish Society of Internal Medicine (SEMI)

Spanish Nephrology Society

Spanish Society of Haematology and Haemotherapy

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Spanish Society of Family and Community Medicine (semFYC)

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**Declaration of interest:** All members of the Development Group, as well as those who participated in the expert collaboration and external review, made the declaration of interest appearing in Appendix 1.

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# Key questions

## DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS

### Early detection

1. Do early detection and early treatment improve the prognosis and survival of people with systemic lupus erythematosus?
2. What are the main symptoms and signs that should make us suspect systemic lupus erythematosus?

### Diagnostic confirmation

3. What is the technique of choice to detect antinuclear antibodies?
4. What is the validity of laboratory tests to confirm the diagnosis of systemic lupus erythematosus?
5. What are the classification criteria for systemic lupus erythematosus? Should the new classification criteria proposed by the SLICC 2012 group be used as diagnostic criteria?
6. After confirming the diagnosis, what test should be carried out to make an initial evaluation of any patient with systemic lupus erythematosus?

## GENERAL MANAGEMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

### Monitoring

7. What is the most recommendable clinical monitoring protocol for people with systemic lupus erythematosus?
8. What complementary tests should be carried out on people with systemic lupus erythematosus, and how often, in monitoring and control consultations? Which are the most effective and cost-effective disease activity biomarkers for monitoring systemic lupus erythematosus? Should the 25-HO vitamin D levels be monitored as an SLE activity marker?
9. Are the available standardised tools effective to assess the disease in clinical practice? Should they be used in normal clinical practice?
10. What are the analytical or biological markers that can predict a lupus flare or which factors have been associated with an increase in activity of systemic lupus erythematosus?

### General therapeutic approach

11. What are the therapeutic objectives in people with systemic lupus erythematosus?
12. What non-biological immunosuppressive treatments are effective in extrarenal lupus?

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13. Is the use of anti-malarial drugs indicated in all people with systemic lupus erythematosus? What is the effectiveness, cost-effectiveness and safety of these drugs in preventing flares? Have they got other additional beneficial effects that may justify their generalised use?

14. What is the recommended dose of glucocorticoids to keep the disease controlled with an assumable risk of adverse effects?

15. Which biological therapies are effective and safe in people with systemic lupus erythematosus?

16. What is the effectiveness and safety of immunoglobulins in treating systemic lupus erythematosus?

17. What are the complications and adverse effects of the most usual biological and immunosuppressive treatments of systemic lupus erythematosus? Which are the most advisable monitoring guidelines?

18. What is the effectiveness and safety of therapeutic apheresis in treating systemic lupus erythematosus?

19. Which measures are effective to prevent the reactivation of systemic lupus erythematosus?

20. Which therapeutic options are effective to help people with asthenia associated with systemic lupus erythematosus?

### Lifestyle measures

21. Which lifestyle-related measures should be advised for people with systemic lupus erythematosus?

### Photoprotection

22. Is photoprotection indicated in all people with systemic lupus erythematosus? Which photoprotection measures are effective?

### Educational programmes

23. Are structured nursing-based educational programmes addressed to people with systemic lupus erythematosus effective?

## MANAGEMENT OF SPECIFIC CLINICAL MANIFESTATIONS

### Lupus nephritis

24. What are the criteria for recommending a renal biopsy?

25. What are the specific therapeutic objectives?

26. Which circumstances define a therapeutic guideline as ineffective/refractory to treatment?

27. What should be the induction treatment of proliferative lupus nephritis?

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28. Under what conditions would induction treatment with mycophenolate afford advantages over other drugs?

29. What induction treatment in lupus nephritis with renal insufficiency should be administered?

30. What is the immunosuppressive maintenance treatment of proliferative lupus nephritis?

31. When and how should a maintenance treatment be suspended?

32. What should be the immunosuppressive therapeutic strategy of first choice for type V lupus nephritis?

## Haematological manifestations

33. What is the immunosuppressive first-line treatment for severe cytopenia?

34. When should thrombocytopenia be treated?

35. What are the indications of thrombopoietic agents?

## Neuropsychiatric lupus

36. What is the usefulness of certain types of autoantibodies for diagnosing neuropsychiatric complications?

37. Which are the imaging techniques of choice in the diagnostic process of neuropsychiatric complications of systemic lupus erythematosus?

38. Should neuropsychological tests be performed in all patients with suspected neuropsychiatric systemic lupus erythematosus?

39. When are high-intensity immunosuppressive drugs indicated in people with neuropsychiatric lupus?

## Lupus arthritis

40. Should a standardised tool be used to assess the state of arthritis? If so, which would be the most advisable?

41. Which treatments are efficient and safe for lupus arthritis?

## Mucocutaneous manifestations

42. Should a standardised tool be used to evaluate the stage of the disease? If so, which would be the most appropiate?

43. What is the effectiveness, safety and cost-effectiveness of topical therapies in treating systemic lupus erythematosus with cutaneous manifestations? In which situations would they be indicated?

## Antiphospholipid syndrome

44. What types and combinations of antiphospholipid antibodies increase the risk of thrombosis in people with systemic lupus erythematosus?

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45. What preventive and treatment measures should be taken for thrombotic complications in people with systemic lupus erythematosus and antiphospholipid antibodies?

## SEXUAL AND REPRODUCTIVE HEALTH

### Pregnancy

46. How would pregnancy be planned in women with systemic lupus erythematosus in order to maximise success possibilities?

47. What specific monitoring should be carried out and how often in pregnant patients with systemic lupus erythematosus?

48. Should anti-malarial drugs be maintained if a pregnancy occurs? Which would be the medication of choice?

49. What preventive measures should be taken for obstetric complications in people with antiphospholipid antibodies

### Fertility and contraception

50. Are assisted reproduction procedures safe and efficient in systemic lupus erythematosus? Is ovarian stimulation safe in women with systemic lupus erythematosus?

51. What contraception methods are safe in women with systemic lupus erythematosus?

## COMORBIDITY

### Cardiovascular risk

52. Have people with systemic lupus erythematosus got a greater cardiovascular risk? Is this risk similar in different ethnic groups? Should the cardiovascular risk be evaluated in people with systemic lupus erythematosus? How should this be done and how often?

53. Is there evidence about specific cholesterol figure targets, or can we only transfer those recommended for other high cardiovascular risk pathologies such as diabetes?

54. In which people with systemic lupus erythematosus is the use of aspirin indicated?

55. Is there evidence that favours the use of certain high blood pressure drugs such as angiotensin blockers, in people with systemic lupus erythematosus?

### Infection

56. What should the latent infection screening protocol be for people with systemic lupus erythematosus (tuberculosis, HCV, HBV, cytomegalovirus,...)?

57. What is the safety and efficacy of a pneumococcal vaccine in people with systemic lupus erythematosus? Should this vaccine be administered to all patients?

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## Cancer

58. What are the most frequent types of cancer in people with systemic lupus erythematosus? Should specific screening be carried out for this type of patients?

## Osteoporosis

59. Should a bone densitometry be carried out on all people with systemic lupus erythematosus? If so, how often?

60. Which measures should be taken to prevent steroid-induced osteoporosis in people with systemic lupus erythematosus?

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# Levels of evidence and recommendation grades

**SIGN (Scottish Intercollegiate Guidelines Network)[1] levels of evidence and grades of recommendation.**

| | |
|---|---|
| **Levels of scientific evidence** | |
| 1++ | High quality meta-analysis (MA), systematic reviews (SR) of clinical trials or high-quality clinical trials with very little bias risk. |
| 1+ | Well-performed MA, SR of clinical trials or well-performed clinical trials with little bias risk. |
| 1- | MA, SR of clinical trials or clinical trials with high bias risk. |
| 2++ | High-quality SR of case control or cohort of studies. Well-conducted studies of case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal. |
| 2+ | Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal. |
| 2- | Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal. |
| 3 | Non-analytic studies, such as case reports and case series. |
| 4 | Expert opinion. |
| **Grades of recommendation** | |
| A | At least one MA, SR or clinical trial classified as 1++ and directly applicable to the target population of the guidelines; or a volume of scientific evidence comprised of studies classified as 1+ and with great consistency between them. |
| B | A volume of scientific evidence comprised of studies classified as 2++, directly applicable to the target population of the guideline and that show great consistency between them; or scientific evidence extrapolated from studies classified as 1++ or 1+. |
| C | A volume of scientific evidence comprised of studies classified as 2+, directly applicable to the target population of the guideline and that show great consistency between them; or scientific evidence extrapolated from studies classified as 2 ++. |
| D | Scientific evidence of level 3 or 3; or scientific evidence extrapolated from studies classified as 2+. |

*The studies classified as 1- and 2- must not be used in the recommendations preparation process due to their high bias possibility.*

| | |
|---|---|
| √* | Recommended practice based on clinical experience and the consensus of the drafting team. |

** At times, the development group finds important practical aspects that must be highlighted and for which no scientific evidence has been found. In general these cases are related to some aspects of the treatment that nobody would normally question and they are evaluated as points of "good clinical practice".*

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# Levels of evidence and recommendation grades for questions on diagnosis

**NICE (*National Institute for Health and Care Excellence*) adaptation of the levels of evidence of the Oxford Centre for Evidence-based Medicine and the Centre for Reviews and Dissemination.[2]**

| Level of scientific evidence | Type of scientific evidence |
|---|---|
| Ia | SR with homogeneous level 1 studies. |
| Ib | Level 1 studies. |
| II | Level 2 studies.<br>SR of level 2 studies. |
| III | Level 3 studies.<br>SR of level 3 studies. |
| IV | Consensus, expert opinions without explicit critical evaluation. |
| Level 1 studies | They meet:<br>• Blinded comparison with a valid (golden standard) comparator test.<br>• Suitable range of patients. |
| Level 2 studies | They only show one of these biases:<br>• Non-representative population (the sample does not reflect the population in which the test will be used).<br>• Comparison with unsuitable comparator ("gold standard") (the test to be assessed is part of the gold standard or the result of the test affects the performance of the gold standard).<br>• Non-blinded comparison.<br>• Case and control studies. |
| Level 3 studies | They meet two or more of the criteria stated for level 2 studies. |

| Recommendation | Evidence |
|---|---|
| A | Ia or Ib |
| B | II |
| C | III |
| D | IV |

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# Recommendations

Key Recommendations

## Diagnosis of systemic lupus erythematosus

### Early detection

*Prognosis*

| | |
|---|---|
| D | We do not recommend screening for SLE in the general asymptomatic population. |
| C | We suggest the early determination of antinuclear (anti-dsDNA, anti-Ro, anti-La, anti-Sm, anti-RNP) and antiphospholipid antibodies in individuals with symptoms tht are suggestive of SLE, in order to detect early and less severe forms of the disease. |
| C | We recommend early treatment with hydroxychloroquine in people with incomplete forms of SLE (understood as those that do not meet the classification criteria), who are carriers of suggestive autoantibodies, to delay the development of the disease and the development of renal impairment. |

*Suspect symptoms*

| | |
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| B | We recommend clinically monitoring women under the age of 50 with onset of arthritis or else arthralgias associated with skin lesions, photosensitivity, Raynaud or systemic symptoms, especially if there are haematological alterations (cytopenias), or of the urine sediment, bearing SLE in mind in the differential diagnosis. Determining antinuclear antibodies and, where appropriate, specific antibodies, may be indicated in these women. |

### Diagnostic confirmation

*Laboratory tests*

| | |
|---|---|
| A | As a general rule, we do not recommend carrying out the antinuclear antibody detection test if there are not at least two clinical manifestations that suggest SLE. |
| A | The method of choice to detect antinuclear antibodies in the diagnostic process of SLE is the indirect immunofluorescence due to its high sensitivity. |
| B | The antinuclear antibody detection test by indirect immunofluorescence should preferably be carried out with human epithelial cellular (HEp-2) substrate. |
| A | If an ELISA method is used to detect antinuclear antibodies, using a traditional technique or based on antigen microspheres with proven sensitivity similar or higher than indirect immunofluorescence, the positive result should also be confirmed via indirect immunofluorescence. |
| B | To establish the cut-off point and interpret the titre of antinuclear antibodies, we recommend knowing the antinuclear antibodies levels of reference in the general population of application, with no antinuclear antibody-related diseases. |

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| | |
|---|---|
| A | Titres below 1:40 (<5 UI/ml) of antinuclear antibodies detected through indirect immunofluorescence should be considered as negative. |
| B | We recommend considering as clinically relevant a titre of antinuclear antibodies detected by indirect immunofluorescence of 1:160 (≥20 UI/ml) or more in the Caucasian population of our context, and proceeding with the diagnostic confirmation cascade through the detection of specific anti-dsDNA and anti-ENA (mainly anti-Sm) antibodies. |
| A | We recommend interpreting a positive result in the antinuclear antibody detection test in the patient's clinical context since, on its own, it does not establish the diagnosis of SLE at all. |
| C | In people with suggestive symptoms of SLE and antinuclear antibody detection test by indirect immunofluorescence with result persistently negative, we suggest performing the antinuclear antibody detection via an ELISA technique that includes Ro (SSA) antigen reagents or the direct determination of anti-Ro (SSA). |
| B | We recommend assessing the fluorescence pattern obtained in the antinuclear antibody detection test via indirect immunofluorescence to have useful additional information in the differential diagnosis of SLE with other systemic autoimmune diseases. |
| D | We suggest that result report of the antinuclear antibody detection test includes the detection technique used, the positive dilution titre or the concentration of autoantibodies in UI/ml, together with the percentage of healthy individuals or individuals with no diseases associated with antinuclear antibodies that present the same titre in the reference population, as well as the intensity and the nuclear, cytoplasmic and/or mitotic fluorescence patterns identified. |
| A | In people with symptoms or signs related to SLE and a positive antinuclear antibody test, we recommend determining specific high-affinity IgG type anti-dsDNA and anti-Sm antibodies to confirm the diagnosis of SLE. |
| A | For the differential diagnosis of SLE with other connective tissue diseases in patients with positive antinuclear antibody test, we recommend determining anti-dsDNA antibodies via indirect immunofluorescence with Crithidia luciliae substrate. |
| A | SLE should be considered as first diagnostic option in patients with suggestive symptoms, a positive ANA test and a high titre of anti-dsDNA antibodies. |
| B | For the differential diagnosis of SLE with other connective tissue diseases in people with positive antinuclear antibody test, we recommend determining anti-Sm antibodies with ID, IB, CIE, ELISA or multiple simultaneous immunoassay with antigen microspheres. |
| A | We do not recommend determining anti-RNP antibodies with diagnostic purposes in people with symptoms that are suggestive of SLE. |
| B | In people with symptoms or signs related to SLE, a positive ANA test and negative high affinity specific anti-dsDNA, anti-Sm and anti-nucleosome antibodies, determining specific anti-RibP antibodies could be useful to diagnose SLE. |
| C | We do not recommend determining anti-Ro and anti-La antibodies in order to diagnose SLE, unless there is an absence of other autoantibodies in people with suggestive symptoms. |
| C | We recommend determining anti-histone antibodies only when people are suspected of having drug-induced SLE. |

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*Diagnostic and classification criteria*

| | |
|---|---|
| √ | We recommend basing the diagnosis of SLE on expert clinical opinion, combining suggestive clinical characteristics with the relative serological confirmation. |
| √ | The classification criteria should not be used with a diagnostic purpose; however, the SLICC classification criteria may provide useful guidance for the diagnosis. |
| B | We recommend using the SLE classification criteria of the ACR 1982-1977 and/or those of SLICC 2012 to select homogeneous patients in clinical research and epidemiological studies. |

*Initial evaluation tests after diagnosis*

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|---|---|
| B | For the initial evaluation of patients diagnosed with SLE, we recommend quantifying the different specific antibodies as activity markers and disease prognosis. |
| A | We do not recommend the isolated use of anti-dsDNA antibodies to diagnose a flare of SLE. |
| C | We recommend the joint assessment of the anti-dsDNA antibodies titre and the C3 and C4 complement levels as support to assess activity. |
| A | We do not recommend the isolated determination or monitoring of anti-Sm or anti-RNP antibody levels to evaluate the global activity or risk of nephropathy of SLE. |
| B | We do not recommend determining anti-ribosomal P antibodies as prognostic markers of neuropsychiatric episodes or of general activity of SLE, or in the initial assessment of patients diagnosed with SLE or during its evolution. |
| B | We recommend determining anti-Ro and anti-La antibodies in all women with SLE before planning pregnancy or as soon as a unplanned pregnancy is acknowledged. |
| C | Due to its thrombosis and obstetric complication predictive value, we suggest the periodic combined determination of antiphospholipid (anticardiolipin, lupus anticoagulant and anti-β2-glycoprotein I) antibodies in order to determine their persistence (if positive) or their positivisation with the course of the diseases (if negative). |
| B | We do not recommend using the erythrocyte sedimentation rate as an SLE activity marker. |
| C | We suggest carrying out urine sediment, protein/creatinine quotient in an early morning urine sample, proteinuria in 24-hour urine and serum creatinine, both at the time of diagnosis of SLE and during successive medical visits, to predict the presence and evolution of lupus nephropathy. |
| D | We suggest performing complete routine blood tests to evaluate the existence of anaemia, leucopoenia, lymphocytopenia and thrombocytopenia, both at the time of diagnosis of SLE and during successive medical visits. |

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# General management of systemic lupus erythematosus

## Monitoring

*Clinical monitoring protocol and complementary tests*

| | |
|---|---|
| √ | We suggest performing a comprehensive, clinical and analytical assessment at the time the diagnosis of SLE is confirmed. |
| √ | In the monitoring protocol of SLE patients, we suggest monitoring the activity of the disease, organ damage, comorbidities (including the presence of vascular risk factors) and the possible toxicity of the pharmacological treatment. To this end, the clinical interview, physical examination, blood pressure testing will be used, as well as basic analytical determinations that will include complete blood test, biochemical analysis with renal profile and urine analysis, complement and determination of anti-dsDNA antibodies. |
| √ | In patient with active SLE, the monitoring intervals should be adapted to the clinical situation and they are, therefore, variable. |
| √ | If the disease is in clinical and analytical remission, we suggest monitoring every 6-12 months, depending on the disease evolution time and the treatment intensity. |
| C | In clinical quiescent patients with maintained activity analytical criteria, we suggest closer monitoring, every 3-4 months, at least during the first years. |
| D | We suggest periodically determining the levels of 25-HO vitamin D in SLE patients, above all if there is a presence of osteoporotic fracture risk factors. |
| D | We suggest the regular use of activity biomarkers such as levels of C3 and C4 and of anti-dsDNA in SLE patients, above all in those with renal involvement. |

*Disease assessment tools*

| | |
|---|---|
| √ | SLE patients require the highest standardised and objective monitoring of their disease as possible, so we suggest the use of validated instruments to quantify the degree of activity, accumulated damage and quality of life. |

*Predictive factors of flare or increase in disease activity*

| | |
|---|---|
| B | When following-up SLE patients, we recommend using periodic determinations of C3, C4 and anti-dsDNA as predictors of active disease. |
| C | Although anti C1q and antinucleosome antibodies are probably more sensitive and specific as lupus nephritis markers, the current lack of standardisation advises against their routine use for this purpose. |

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## General therapeutic approach

*Therapeutic objectives*

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|---|---|
| B | As the main therapeutic objective in SLE patients, we recommend establishing, the control of perceived or verifiable clinical lupus activity, avoiding secondary irreversible damage both to the actual disease (particularly renal and neurological damage) and cardiovascular events) and to its treatment, above all glucocorticoids (osteonecrosis, osteoporotic fractures, diabetes mellitus, cataracts, etc.), minimising the impact on the patients' quality of life and survival. |
| B | We recommend minimising the risk of infections. |

*Treatment indications*

Non-biological immunosuppressive treatments

| | |
|---|---|
| B | We recommend intravenous cyclophosphamide as first immunosuppressive drug in the treatment of SLE and of severe non-renal manifestations. |
| A | We recommend methotrexate as first immunosuppressive drug in the treatment of non-renal SLE with moderate activity, specially in those cases with cutaneous and joint manifestations. |
| √ | As an alternative, we suggest using other immunosuppressive drugs such as azathioprine, cyclosporine A, leflunomide or mycophenolate for the treatment of non-renal SLE. |

Anti-malarial drugs

| | |
|---|---|
| B | We recommend using anti-malarial drugs as the basic treatment for all SLE patients who have no contraindications for its administration. |
| B | We recommend maintaining indefinite treatment with anti-malarial drugs due to their effects on activity, damage, thrombosis, infections and long-term survival. |
| B | For its greater safety, we recommend hydroxychloroquine instead of chloroquine as the anti-malarial drug of choice. |
| D | We suggest combining anti-malarial treatment with mepacrine and hydroxychloroquine in patients with refractory lupus activity, specially cutaneous, as this may produce synergic effects. |
| D | In patients with retinal toxicity caused by anti-malarial drugs, we suggest replacing hydroxychloroquine or chloroquine by mepacrine (not sold in Spain). |
| D | We suggest active monitoring of retinal toxicity in patients treated with hydroxychloroquine or chloroquine. |
| D | We suggest at least a baseline eye examination during the first year of treatment, and every year after five year treatment, although the control should be started much earlier in patients with maculopathy of another origin or with additional risk factors. |
| D | We suggest including at least one of the most sensitive techniques: Spectral domain optical coherence tomography (SD-OCT), retinal autofluorescence or mutifocal electroretinogram, together with automated visual field 10-2. |

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Glucocorticoids

| | |
|---|---|
| B | We suggest not exceeding a dose of 30 mg/day of prednisone in the treatment of patients with lupus nephritis. However, the dose should be personalised. |
| √ | In general, we recommend not exceeding a dose of 30 mg/day of prednisone in other SLE manifestations. However, the dose should be individually assessed for each patient. |
| B | In serious flares, we recommend coadjuvant treatment with methylprednisolone pulses. |
| C | We suggest a rapid reduction of glucocorticoid doses (prednisone) in order to reach 5 mg/day, within six months at the very latest, trying to complete withdraw as soon as possible. |
| B | If necessary in maintenance treatments, we recommend that the prednisone dose does not exceed 5 mg/day |
| √ | We suggest the use of methylprednisolone pulses below 1000 mg, although we cannot recommend a specific dose. |

Biological therapies

| | |
|---|---|
| A | We recommend belimumab treatment for people with active SLE who have not responded to standard treatment and whose activity is not fundamentally due to renal or neurological impairment. |
| B | We suggest considering as candidates to belimumab treatment those people with active SLE not responding to a treatment for at least three monthsthat includes anti-malarial drugs, prednisone and at least one immunosuppressive drug at adequate dose. We also suggest considering as candidates to belimumab treatment those who need prednisone at a dose of 7.5 mg/day or more to maintain the remission, despite anti-malarial drugs and at least one immunosuppressive drug, or contraindication for the use of clinically indicated immunosuppressive drugs for toxicity. |
| C | We suggest administering rituximab in patients with severe renal, neurological or haematological impairment who do not respond to first line immunosuppressive treatment. |
| √ | Nowadays, there is no approved indication for the use of other biological agents in SLE. However, in certain situations where normal therapeutic measures (including the use of belimumab and rituximab) have failed or cannot be used, the use of any one of the following agents could be considered. infliximab (in refractory arthritis and nephritis), etanercept (arthritis and serositis), abatacept (especially in arthritis) and tocilizumab (in patients with bad control of their clinical activity). |

* DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION from La Roche Ltd. in agreement with the European Medicines Agency and the Spanish Agency of Medicines and Medical Devices (27 de Junio de 2019)

Serious cases of drug-induced liver injury, including acute liver failure, hepatitis and jaundice, in some cases requiring liver transplantation, have been observed in patients treated with tocilizumab. The frequency of serious hepatotoxicity is considered rare.

For additional information, please consult:
https://sinaem.agemed.es/CartasFarmacovigilanciaDoc/2019/DHPC_Tocilizumab_27062019.pdf

Immunoglobulins

| | |
|---|---|
| D | The use of intravenous immunoglobulins would be justified in severe immune life-threatening thrombocytopenia due to active bleeding or when surgical intervention is required or haemorrhagic risk procedure. |

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|---|---|
| D | We suggest taking the necessary measures to reduce the toxicity risk: adequate infusion rate, avoiding products with high saccharose content, ruling out immunoglobulin A deficiency and carefully considering the risk-benefit balance. We suggest considering the use of thromboprophylaxis with heparin if thrombosis risk factors exist, guaranteeing adequate hydration. Likewise, in patients with associated renal failure risk factors, we suggest watching over the renal function during the days following the infusion. |
| √ | Intravenous immunoglobulins could also be used in patients with high activity whose major organs are compromised in the presence of or suspected severe infection that contraindicates or substantially limits immunosuppressive treatment. |
| √ | We suggest administering the dose of intravenous immunoglobulins of 0.4 g/kg/day for five consecutive days. However, lower doses (for example, 0.5 g/kg on day) may also be effective, except in the case of thrombocytopenia. |
| √ | We do not recommend the use of intravenous immunoglobulins as maintenance treatment in any of the manifestations of LSE, as there are other therapeutic alternatives with more consolidated effectiveness and lower cost. |

*Adverse effects and monitoring patterns for immunosuppressive and biological treatments*

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|---|---|
| B | To monitor haematological and hepatic toxicity of immunosuppressive drugs, we recommend carrying out complete blood tests and hepatic biochemical analyses at intervals of one to three months. |
| B | In patients treated with cyclophosphamide, we recommend active surveillance of bladder cancer through an urine analyses in order to detect microhaematuria. This surveillance should not cease after stoping the treatment. |
| D | We recommend determining the activity of the thiopurine methyltransferase enzyme or its polymorphisms before start the treatment with AZA. |

*Indication for therapeutic apheresis*

| | |
|---|---|
| A | We do not recommend plasmapheresis as first or second line treatment in SLE patients, either generally or in those with nephritis. |
| C | In severe cases that are refractory to other therapies, we suggest considering the use of plasmapheresis in an individualised manner. |

*Prevention of disease reactivation*

| | |
|---|---|
| A | We recommend prolonged treatment with antimalarial drugs, to prevent reactivations of SLE, even during pregnancy. |
| A | Due to the unfavourable balance between the beneficial effect observed and the potential toxicity associated with excess of treatment with glucocorticoids, we do not recommend the preventive administration of prednisone to patients with serological activity without associated clinical administrations. |
| B | We do not recommend that patients with clinically quiescent and serologically active SLE should receive immunosuppressive treatment to prevent flares beyond their basic treatment or the remission maintenance treatment of a lupus nephritis. |

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| | |
|---|---|
| C | Although we do not recommend vitamin D supplements with the sole objective of preventing activity flares, we do suggest correcting the vitamin D deficiency due to its unfavourable effects on the bone mass and asthenia, not ruling out a beneficial effect in the control of lupus activity. |
| C | In addition to its harmful impact on other aspects of the disease and on general health, we suggest avoiding smoking due to its possible effect on lupus activity, especially at cutaneous level. |

*Treatment of associated asthenia*

| | |
|---|---|
| B | We recommend gradual sessions of aerobic physical exercise at home, controlled by a health professional (walking, static cycling, swimming), in people with stable SLE, due to its global improvement effect on a series of self-perceived measures by SLE patients. |
| B | Psycho-educational support should be offered to SLE patients to improve their knowledge and understanding of the disease, restructuring beliefs, improving coping and social support. |
| √ | We do not recommend vitamin D supplements in patients with asthenia and normal levels of 25-HO vitamin D. |
| √ | Despite the effectiveness-related data derived from the RCTs, we do not recommend the administration of belimumab with the sole objective of improving asthenia. |

**Lifestyle measures**

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| √ | We recommend adopting active measures in order to help give up smoking in all SLE patients. This objective is especially important, not just because of the effect that smoking has on the activity of the disease and quality of life, but also because of its causal association with the increase in risk of CVD, infection and cancer. |
| B | We recommend promoting regular physical exercise in people with stable SLE with low to moderate disease activity. |
| C | We suggest avoiding being overweight and a sedentary lifestyle in all SLE patients. |
| C | We suggest recommending a diet that is low in saturated fats and rich in omega-3 fatty acids in SLE patients. |

**Photoprotection**

| | |
|---|---|
| A | We recommend that the regular use of broad spectrum photoprotectors with high solar photoprotection index should be applied in adequate quantity (2 mg/cm$^2$), evenly over all the areas exposed to the sun, between 15 and 30 minutes before exposure and reapplied every two hours and/or after immersion and perspiration. |
| √ | We suggest systematically informing and educating SLE patients, especially those with cutaneous lupus and who have a history of photosensitivity, about the photoprotection measures and the importance of their use to control their disease better and to avoid the appearance of other symptoms. |

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**Educational programmes for patients**

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|---|---|
| C | We suggest to perform structured educational programmes address to SLE patients and given by nursing professionals. |

# Management of specific clinical manifestations

**Lupus nephritis**

*Indication for renal biopsy*

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| B | We recommend performing a renal biopsy on all SLE patients who present confirmed proteinuria ≥ 0.5 g/day, especially in the presence of active sediment and/or isolated renal insufficiency without alternative explanation. |
| C | The renal histopathological study should also inform of the class, degree of activity, chronicity, and presence of vascular and interstitial lesions. |
| C | We do not recommend the routine repetition of renal biopsies, which would be limited to refractory patient or patients with renal relapse when it is considered that the result may determine a therapeutic change. |

*Therapeutic objectives and refractoriness*

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|---|---|
| D | The main therapeutic objective for LN are:<br>1.- Preserving the renal function in the long term.<br>2.- Preventing relapses.<br>3.- Avoiding adverse effects of the treatment.<br>4.- Improving survival and HRQoL. |
| C | To increase the probabilities of remission, we recommend adjutant treatment with angiotensin converting enzyme inhibitors, or angiotensin receptor blockers for a good blood pressure control and to reduce proteinuria. |
| D | We suggest considering as refractory those patients who do not reach at least partial remission after six months' treatment. |
| D | In patients with refractory lupus nephritis we suggest, as a first measure, ensuring correct therapeutic compliance and verifying that the renal lesions are reversible. |
| D | In patients with nephritis who are refractory to treatment with cyclophosphamide or mycophenolate, we suggest changing to another first line drug (mycophenolate or cyclophosphamide). |
| D | In cases of refractory nephritis without satisfactory response to the change in first line treatment (cyclophosphamide and mycophenolate), we suggest using rituximab, anticalcineurinics, immunoglobulins, belimumab or drug combinations. |

*Induction treatment*

<u>Induction treatment of proliferative lupus nephritis</u>

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| A | We recommend to all patients with proliferative lupus nephritis to be treated with immunosuppressive drugs in addition to corticosteroid therapy. |

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| A | The recommended therapeutic strategy should include a response induction phase and a maintenance phase of this response with lower drug doses. |
| A | The immunosuppressive drug of choice recommended for the induction phase of a first flare of LN is cyclophosphamide in pulse therapy or oral mycophenolate. |
| A | We do not recommend azathioprine for induction treatment. |
| C | In Hispanic patients from Latin America or African Americans, we suggest administering mycophenolate instead of cyclophosphamide. |
| A | The recommended dose of intravenous cyclophosphamide for induction is 0.5 g/2 weeks (3 months) or 0.75-1 g/m$^2$/month (6 months). |
| B | The recommended dose of mycophenolate mofetil for induction is 2-3 g/day or the equivalent of sodium mycophenolate. |
| C | In women over 30 or with a risk of ovarian insufficiency, we suggest using minimum doses of cyclophosphamide (ELNT standard), or choosing mycophenolate both for induction and maintenance. |
| C | In women of childbearing age who have received cyclophosphamide reaching an accumulated dose greater than 8 g (or 5 g in women over 30), we suggest mycophenolate (or azathioprine) as drug of first choice for maintenance in the current episode, and as induction and maintenance in successive episodes. |
| √ | We suggest pulse therapy with methylprednisolone in the most severe cases (nephrotic syndrome and/or renal insufficiency), with nephritic syndromes and/or renal insufficiency and as oral prednisone saver. |
| C | In general, we suggest starting with oral prednisone doses no greater than 30 mg/day. |
| C | The reduction rate of prednisone should be fast up to doses of ≤5 mg/day, recommending reaching 5 mg/day after about 3 months and never after 6 months. |
| √ | We suggest pulse therapy with cyclophosphamide instead of mycophenolate in cases where therapy non-compliance is suspected. |
| C | We suggest anticalcineurin therapy as alternative induction treatment, supervising the levels of the drug reached to reduce the risk of nephrotoxicity. |

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Induction treatment of lupus nephritis with renal insufficiency

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| C | Both in cases of mild-moderate acute renal insufficiency (creatinine clearance >30 ml/min/1.73m$^2$) and severe renal insufficiency (creatinine clearance <30ml/min/1,73m$^2$), we suggest using cyclophosphamide or MMF as induction immunosuppressive treatment. |
| √ | We suggest adapting the dose of cyclophosphamide in patients with renal insufficiency according to the estimated glomerular filtration and in patients receiving renal replacement treatment with dialysis. |
| √ | We suggest corticoid pulse therapy in all cases of LN with acute renal insufficiency, unless it is contraindicated. |
| D | In LN lesions associated with ANCA+ necrotising glomerulonephritis, we suggest induction treatment with CPM. |

*Maintenance treatment*

Maintenance treatment of proliferative lupus nephritis

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| A | We recommend oral mycophenolate or azathioprine for maintenance therapy of proliferative lupus nephritis. |
| B | As an alternative to these, we suggest intravenous cyclophosphamide in quarterly pulses or cyclosporine A. |

Suspension of maintenance treatment

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| B | We recommend prolonging this maintenance treatment for 2 to 3 years at least. |
| C | We suggest that in cases where the complete discontinuance of the maintenance immunosuppressive treatment is proposed, this should not be done before a clinical-analytical quiescence period of less than 12 months. |
| √ | In patients with frequent relapses without any justifiable cause, or with risk factors for renal relapse, we suggest prolonging the maintenance treatment for at least 5 years. |
| C | We suggest that the total suspension of the maintenance immunosuppressive treatment should be slow and progressive. |
| C | We suggest maintaining treatment with hydroxychloroquine for a long period, provided that it has no contraindications or side effects. |

*Immunosuppressive treatment for type V lupus nephritis*

| | |
|---|---|
| A | We recommend immunosuppressive treatment in all patients with membranous lupus nephritis. |
| √ | As in other types of nephritis, we suggest not initially exceeding 30 mg/day of prednisone and then reducing it as soon as possible to 5 mg/day. |
| B | In induction treatment for patients with lupus nephritis type V and nephrotic proteinuria, we recommend MMF and glucocorticoids as the treatment of choice. As an alternative and with the same induction efficacy although with more adverse effects, we recommend cyclophosphamide in intravenous pulses. |
| A/B | For maintenance regimens in patients with membranous lupus nephritis, we recommend treatment with mycophenolate (A) or azathioprine (B). |

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|---|---|
| B | We recommend using anticalcineurinics in membranous lupus nephritis when seeking alternative drugs to mycophenolate or cyclophosphamide. |
| √ | We suggest combined therapy with mycophenolate and anticalcineurinics if complete remission is not achieved or if significant proteinuria persists. |
| C | We suggest using rituximab associated with mycophenolate and methyl-prednisolone pulses when avoiding oral glucocorticoids is considered to be especially important. |

**Haematological manifestations**

*Immunosuppressive treatment*

First-line treatment for severe cytopenias

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|---|---|
| D | We suggest corticosteroid therapy as first-line immunosuppressive treatment for severe cytopenias of SLE. |
| √ | Although oral prednisone is considered first-line treatment for immune cytopenias, there are no data supporting the use of higher doses over lower doses. We suggest using intravenous pulses of methyl-prednisolone and the association of immunosuppressants, which would permit the initial use of lower daily doses of prednisone and quickly reducing to doses of no more than 5 mg/day. |
| √ | We suggest oral treatment with dexamethasone at high doses (40 mg/day for four days), either combined with rituximab or not, as an alternative regimen that achieves a similar remission rate with a probably faster and longer-lasting response in idiopathic cytopenias. |

Thrombocytopenia treatment

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|---|---|
| √ | In thrombocytopenia, the decision to start treatment is mainly based on the presence of bleeding manifestations and, on certain occasions, on a platelet count less than 20-30x$10^9$/L. |
| √ | Patients with platelet counts between 20-30 and 50x$10^9$/L and a stable course, without haemorrhagic complications, are not candidates to receive treatment, except for those who present a haemorrhage or are going to undergo surgery or an invasive procedure. |
| √ | We suggest treatment with platelet counts of more than 50x$10^9$/L to be reserved for patients with a high risk of bleeding. |
| √ | Despite the fact that platelet transfusions may be necessary before potentially bleeding procedures in patients with severe thrombocytopenia (platelet counts <10-30x$10^9$/L), transfusion should be avoided as a general rule if an underlying immune mechanism is suspected. |

*Treatment with thrombopoietic agents*

| | |
|---|---|
| √ | We suggest considering the temporary use of thrombopoietic agents only in patients with severe symptomatic thrombocytopenia who do not respond to the initial standard treatment. |

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## Neuropsychiatric lupus

*Diagnosis of neuropsychiatric complications*

Usefulness of certain antibodies

| | |
|---|---|
| B | There is no determination of autoantibodies that enables the execution of a confirmation diagnosis of neuropsychiatric SLE. |
| B | The diagnosis of neuropsychiatric SLE continues to be by exclusion and mainly clinical. However, determining autoantibodies in serum or in cerebrospinal fluid could support the clinical presumption of neuropsychiatric SLE. |
| B | We recommend determining anti-NMO antibodies in the event of suspected optical neuromyelitis associated with SLE. |

Imaging techniques

| | |
|---|---|
| A | We recommend performing a MRI to patients with acute NP-SLE involving the central nervous system, mainly as a differential diagnosis tool, especially when neurological focalty appears. |
| A | We recommend MRI using T2 sequences in order to increase sensitivity. |
| C | If no explanation to the patient's symptoms is found after the evaluation with the recommended first line techniques, we suggest using other magnetic resonance modalities or other types of imaging techniques such as the SPECT. |
| C | We suggest using diffusion –weighted magnetic resonance or angio– MR to identify the aetiology of lesions detected in traditional MR, and also in the case of suspected ischemic origin, in order to establish whether they are acute. |

Indication for neuropsychological tests

| | |
|---|---|
| B | We recommend using structured interviews for the neuropsychological assessment of SLE patients. |
| C | We suggest using the battery of neuropsychological tests proposed by ACR to assess neuropsychiatric manifestations of SLE, especially in cases of cognitive impairment. |
| C | We suggest using validated neuropsychological tests validated in Spanish to monitor the neuropsychiatric outcomes of the progression of SLE, as well as to assess the effects of the interventions applied. |

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*Indication for high intensity immunosuppressants*

| | |
|---|---|
| D | We suggest restricting treatment with glucocorticoids and/or immunosuppressants for neuropsychiatric SLE to those syndromes that express an underlying inflammatory process (organic brain syndrome, aseptic meningitis, myelitis, cranial or peripheral neuropathies, and psychosis) after excluding other causes not related to SLE. |
| A | We recommend considering cyclophosphamide as immunosuppressive first-line treatment for severe neuropsychiatric SLE. |
| C | In people with neuropsychiatric SLE in whom the use of cyclophosphamide is contraindicated, we suggest using mycophenolate as an alternative. |
| C | Rituximab may be used as second-line in people with neuropsychiatric SLE that are refractory to intravenous cyclophosphamide. |

**Lupus arthritis**

*Evaluation tools*

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| √ | We suggest using the DAS-28 index to assess the state of arthritis in SLE patients only in those cases with arthritis of more than six weeks evolution. |

*Treatment*

| | |
|---|---|
| A | Methotrexate and anti-malarial drugs are the medications of choice in the case of joint manifestations of SLE. |
| C | There is little evidence about the use of other drugs for the specific treatment of lupus arthritis. The concrete indication for each one of them will depend, therefore, on the accompanying symptoms, the potential toxicity (including the possibility of pregnancy) and economic considerations. |
| √ | We recommend hydroxychloroquine with or without low doses of glucocorticoids (or pulses of 125 to 250 mg of methylprednisolone) in patients with: inflammatory arthralgias, intermittent arthritis or arthritis of less than six weeks evolution. |
| √ | Patients who do not respond to the treatment, require >5mg of prednisone (or equivalent) for its control, with symptoms that last for more than six weeks or in cases where erosions or deformities appear, should be treated as chronic patients. The following regimens are recommended to treat chronic arthritis:<br>Methotrexate as drug of choice<br>If a satisfactory response is not obtained at full and subcutaneous doses within three months, add (or change) to another synthetic disease-modifying drug (leflunomide, azathioprine, cyclosporine A or mycophenolate), bearing in mind the other manifestations of SLE and the toxicity of each synthetic disease-modifying drug.<br>If there is no response in three months, we recommend adding biological therapy, more specifically, starting with belimumab. If remission is not achieved within six months, rituximab, abatacept, etanercept, tocilizumab or other biological disease-modifying drugs could be used, although, unlike belimumab, none of them have authorised indication in SLE. |

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## Mucocutaneous manifestations

*Evaluation tools*

| | |
|---|---|
| √ | In patients in whom there is a prevalence of skin impairment, we suggest using a standardised cutaneous activity index. |
| D | We suggest using CLASI to assess the activity, damage and evolution of skin lesions in SLE patients. |

*Topical treatment*

| | |
|---|---|
| √ | In cutaneous lupus, we suggest using high-potency topical glucocorticoids. |
| √ | In refractory cases, we suggest using topical treatments with calcineurin inhibitors (tacrolimus or pimecrolimus). |

## Antiphospholipid syndrome

*Antiphospholipid antibodies*

| | |
|---|---|
| C | We recommend determining antiphospholipid antibodies (lupus anticoagulant, aCL and anti-β2-GPI) on a regular basis as thrombotic risk markers in SLE patients. |

*Prevention and treatment of thrombotic complications*

| | |
|---|---|
| C | We suggest the use of hydroxychloroquine to reduce the risk of thrombosis in SLE patients, especially in those with antiphospholipid antibodies. |
| C | In SLE patients and high-risk antiphospholipid antibodies (presence of lupus anticoagulant, alone or combined with aCL or persistently positive aCL at medium-high titres or triple positivity), we suggest treatment with low-dose aspirin to reduce the risk of thrombosis. |
| B | In patients with SLE and antiphospholipid syndrome with venous thrombosis, we recommend anticoagulation with a target INR 2.0-3.0. |
| C | In patients with SLE and antiphospholipid syndrome with arterial thrombosis, we suggest anticoagulation with a target INR >3.0, or combining anticoagulants with INR 2.0-3.0 + low-dose aspirin. |
| C | In patients with SLE, antiphospholipid syndrome and thrombotic episodes, we suggest indefinite anticoagulation. |
| √ | We suggest early identification and strict control of vascular risk factors in patients with SLE and antiphospholipid syndrome. |

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* INFORMATIVE NOTE Spanish Agency of Medicines and Medical Devices (20th May 2019)

New recommendations have been stablished on the use of direct oral anticoagulants (DOACs) in patients with antiphospholipid syndrome (APS) and a history of thrombosis.

For additional information, please consult:
https://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2019/NI_MUH_FV-8-2019-anticoagulantes-orales.htm

Commentary from the guideline coordinators:
"According to the new available evidence, the use of direct oral anticoagulants (DOACs) is not recommended, as a general rule, in patients with antiphospholipid syndrome (APS) in association with systemic lupus erythematosus (SLE), since DOACs could be ineffective for the prevention of recurrent thrombosis, especially in arterial thrombosis. DOACs could be considered in certain clinical scenarios such as in patients with allergy to vitamin K antagonists, they could be also an alternative in patients with a history of exclusively venous thrombosis and without a high risk antiphospholipid antibody profile (presence of lupus anticoagulant, aCL antibodies and antibeta2 glycoprotein I antibodies)"

For additional information, please consult: Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N, Cuadrado MJ, Dörner T, Ferrer-Oliveras R, Hambly K, Khamashta MA, King J, Marchiori F, Meroni PL, Mosca M, Pengo V, Raio L, Ruiz-Irastorza G, Shoenfeld Y, Stojanovich L, Svenungsson E, Wahl D, Tincani A, Wahl MM. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis. 2019 May 15.

* DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION from La Roche Ltd. in agreement with the European Medicines Agency and the Spanish Agency of Medicines and Medical Devices (27th June 2019)

Serious cases of drug-induced liver injury, including acute liver failure, hepatitis and jaundice, in some cases requiring liver transplantation, have been observed in patients treated with tocilizumab. The frequency of serious hepatotoxicity is considered rare.

For additional information, please consult:
https://sinaem.agemed.es/CartasFarmacovigilanciaDoc/2019/DHPC_Tocilizumab_27062019.pdf

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# Sexual and reproductive health

## Pregnancy

*Planning pregnancy*

| | |
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| D | We suggest planning the pregnancy, including a preconception consultation, so that the gestation takes place in a clinical situation that minimises the risks for the foetus and for the mother. If it has not been planned, we suggest assessing the patient as soon as the pregnancy has been acknowledged. |
| B | In the pre-gestation consultation we recommend estimating the maternal risk profile based on the lupus activity, the extent to which the organs are affected, the autoantibody profile and the treatment received. |
| √ | In the preconception consultation, we suggest adjusting the treatment, substituting the medications that are contraindicated during pregnancy with others that are safe. |
| C | In planned pregnancies, the positivity or negativity of antiphospholipid and anti-Ro antibodies should be known in order to plan the monitoring of specific complications (heart block, placental insufficiency, preeclampsia). |
| √ | We suggest postponing pregnancy after a lupus flare until at least six months after remission, especially if the flare has affected vital organs. |
| B | We recommend advising against pregnancy in women with SLE with pulmonary hypertension or with severe organ damage (kidney, heart or lung) due to severe risk for the lives of mother and foetus. |

*Monitoring pregnancy*

| | |
|---|---|
| C | We suggest multidisciplinary management of pregnant woman with SLE by the obstetrician and the specialist in autoimmune diseases, with the participation of other specialists if considered necessary. |
| √ | From the medical viewpoint, we suggest making one visit during the first trimster, every 4-6 weeks until week 26 of gestation, and every two weeks from week 27 until birth. This is subject to modifications according to obstetric and medical criteria. |
| √ | During each visit, we suggest monitoring the weight, blood pressure and the presence of proteinuria, especially in women with risk of lupus nephritis and/or preeclampsia. |
| √ | We suggest determining C3 and C4 to monitor lupus activity, even though their levels are altered by the actual pregnancy. |
| √ | We do not recommend repeatedly determining antinuclear antibodies, anti-ENA and antiphospholipid antibodies. |
| √ | We suggest requesting anti-DNA in agreement with the clinically suspected flare. |

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| | |
|---|---|
| √ | We recommend performing a series of ultrasound examinations similar to the following, always subject to the obstetrician's criterion:<br>- Week 8-9: Pregnancy confirmation ultrasound.<br>- Week 12: Ultrasound for triple screening of chromosomopathies. During this week, a first Doppler study of uterine arteries may be carried out in order to estimate the probability of preeclampsia in women at risk (those who test positive to antiphospholipid antibodies, have a history of nephritis, preeclampsia and/or high blood pressure).<br>- Week 20: Malformation ultrasound. If the uterine artery Doppler has not been carried out during week 12 or it was abnormal, we recommend carrying it out this week.<br>- Week 24: The uterine artery Doppler can be repeated for the last time if it was abnormal, to see if has become normalised. If not, the pathology is considered as definite.<br>- Starting in week 24, growth ultrasounds and umbilical Doppler according to the obstetrician's criterion. |
| √ | When the pregnant woman has positive anti-Ro and/or anti-La antibodies, we suggest regular monitoring the foetal heart calculating the ultrasound PR interval between week 16 and 34, always in agreement with the criteria of the obstetrician and of the specialist in foetus cardiology. |

*Treatment with antimalarial drugs*

| | |
|---|---|
| B | We recommend maintaining hydroxychloroquine during pregnancy. |
| √ | As hydroxychloroquine is safer during the pregnancy and more studies have been performed than with chloroquine, we suggest using it as the antimalarial drug of choice in this situation. |

*Prevention of obstetric complications in patients with antiphospholipid antibodies*

| | |
|---|---|
| √ | We suggest that patients with obstetric antiphospholipid syndrome and a history of repeated early miscarriages (≤10 weeks) should be treated with aspirin, with or without associated heparin. |
| √ | We suggest that patients with obstetric antiphospholipid syndrome and a history of foetal death (>10 weeks) or severe preeclampsia with placental insufficiency should be treated with aspirin and heparin at prophylactic doses. |
| √ | We suggest that asymptomatic carriers of antiphospholipid antibodies should be treated with aspirin. |
| C | We suggest starting with aspirin prior to conception. |
| √ | Due to its availability in Spain and its convenience, we suggest using low molecular weight heparin rather than unfractionated heparin. |
| A | We do not recommend using intravenous immunoglobulins for treating obstetric manifestations of the antiphospholipid syndrome. |
| √ | Prednisone at a dose of ≤10 mg/day can be used in refractory cases, although this measure is not risk-free. |

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### Fertility and Contraception

*Assisted reproduction techniques*

| | |
|---|---|
| √ | We suggest carrying out a comprehensive assessment of the cardiovascular risk and of the activity of the disease before starting assisted reproduction procedures, including ovarian stimulation, programming them under controlled disease situation. |
| √ | We suggest administering prophylactic treatment with low molecular weight heparin in patients with positive antiphospholipid antibodies. |

*Contraception methods*

| | |
|---|---|
| √ | Although the benefits of hormone contraception may be greater than the risks in many women with SLE, we suggest carrying out a comprehensive assessment of the cardiovascular risk and of the activity of the disease before starting treatment with combined hormone contraceptives. |
| B | In women with positive antiphospholipid antibodies, we recommend avoiding combined hormone contraceptives due to having a greater risk of suffering arterial and venous thrombotic phenomena. |
| B | For their safety, we recommend bearing in mind the use of the IUD (including devices with progestogens) or barrier methods, within the possible contraceptive methods for women with SLE, especially for women for whom the use of oestrogen contraceptives is contraindicated. |

# Comorbidity

### Cardiovascular risk

*Cardiovascular risk level and cardiovascular risk assessment*

| | |
|---|---|
| √ | We suggest assessing the cardiovascular risk with the same frequency as recommended for other high cardiovascular risk diseases such as diabetes, using the instruments available for the general population until specific and validated instruments for SLE are available, and individualising the estimation according to specific risk-increase associated factors of SLE. |

*Prevention of cardiovascular events*

| | |
|---|---|
| √ | We recommend establishing the recommended cholesterol figures for people with increased cardiovascular risk as those desirable for SLE patients. |

*Indication for aspirin*

| | |
|---|---|
| A | We recommend treating SLE patients who persistently present medium to high values of antiphospholipid antibodies with low doses of aspirin, for the primary prevention of thrombosis. |
| D | We suggest treating SLE patients and previous cardiovascular disease with low doses of aspirin under the same terms as for the general population. |

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*Indication for high blood pressure drugs*

| | |
|---|---|
| D | In patients with nephritis with proteinuria, we suggest the use of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers. |
| C | In patients with lupus and high blood pressure, we suggest the use of angiotensin converting enzyme inhibitors due to their possible added value in the primary prevention of renal impairment. |

**Infection**

*Latent infection screening*

| | |
|---|---|
| √ | We cannot give a general recommendation on the indication or periodicity of repeated assessments of latent infection due to the human immunodeficiency virus, the hepatitis B virus, the hepatitis C virus and tuberculosis. Therefore these should be adapted to the clinical situation and the individual risk factors of each patient. |
| √ | We suggest examining all patients who are going to be submitted to immunosuppressive treatment for human immunodeficiency virus, hepatitis B virus, hepatitis C virus and tuberculosis, above all when this treatment involves high doses of glucocorticoids or biological therapies, regardless of the existence of risk factors. |
| D | For patients whose first tuberculin skin test is negative, we suggest carrying out a second test one week later to induce the immunological memory (booster effect) as false negatives are more frequent in the elderly and in immunosuppressed patients. |
| √ | The tuberculin skin test is the test of choice to detect tuberculosis thanks to its sensitivity in diagnosing tuberculosis in the standard cut-off point (5 mm). However, previous BCG vaccination and/or immunosuppression, could make the QFT-G a more reliable test for detecting latent infection. |

*Pneumococcal vaccine*

| | |
|---|---|
| √ | We suggest administering the pneumococcal vaccine to SLE patients. |
| √ | We suggest administering the pneumococcal vaccine, preferably, during a stable phase of the disease. |
| √ | For pregnant women with SLE, we suggest following the existing recommendations for pregnant women in the general population, if any. If there are none, we suggest not vaccinating until there is available scientific evidence. |

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## Cancer

| | |
|---|---|
| C | We suggest maximising early cancer detection measures in people with long-lasting SLE, organ damage and/or haematological participation, especially in patients treated with high doses of cyclophosphamide. |
| D | We suggest that SLE patients should undergo a cervical cancer screening programme more frequently than recommended for the general population, especially in presence of associated risk factors such as the use of immunosuppressants, a history of four or more sexual partners and/or a history of prior infection by HPV or of dysplasia. |

## Osteoporosis

*Indication for bone densitometry*

| | |
|---|---|
| D | Given the lack of evidence, we do not recommend carrying out a BMD test on all SLE patients. |
| √ | For the estimation of fracture risk, including BMD, we suggest following the recommendations applied to the general population, with special diligence in case of additional risk factors such as chronic treatment with glucocorticoids or menopause. |

*Prevention of steroid-induced osteoporosis*

| | |
|---|---|
| B | The use of calcium in monotherapy is not recommended to prevent steroid-induced osteoporosis. |
| C | In order to reduce the risk of steroid-induce osteoporosis in SLE, we suggest avoiding long-term sustained doses of prednisona >5mg/day in SLE. If it is necessary, steroid-saving drugs such as immunosuppressants should be used. |
| √ | We suggest recommending an adequate diet, resistance exercises, periodic measurement of BMD if prednisone >5 mg/day or equivalent are used for ≥ 2-3 months, calcium and vitamin D supplements, and evaluation of the need for pharmacological prophylaxis of osteoporosis with antiresorptive therapy. |

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# 1. Introduction

SLE is a systemic autoimmune disease. Lupus is one of the most frequent autoimmune diseases in terms of global rarity.[3] In our country, its prevalence has been estimated at nine out of every 10,000 inhabitants according to the population study EPISER.[4,5]

Although mild or moderate cases are frequent in our environment, SLE is a potentially fatal disease. Although the vital prognosis of the disease has improved over the last few years, the risk of death is still from two to three times that of the general population.[6,7] Furthermore, health-related quality of life (HRQoL) is clearly lower than the rest of the population.[8]

Although sufficient studies have not been conducted on the economic impact of SLE, this disease entails a high cost, resulting from medical care, including the repeated hospitalisations that it usually entails, and the indirect costs derived from the disability. In the European multicentre study LUCIE, a study on the costs associated with the disease, a cost of up to €4,748 per year were calculated for our country in the case of most serious patients. Likewise, around 50% of working age patients were unemployed as a result of their disease.[9]

The clinical manifestations of SLE, its course and prognosis are tremendously heterogeneous. This circumstance, together with its low prevalence, makes it difficult not just to acquire sufficient clinical experience, but also to study the disease when there is a lack of collaborative and standardisation efforts. Until not very long ago, no data were available from randomised and clinical trials that were able to generate quality evidence, and the majority of existing recommendations were based on expert opinions, often outside the framework of systematically developed consensus. The recent appearance of guidelines issued by the main international scientific societies, *American College of Rheumatology* (ACR) and *European League Against Rheumatism* (EULAR) in specific aspects of SLE such as lupus nephritis (LN),[10-12] clearly shows the urgent need to have guidelines, based on evidence and on rigorous expert consensus methodology. These guidelines should consider SLE globally as a systemic disease and include aspects such as healthcare management and patients' opinions, not often reflected in available guidelines.

Although there are no specific studies that address variability in clinical practice referring to SLE in our environment, different international experts have given their opinions in this sense, indicating the existence of considerable undesired variability and the need to develop strategies aimed at reducing it.[13] Among these strategies, evidence and expert consensus-based CPGs undoubtedly occupy a prominent place.[14] The complexity of an eminently systemic disease such as SLE, which requires the involvement of a considerable number of specialists in the healthcare process, requires coordination and multidisciplinary integration efforts. It is, therefore, advisable for these to be expressed in documents such as CPGs with recommendations based on scientific evidence and on broadly accepted principles.

A subsequent justification for developing a national CPG on SLE is the recent approval of specific biological therapies which are highly costly for the Spanish NHS and potentially toxic based on evidence from clinical trials that are complicated to interpret. Thus, the cooperation of experts within a CPG is necessary, to carry out an adequate assessment of the evidence and transfer the results to the physicians involved in managing SLE. This, in turn, will help decision-making easier, the adequate selection of candidate patients, as well as the conduction of unavoidable rigorous monitoring of its efficacy, effectiveness and safety in a real clinical practice situation.[15]

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# 2. Scope and objectives

This guideline has been developed according to the following principles:

- Become a useful instrument for all professionals involved in caring for SLE patients, whatever their healthcare level.
- Consider the perspectives of SLE patients and of their caregivers.
- Be based on the principles of Evidence-Based Medicine and on expert consensus methodology.
- Delimit the areas of uncertainty or controversy that require further research.

## 2.1. Objectives

### 2.1.1. General Objective

To develop a CPG that will serve as an instrument to improve the comprehensive healthcare of SLE patients, establishing systematically developed recommendations based on scientific evidence that will help professionals and patients to make decisions about the most appropriate healthcare, and to select the most adequate and efficient diagnostic or therapeutic options to address their health problem, integrating in a coordinated mannerthe different NHS resources involved.

Under any circumstances, the aim is not, to substitute the clinical judgement of professionals, but to provide a useful instrument on which to base that judgement in the best possible manner.

### 2.1.2. Specific objectives

- To develop a useful tool to standardise the diagnosis and treatment of SLE.
- To reduce unjustified variability in clinical practice in the comprehensive healthcare of SLE, both in terms of its diagnostic aspects and its therapeutic management.
- To foster a comprehensive and integrated healthcare for the person, relatives and environment with a multidisciplinary perspective.
- To facilitate coordination both among the different specialists involved in caring for SLE patients and among the different healthcare levels, helping to advance in the integrated management of the disease.
- To improve the clinical skills of the health professionals involved in the healthcare of SLE patients.
- To provide useful information on the efficacy, safety and efficiency of the different diagnosis techniques and of the (specific and symptomatic) pharmacological and non-pharmacological therapeutic options.
- To provide useful information so that the people affected, their relatives and/or caregivers, and the health professionals involvedon SLE can make decisions.
- To help to homogenise the language used by the different experts, thus facilitating communication.
- To detect research needs and establish recommendations for future research on SLE.

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# 2.2. Scope

## 2.2.1. Target population

Adults with SLE according to diagnostic criteria of expert physician, regardless of the onset age and severity. The most frequent manifestations are considered, excluding the disease that is restricted to the skin (cutaneous lupus), and the disease with terminal renal insufficiency, in a situation of dialysis or kidney transplant. Likewise, all the situations of the disease are considered, whether it is active, in remission, clinically quiescent or serologically active, pregnant patients, etc., adapting the management recommendations to each one of the situations described.

## 2.2.2. Healthcare Levels

The guideline will cover the healthcare that NHS primary care and specialised care professionals give to individuals with SLE.

## 2.2.3. Healthcare process

This guideline focuses on key questions that affect the healthcare of SLE patients and addresses questions related to the diagnosis, the standardised evaluation of the situation of the disease, the treatment (both specific and symptomatic, pharmacological and non-pharmacological, and of comorbidity), the prevention of complications, the clinical monitoring of patients and educational aspects.

Due to the limited availability of cost/benefit studies both on therapies and on the diagnostic procedures, this guideline does not directly address aspects related to the efficiency of the healthcare processes.

## 2.2.4. Users to whom this CPG is addressed

This CPG addresses health professionals who have direct contact with SLE patients and have to take decisions about caring for these people (rheumatologists, internists, nephrologists, dermatologists, haematologists, and other potentially involved specialists, as well as general practitioners and specialised nursing staff).

This guideline also addresses SLE patients and their relatives, educational groups or scientific societies, as well as health agents.

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# 3. Methodology

The methodology used to develop the CPG is the one proposed in the CPG Development Methodological Manual in the NHS[14].

The steps followed are listed below:

- Establishment of the CPG development group, made up of primary care physicians, medical specialists in rheumatology, internal medicine, nephrology, haematology, dermatology, immunology and clinical pharmacy, nursing staff attached to a hospital rheumatology unit, specialists in methodology and a representative from the federation of SLE associations of relatives and patients. The development group has been managed by a clinical and methodological coordination team. All the members of the group have provided a "declaration of interests" that is shown in Annex 1.

- To incorporate the perspective, experience and interests of SLE patients into this CPG, specifically in the scope, objectives and formulation of questions, apart from the participation of patients in all the stages of the guide development process (participating in the development group, participating in the experts group and participating in the external reviewer group), 16 a systematic review (SR) of the literature was carried out of both qualitative and quantitative studies focused on identifying the impact of SLE on the lives of people with the disease and their environment, their experiences and needs for information and support. Furthermore, to complete this information, the perception of patients in the context of our country was explored by means of a Delphi type three-round consultation[17] carried out with the collaboration of FELUPUS. Both the SR and the patient consultation have also allowed identifying those needs of patients that had not been sufficiently studied, in order to transfer them to the researchers interested in SLE.

- Formulation of clinical questions following the, Patient/Intervention/Comparison/Outcome format.

- Bibliographic search in: Medline and PreMedline via OvidSP, Embase via Elsevier and Science Citation Index Expanded (SCI-EXPANDED) and the Social Science Citation Index (SSCI) via Web of Knowledge, The Cochrane Library, Psycinfo, Scopus, TripDatabase, Canadian Medical Association (CMA) Infobase, International Guidelines Library (GIN), National Guidelines Clearinghouse (NGC), National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), New Zealand Guidelines Group, Institute for Clinical Systems Improvement (ICSI) and National Health and Medical Research Council (NHMRC). Timeline: from May to December 2013. Languages: English and Spanish. The first phase involved a preliminary search for CPGs and systematic reviews in the aforementioned databases. Identified CPGs and systematic reviews were assessed with the AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II),[18] evaluated according to the criteria of SIGN,1 respectively. These documents have been included as a secondary source of evidence to respond to some specific sections of the guideline due to their rigour and clarity. An extensive search for primary studies (randomised clinical trials -RCT-, observational studies, and diagnostic test studies) was carried out in a second stage. Later, to identify further possible relevant studies, the entire development group was consulted until April 2014, the deadline for the first draft of the CPG.

- Quality assessment of the studies and summary of evidence for each question following SIGN recommendations.1 As suggested by the SNS CPG development manual for

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diagnostic test studies, the Oxford Evidence-Based Medicine Centre system has been used for the diagnosis questions.[19]

- The determination of the evidence levels and the formulation of recommendations was based on SIGN methodology.1 To determine the strength of each one of the formulated recommendations, the development group has considered not only the level of evidence available but also the equilibrium between desirable and undesirable consequences of carrying out the recommendation.[20] The good clinical practice recommendations have been formulated and agreed by consensus following a transparent methodology with a face-to-face meeting of the development group and a subsequent series of successive consultation rounds with a panel of experts. Depending on the nature of the recommendations, different groups of experts were formed (10-13 professionals) with members of the development group and the group of collaborating experts, representing the different medical and health specialities involved. The consultation was carried out individually and by means of the successive interaction of an online questionnaire supported by the mean results from the previous round, in order to generate convergence of opinions, following a modified Delphi methodology.[17] The good clinical practice recommendations proposed by the development group were presented in the questionnaire, and the panel had to assess the appropriateness of each one of them (the relationship between benefit and harm) on a scale from 1 to 9, where 1 meant that the recommendation was inappropriate and 9 that it was fully appropriate. An intermediate score of 5 meant that the harm and the beneficial effects were almost the same or that the expert was not able not give an opinion on the recommendation. Finally, it was decided to include only those recommendations with median values between 7 and 9, and with a percentage of panelists scoring within that range of 70% or more, after the first or the second round.

- In order to promote and facilitate the shared decision-making (SDM) process between SLE patients/relatives and the health professionals, the CPG development group identified grade A and B recommendations which, under their judgment, were more sensitive to the values and preferences of the patients, and therefore, in which the SDM process should be favoured (Annex 2).

- The collaborating experts have participated in the formulation of questions, in the development of search strategies, in the clinical good practice recommendations consensus process, and in the review of the first draft of the CPG.

- External reviewers have participated in the review of the second draft. The purpose of submitting the CPG to external review was to improve the overall quality, to ensure the appropriateness of recommendations, to disseminate the evidence, as well as to assess its applicability and feasibility. The methods used to carry out the external review were the use of the Word track changes tool and comments in the margin of the text, or an evaluation of the different sections of the CPG by means of a template.

- As the first step in the development process of this CPG, the different Scientific Societies involved were contacted (Rheumatology, Internal medicine, Nephrology, Haematology and Haemotherapy, Dermatology and Venereology, Neurology, Primary Care Phycisians, Hospital Pharmacy, Primary Care Pharmacists, Family and Community Medicine, Nursing), agreeing on the representatives for the development group. They were also represented in the group of expert collaborators and the group of external reviewers.

- A document with the detailed information on the methodological process of the CPG (search strategies for each clinical question, critical reading datasheets of the selected studies, synthesis tables of the evidence, and formal assessment tables) is available at www.guiasalud.es.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

– An update of the CPG is planned every three to five years, or earlier if there is new scientific evidence that may substantially modify any of the recommendations offered in this CPG. Updates will be carried out on the electronic version of the CPG, available at the URL: http://www.guiasalud.es

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

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# 4. Diagnosis of systemic lupus erythematosus

## 4.1. Early detection

### 4.1.1. Prognosis

**Questions to be answered:**

- Do early detection and early treatment improve the prognosis and survival of people with systemic lupus erythematosus?

SLE is a chronic autoimmune disease, with an inflammatory nature and multi-system impairment. The disease can affect any organ or system, although the most frequently involved are the joints, the skin and the kidneys, with geographical and ethnic variations.[21-30] In clinical practice, the diagnosis is carried out by combining symptoms, signs and immunological disorders. There are no pathognomonic findings. This, associated with the complexity of the disease, the heterogeneity at onset and the time required for it to fully develop, may be the reason why it is difficult to identify SLE patients at an early stage.

In the natural history of SLE, a subclinical period is distinguished, followed by a clinical phase with the onset of symptoms and signs. The phase between the clinical onset and the diagnosis is often framed within the undifferentiated connective tissue disease group.[31]

Cohort studies show that, in the natural history of SLE, the delay between clinical onset of the disease and diagnosis has been reduced, going from 26 months in patients diagnosed during the decade of the 80s, to 15 months in the decade of the 90s, and nine months as from 2000.[32-34]

The delay in diagnosis is highly influenced by the epidemiological and clinical characteristics of the onset of SLE, so, when it begins in people over the age of 20 and with arthritis, the diagnostic delay is significantly greater than in individuals aged under 20, or initial appearance with malar -butterfly- *rash* or renal impairment.[35] However, the progressive reduction in diagnosis time was quite significant between the 80s and 90s, related to the introduction of the detection of antinuclear antibodies (ANA). This was not the case between the 90s and the 2000s, given that no new relevant advances have taken place in the diagnostic methods of this disease.

There are no scientific tests that guarantee screening for SLE in the general population, using the ACR classification criteria for this disease, the Boston criteria or the classification of the *Systemic Lupus International Collaborating Clinics-SLICC group* (Annexes 5, 6 and 7),[36-39] by means of the detection of ANA or other auto-antibodies. Only a small percentage of positive ANA asymptomatic individuals will develop SLE and it is not possible to discriminate them with the diagnostic techniques available today.

Diagnostic studies 2

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

In the retrospective case-control study of Arbuckle *et al*., carried out with serums stored from the USA armed forces personnel, 130 cases diagnosed with SLE were analysed. 78% presented high titres of ANA with a mean of 2.25 ± 0.27 years before the onset of symptoms, and 3.01 ± 0.2 years before diagnosis. 55% presented high titres of anti-dsDNA antibodies (dsDNA), a mean of 1.24 0.31 years before the onset of symptoms, and 2.24 ± 0.2 years before diagnosis. 47% presented high titres of anti-Ro antibodies, a mean of 2.97 ± 0.39 years before the onset of symptoms, and 3.68 ± 0.2 years before diagnosis. 32% presented high titres of anti-Smith (Sm) antibodies, a mean of 0.47 ± 0.44 years before the onset of symptoms, and 1.47 ± 0.2 years before diagnosis. 26% presented high titres of anti-ribonucleoprotein (anti-RNP) antibodies, a mean of 0.47 ± 0.20 years before the onset of symptoms, and 0.88 ± 0.2 years before diagnosis. ANA, anti-Ro and antiphospholipid antibodies appear much earlier on than anti-Sm and anti-RNP antibodies (mean of 3.4 years before diagnosis v. 1.2 years, *P*=0.005). Anti-dsDNA antibodies are detected later than ANA (*P*=0.06), but earlier than anti-RNP antibodies (*P*=0.005). Therefore, the sequential accumulation of autoantibodies occurs prior to the clinical onset of SLE.[40]

Observational
S.
2+

In the Swedish study of Eriksson *et al*., carried out on 38 SLE patients, for whom serum was available prior to the onset of symptoms, paired by age and gender with 152 controls, the ANAs were detected on average 5.6 ± 4.7 years before the onset of symptoms, and 8.7 ± 5.6 years before diagnosis. The future risk of developing SLE increased in carriers of anti-dsDNA (*OR*=18.13; 95% CI: 3.58-91.84) and of ANA (*OR*= 11.5; 95% CI: 4.54-28.87).[41]

Case-control study
2+

In the review case study of Heinlen *et at*., which included 130 patients who satisfied the ACR criteria for SLE classification, discoid lupus and comitial crises developed on average 1.74 and 1.70 years, respectively, before SLE was diagnoses. Arthritis, although this is a more frequent criterion before diagnosis (54%) preceded it by 0.68 years. Anti-dsDNA were detected in 92% of the patients before having evidence of nephritis (*P*<0.001) and anti-C1q were identified 1.4 years before the onset of nephritis (*P*<0.0043). In contrast, antibodies not associated with specific clinical criteria did not have any significant time relationship with the appearance of SLE symptoms.[42]

Observational
S.
2-

In agreement with a study published in 2005, only one third of the individuals who started with unspecific manifestations of SLE, such as arthralgias or Raynaud's phenomenon, would develop a connective tissue disease, and of these, only 30% would be SLE.[31]

Observational
S.
2+

Some predictors of the appearance of SLE were assessed in a cohort of 213 patients with undifferentiated connective tissue disease monitored for five years. In a univariate analysis, it was observed that patients who evolved to SLE (13%) had more possibilities of being young, Afro-American and of having alopecia, serositis, discoid lupus, positive Coombs test, positive anti-Sm antibodies, anti-dsDNA and positive ANA and/or false positive for syphilis. Discoid lupus (relative risk-RR=15.8), serositis (RR=4.1), homogeneous ANA (RR=4.8), and positive anti-SM (RR=28.2) were maintained as predictors of the appearance of SLE in the Cox regression model.[43]

Observational
S.
2+

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There are no randomised clinical trials that assess the benefits of early diagnosis interventions of SLE in symptomatic individuals, in terms of improving survival or reducing damage. Based on the evidence provided by longitudinal observational studies, it is suggested that the progressive increase of survival observed over the last five decades may be related, partly, to the early identification of the disease.

In the aforementioned retrospective study of 130 members of the US armed forces who developed SLE, treatment with hydroxychloroquine (HCQ) administered for reasons other than lupus in clinical phase, prior to the confirmatory diagnosis of the disease, increased the time between the onset of symptoms and the diagnostic classification of SLE with respect to patients who did not receive this treatment (mean 1.0 v. 0.29 years, $P$=0.018). In addition, it decreased the autoantibody accumulation rate and the number of specific autoantibodies, both at the time of diagnosis and during evolution. From the clinical viewpoint, patients who received HCQ developed proteinuria ($P$<0.05), leucopoenia ($P$<0.05) or lymphopenia ($P$<0.001) less frequently at the time of the diagnosis of SLE.[44]

Observational
S.
2+

In the forms that start with severe manifestations of SLE, such as LN, early identification and early treatment are favourable prognostic factors of the evolution of kidney damage. In the recent guideline for diagnosis and treatment of LN of the Spanish Society of Nephrology and the Spanish Society of Internal medicine, the early treatment of LN is recommended with a degree of 1B, given that a delay of over three months is associated with an increase in the risk of terminal renal insufficiency in cohort studies.[45]

Expert
opinion
4

**Summary of evidence**

| | |
|---|---|
| | There is no scientific evidence about the benefits of early detection of SLE in general asymptomatic population. |
| 2+ | The appearance of anti-Ro, anti-La, anti-dsDNA, anti-Sm, anti-RNP and antiphospholipid autoantibodies may precede the clinical onset and the confirmation diagnosis of SLE by between 0.5 and six years.[40,41] |
| 2- | The symptoms of SLE precede its clinical diagnosis by 0.5 to two years.[42] |
| 2+ | One third of individuals with suggestive unspecific manifestations of SLE will develop a connective tissue disease and, of these, one third will develop SLE.[31] |
| | There are no RCTs that assess the benefits of early diagnosis of SLE in symptomatic individuals. |
| 2+ | Start of treatment with HCQ in early phases, between the onset of the clinical symptoms with presence of autoantibodies and the classificatory confirmation of SLE, delays the evolution of the disease, decreases the accumulation of autoantibodies and reduces the risk of onset with proteinuria.[44] |

**Recommendations**

| | |
|---|---|
| D | We do not recommend screening for SLE in the general asymptomatic population. |

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| | |
|---|---|
| C | We suggest the early determination of antinuclear (anti-dsDNA, anti-Ro, anti-La, anti-Sm, anti-RNP) and antiphospholipid antibodies in individuals with symptoms that are suggestive of SLE, in order to detect early and less severe forms of the disease. |
| C | We recommend early treatment with hydroxychloroquine in people with incomplete forms of SLE (understood as those that do not meet the classification criteria), who are carriers of suggestive autoantibodies, to delay the development of the disease and the development of renal impairment. |

## 4.1.2. Suspect symptoms

**Questions to be answered:**

- What are the main symptoms and signs that should make us suspect systemic lupus erythematosus?

The different forms in which SLE appears and the many different clinical manifestations during its evolution, with periods of remission and relapses, make its diagnosis especially difficult. The variety of symptoms and signs of SLE include systematic manifestations at multiple levels (Annexes 5, 6 and 7).

A review of studies published between 1996 and 2003 established that the most frequent clinical pattern in the initial appearance of SLE is characterised by a mixture of symptoms and signs affecting joints, skin, haematology and serology, frequently accompanied by constitutional symptoms. In other patients, however, certain organs or systems are mainly affected, essentially the kidneys, or the central nervous system (CNS). In any case, the main clinical pattern over the first years of the disease tends to prevail later on.[46]

Expert opinion 4

**General symptoms**

Expert opinion 4

**Fever, asthenia or weight loss** are present in the majority of SLE patients, as onset symptoms (50%) or in any phase of its evolution (74-100%).[47]

Fever related to the activity of SLE occurs as a first manifestation of the disease in up to 36% of the patients.[22]

Natural history S. 2+

**Organ impairment symptoms**

Prevalence S. 3

**Arthritis or arthralgia** is the most frequent initial symptom to appear in SLE, being present in up to 68% of the cases. Throughout the progression of SLE, more than 90% of patients will develop arthralgia or arthritis, predominantly located in hands, and rarely erosive. Its association with asthenia is a frequent fact in the initial appearance of SLE.[22,46,48-53]

Natural history S. 2+

Prognostic s. 2-

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**Mucocutaneous symptoms** are also frequent as appearance symptoms in up to 60% of the cases, or in up to 80% of patients throughout the evolution. Among these, the most common are, in order of frequency, malar *rash* and on the nose, generally related to photosensitivity, and which usually respects the nose-lip wrinkles; alopecia and mouth ulcers, normally not painful. Much less frequent are purpura and urticaria. [22,46,48-53]

Prevalence S. 3

Natural history S. 2+

Prognostic s. 2-

**Raynaud's phenomenon** is a frequent onset symptom, which may or may not be accompanied by other symptoms, affecting 17-33% of patients, with regional and ethnic variability. During the progression of SLE, up to 70% of patients will present Raynaud's phenomenon.[22]

Natural history S. 2+

**Renal disease** is clinically important in 30-70% of SLE patients during the progression of the disease, although it may also be the predominant manifestation at onset of the disease in 16-40%. In any case, the development of renal disease is typical of the first years of evolution of SLE and it may progress to terminal renal disease.[22,48,49,51,52,54]

Natural history and prognostic S. 2+

Prevalence S. 3

Prognostic s. 2++

**Neuropsychiatric impairment** includes 19 syndromes defined by the ACR relating to the impairment of the central and peripheral nervous systems (Annex 7). In 28% of patients they appear during the first years of evolution of SLE, and they may even be symptoms marking the onset of the disease. CNS impairment syndromes are more frequent, especially headache, depression, cerebrovascular disease, mainly thromboembolic disease associated with antiphospholipid (APL) antibodies, seizures, anxiety, and cognitive dysfunction, although only one third of the cases can be directly attributed to SLE.[55] There are other entities, such as, for instance, reversible posterior leukoencephalopathy, recently described in SLE patients 56 that do not appear on the ACR list.

Natural history S. 2++

During the progression of the disease, up to 80% of patients may present a neuropsychiatric event.[57]

Natural history S. 2+

**Cardiovascular manifestations** are relatively frequent, although more typical during the evolution than when SLE first occurs. The most frequent is pericarditis (8-48%), although these patients also have an increased risk of coronary artery disease.[46,47]

Prevalence S. 3

Expert opinion 4

**Pulmonary manifestations** include pleurisy, interstitial pneumonitis and pulmonary hypertension, mainly. Pleurisy may occur in up to 50% of SLE patients, but it is less frequent as an initial manifestation (2-3%). The risk of pulmonary thromboembolism is greater in patients with APL.[46,58]

Prevalence studies 3

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

**Gastrointestinal symptoms** are more often secondary to the treatment of SLE than directly caused by the disease, especially gastritis and peptic ulcer, related to NSAID ± glucocorticoids. However, vasculitis, typical of SLE, may cause pancreatitis, peritonitis and colitis.[46,47]

Prevalence S. 3

Expert opinion 4

**Haematological manifestations** are observed at the onset of SLE in 23% of Caucasian patients, but this figure may reach 80% as the disease progresses.[51,52,59] The most frequent are cytopenias, leucopoenia being the most prevalent (43-66%), followed by anaemia of chronic disease, thrombocytopenia and haemolytic anaemia.

Natural history S. 2+

Prevalence S. 3

**Antiphospholipid syndrome** associated with SLE is characterised by arterial or venous thrombosis, or pregnancy complications, with presence of APL (anticardiolipin, lupus anticoagulant and anti-beta2glycoprotein I). The most frequent venous event is deep vein thrombosis of lower limbs, whilst the most frequent arterial event is cerebrovascular accident (CVA). Repeated miscarriages, foetus death, preeclampsia and prematurity may occur in pregnant women.[60]

Natural history S. 2+

In patients with antiphospholipid syndrome (APS), this is the only initial manifestation of SLE in 20%, and in 30% it is accompanied by other characteristic symptoms of SLE. Its association with other manifestations such as thrombocytopenia (20-40%), neutropenia and livedo reticularis is frequent.[61,62]

Natural history S. 2+

**Clinical and serological variations according to region and ethnic group**

The prevalence and incidence of the clinical manifestations and laboratory findings of SLE show great variability between ethnic groups and countries, although in this guideline attention is especially paid to those studies performed with European and Spanish patients.

The sample of mainly Caucasian North American patients used to validate the criteria of the ACR classification of SLE, reviewed in 1982, comprises 177 cases of SLE and 162 controls with other non-traumatic or degenerative connective tissue diseases. In SLE patients, the clinical and laboratory manifestations that make up the most prevalent ACR classification criteria are the presence of ANA (99%), arthritis (86%), immunological disorder (85%), haematological disorder (59%), malar *rash* 57%), serositis (56%), and renal impairment (51%), whilst the least frequent criteria are discoid lupus (18%), neurological disorder (20%) and mouth ulcers (27%). However, these symptoms and signs may be present in autoimmune diseases other than SLE, which makes differential diagnosis difficult. In the sample of Tan *et al*., 63% of the control patients presented arthritis, 51% ANA, 14% serositis, 11% haematological disorders, 7% immunological disorders, 6% renal disease, 4% malar *rash*, 4% photosensitivity, 4% mouth ulcers, 2% neurological disorders, and 1% discoid *rash*.[39]

Diagnostic S. 2

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

In the 310 cases of SLE and in the 392 controls, carriers of rheumatic diseases other than SLE, recruited to validate the 2012 SLE classification, performed by the SLICC group, the frequency of symptoms and signs that make up the designed criteria is similar. 79% of the cases of SLE present arthritis, 65% malar *rash* and/or photosensitivity and/or acute cutaneous lupus, 59% low complement levels, 57% anti-dsDNA, 54% APL, 49% lympopenia, 46% leucopoenia, 44% mouth ulcers, 35% serositis and 33% renal impairment. In control patients, the frequency of arthritis is 56%, malar *rash* and/or photosensitivity, and/or acute cutaneous lupus 20%, APL 14%, lymphopenia 12%, mouth ulcers 8%, low complement levels 7%, discoid lupus 6%, leucopoenia 5%, anti-dsDNA 4%, renal disease 4% and ANA 3%.[19] Diagnostic S. 2

The North American multi-ethnic cohort, *Hopkins Lupus Cohort*, which includes 1357 consecutively selected SLE patients, with representation of Caucasians (55.9%), Afro-Americans (39.1%) and Asians (5%), shows how the presence of anti-dsDNA antibodies, anti-cardiolipin and lupus anticoagulant prevail in the Caucasian ethnic group, with a greater incidence of arterial thrombosis (17.4%), venous thrombosis (25.7%) and CVA (12.8%) than in other ethnic groups.[63] Prognosis S. 2++

In the multi-centre and multi-ethnic North American cohort LUMINA, carried up with North American patients with recent SLE (≤5 years) belonging to three ethnic groups (30% Hispanic, 38% Afro-American, and 31% Caucasian), there is greater prevalence of proteinuria, nephropathy, cardiovascular disease (CVD) and presence of autoantibodies, with earlier onset age in Hispano and Afro-American patients than in Caucasian patients.[49,63] Prognosis S. 2+

United States Hispanics (defined as individuals who originate from a Spanish-speaking country, generally have a strong American-Indian ancestral component) show clinical expression variability. Thus, at the time of diagnosis, greater prevalence of serositis is observed (60 v. 8.6%), as well as renal impairment (41 v. 13.6%), thrombocytopenia (21 v. 3.7%), and the detection of anti-dsDNA antibodies (69.5 v. 46.9%) in Texas Hispanics than in Puerto Rico Hispanics, respectively. Puerto Rico Hispanics (with lower American-Indian ancestral component) have, in contrast, greater prevalence of photosensitivity (81.5 v. 41%), malar *rash* (65.4 v. 45.7%), discoid lupus (13.6 v. 2.9%) and detection of anti-Ro antibodies (24.7 v. 11.4%) than Texans.[54] Prognosis S. 2+

In the Puerto Rico cohort of Vila *et al*. (134 SLE patients), different clinical patterns were observed depending on the circulating autoantibody profile. Patients with anti-dsDNA antibodies significantly showed more vasculitis, pleural effusion, nephropathy, anaemia, leucopoenia and thrombocytopenia. Anti-Sm antibodies are associated with renal impairment, ulcers and thrombocytopenia. Anti-Ro antibodies are associated with discoid lupus, serositis, pneumonitis, haemolytic anaemia and leucopoenia. And the three autoantibodies are associated with a greater level of irreversible organ damage.[64] Prognosis S. 2+

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In European Caucasians, the multi-centre cohort of 1,000 SLE of Cervera *et al*., showed that the most frequent clinical characteristics in the first five years' evolution of the disease are arthritis (41%), malar *rash* (26%), nephropathy 822%), photosensitivity (19%, fever (14%), neurological impairment (13.6%), Raynaud's phenomenon (13.2%), and serositis (13%). Thrombocytopenia, mouth ulcers, thrombosis, livedo reticularis, discoid lupus, subacute cutaneous lesions, myositis and haemolytical anaemia are below 10%, in this order. In the next five years' evolution there is a significant decrease of malar *rash*, photosensitivity, subacute cutaneous lesions, Raynaud's phenomenon, fever, arthritis, serositis, nephropathy, myositis and thrombosis.[22]

Natural history S. 2+

In the entire progression of SLE, the highest accumulated prevalences were for musculoskeletal symptoms (84%), malar *rash* (58%), photosensitivity (45%), renal impairment 39%) and serositis (36%).[65]

Natural history S. 2+

In the one-centre cohort of Font *et al*., conformed by 600 consecutively selected Spanish patients, 89% were women with an average age at onset of symptoms of 31, and 33 at the time of diagnosis. The most frequent clinical manifestations throughout the course of the disease were arthritis/arthralgia (83%), haematological disorders (83%), cutaneous impairment (59%), constitutional symptoms (42%), and nephropathy (34%).[51]

Prevalence S. 3

In the multi-centre cohort, with historical data collection from a large representative sample of adults with SLE (n=3679) originating from Spanish rheumatology services, 90% were women and aged 33 on diagnosis. The most frequent clinical manifestations were ANA (99%), immunological disorder (anti-DNA antibodies, anti-Sm, IgM or IgG anticardiolipin, false luetic serology or lupus anticoagulant) (84%), haematological disorders (anaemia/leucopoenia/lymphopenia/thrombocytopenia) (80%), arthritis (78%), photosensitivity (61%), malar *rash* (55%), mucosa ulcers (46%) and nephropathy (34%).[66]

Prevalence S. 3

In other Spanish cohorts, such as that of Alonso *et al*., they observed a similar prevalence of symptoms and signs, but with a higher average age at the time of diagnosis (46.1 years).[52]

Natural history S. 2+

The gypsy population sub-group from the south of Spain presents onset at earlier ages (25.9 v. 32 years, Spanish Caucasians, $P$=0.02), with less frequency of renal, gastrointestinal and eye impairment, and greater frequency of APS, thrombosis and livedo reticularis, as shown by the case study (106 SLE: 81 Caucasians and 25 gypsies) and controls (185 healthy: 105 Caucasians and 80 gypsies) of Ramal *et al*.[67]

Prognosis S. 2-

**Clinical and serological variations according to age**

The clinical and laboratory patterns of SLE show differences in agreement with the age at which the disease appears.

Natural history S. 2+

SLE is diagnoses infrequently after the age of 50. Evidence is consistent with low prevalence in this group, with variations between 3.6 and 20.1% in the different studies. In the European environment, the relative frequency is 9%,[65] and in Spain between 14.9 and 16%.[66,68-70]

Prevalence S. 3

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Late onset is characterised by less severity when it first occurs and during evolution than at earlier ages. A SR of studies published until 2004, with joint analysis of data of 714 cases of SLE with age of appearance of 50 or more, compared with 4,700 people with onset of SLE before the age of 50, shows that the late onset is significantly associated with a greater prevalence of serositis (36.7 v. 28.6%), and pulmonary impairment (21.2 v. 11.3%), and with lower frequency of malar *rash* (31.1 v. 62.4%), photosensitivity (26.2 v. 38.2%), purpura/cutaneous vasculitis (13.4 v. 25.9%), alopecia (24 v. 44.9%), Raynaud's phenomenon (24.8 v. 37.2%), neuropsychiatric manifestations (15.3 v. 20.2%), lymphadenopathy (9.1 v. 19.6%), nephrotic syndrome (8.1 v. 24.3%), and nephritis (28.6 v. 42.7%). Among the laboratory parameters, people with late onset suffer more frequently from rheumatoid factor (32.7 v. 20.1%) and less detection of anti-Sm antibodies (9.1 v. 17.1%), anti-RNP antibodies (10.4 v. 20.9%) and low CH50 complement levels (45 v. 64.9%) with respect to the younger patients. Although literature is not consistent, the majority of studies indicate that the female-male ratio considerably decreases in SLE that start at an age of over 50, with respect to SLE that appear at younger ages (4.4:1 v. 10.6:1), reflecting the likely relationship between SLE and oestrogens.85 In Spain this is situated at 4:1.[69,71]

Prevalence S. 3

Natural history S. 2+

In more recent studies, the clinical characteristics of the late appearance of SLE were confirmed. In a cohort from the north-east of Spain in late forms compared to early forms, lower frequency of renal impairment (13.5 v. 26.4%, *P*=0.07), hypocomplementinemia (72.9 v. 91.2%) the presence of anti-dsDNA antibodies (6.8 v. 49.2%), and anti-Sm antibodies (23.1 v. 68.1%). In contrast, secondary Sjogren's syndrome was more frequent (27.1 v. 12.1%, *P*=0.03).[71]

Natural history S. 2+

In Italy, the comparative study of Cartella *et al.* performed with 40 SLE patients and onset age of over 50, and 476 SLE with earlier onset ages, shows the greater frequency of dry syndrome and lesser frequency of glomerulonephritis, as well as descents of fractions of the C3 and C4 complements in advanced ages.[72]

Prevalence S. 3

In the 1528 cases of SLE that make up the Canadian cohort of Lilani *et al*., appearance at the age of 50 or more represent 10.5%, and these patients have less malar *rash*, nephritis, cytopenias, hypocomplementemia, anti-Sm antibodies and anti-RNP antibodies and similar frequency of anti-dsDNA antibodies with respect to SLE patients that appears under the age of 50. Despite this, they accumulate more organ damage and show more activity of the disease, suggesting a less benign prognosis than that described for other cohorts.[73]

Natural history S. 2+

In the study of cases and control, nested in the LUMINA cohort, 73 patients with age of appearance ≥50 years, were paired by gender and duration of the disease with 144 randomly selected controls with SLE onset at under the age of 50. The cases of SLE at an older age had less renal impairment and anti-Sm antibodies, and more neurological impairment, thrombotic events, osteoporosis and hypertriglyceridemia. The late onset was an independent predictor of irreversible organ damage (*OR*= 23.32; 95% CI: 3.98-141.56) and mortality (*OR*= 10.74; 95% CI: 3.07-37.56) with respect to the appearance of SLE at ages of under 50.[74]

Risk factor s. 2+

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The subgroup of patients aged 65 or more did not show relevant clinical or immunological differences with respect to patients aged 50 to 64, in different countries.[75,76] Prevalence S. 3

Patients who accumulate four ACR classification criteria of SLE in a short period of time –less than four weeks–, which is known as acute onset of SLE, present a clinical pattern characterised by a younger age, less educational level and cutaneous impairment, and greater renal impairment and activity of the disease. In the LUMINA North American multiethnic cohort, this type of appearance was observed in 15% of the selected patients.[77] Natural history S. 2+

**Clinical and serological variations according to gender**

In a case and control study nested in the LUMINA North American multiethnic cohort, characterised by the inclusion of SLE cases of less than five years' evolution, males (10.2%) did not show any age differences with respect to women, but they were more frequently Caucasian, smokers and with greater prevalence of renal impairment (proteinuria), lymphopenia, thrombocytopenia, detection of lupus anticoagulant and irreversible organ damage, both basal (HR: 73.18; 95% CI: 1.99-5.06) and accumulated throughout the course of the disease. In contrast, they had less prevalence of musculoskeletal symptomatology.[78] Case-control study 2+

In the review study of cases of 2,144 males and 426 women with SLE admitted into the hospitals of the Department of Veterans of the United States, it was observed that older males, at the time of admission, more frequently suffered from myocardial infarct and neoplasia, and their mortality rate one year after diagnosis was greater than in women. However, this study had a clear patient selection bias, as well as cases of older ages with respect to other cohorts.[79] Prognosis S. 2-

Within the European environment, the studies that analyse the influence of gender on the clinical pattern offer different results. In the United Kingdom, the study of Aydintug *et al*, compared 16 males with 232 females, belonging to a non-selected series of 247 SLE patients, concluding that males did not express a significantly different clinical or serological pattern to females, with the exception of serositis, which was more frequent among males at the onset of the disease (37% males v. 13% females, $P<0.05$). In this study, the most prevalent clinical manifestations at onset of SLE were arthritis, malar *rash*, Raynaud's phenomenon, discoid lupus, neuropsychiatric manifestations and renal impairment, both in males and in females. Pulmonary impairment, haemolytic anaemia and myositis were more frequent among males, and thrombotic events among females, but, in both cases, there were no significant differences in terms of gender. The serological patterns were similar between genders, the most prevalent being the detection of ANA, anti-dsDNA and anti-SSA (Ro) antibodies, and lupus anticoagulant.[80] Prevalence S. 3

The greater frequency of serositis in males was also observed in the European cohort of 1,000 SLE patients of Cervera *et al*., in which a lower prevalence of arthritis was also verified during the evolution, in comparison with women.[65] Natural history S. 2+

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The more recent study of Renau *et al*., based on a historical assessment of 484 SLE patients according to ACR criteria (90.7% women, 9.3% men and 59% Caucasians), originating from a university rheumatologic centre in the United Kingdom, confirmed the lack of differences between genders, with clinical and serological patterns without changes over the last three decades. The only significant differences between women and men was the greater accumulated prevalence of mouth ulcers (29.2% women v. 13.3% men, $P<0.05$) and titres of Igm anticardiolipin antibodies (9.9% women v. 0% men, $P<0.05$) in women. The most frequent clinical pattern in both genders was arthritis, malar *rash*, serositis, photosensitivity and nephritis. The most frequent laboratory anomalies were lymphopenia and leucopoenia. And the serological pattern of greatest prevalence was the presence of ANA, anti-dsDNA antibodies, low levels of C3, anti-Ro antibodies and positive rheumatoid factor.[79]

Prevalence S. 3

In North American cohorts, the male gender is associated with a worse prognosis. In Hopkins' multi-ethnic cohort, which included 157 males (66% white, 34% Afro-American) and 1822 women (60% white, 40% Afro-American), the males more frequently presented symptoms of high blood pressure, thrombosis, renal impairment, and haematological and serological disorders, as well as more irreversible neuropsychiatric, renal, cardiovascular, peripheral vascular damage and greater mortality, and in terms of glomerulonephritis, a high rate of thrombosis and autoantibodies. Women, in contrast, presented more symptoms of malar *rash*, photosensitivity, mouth ulcers, alopecia, Raynaud or arthralgia ($P<0.05$). In the serological profile, males showed greater prevalence of anti-Sm, anti-dsDNA, and anti-RNP antibodies, lupus anticoagulant and low levels of C3 ($P<0.05$).[77]

Natural history S. 2++

The only European study that shows a clear difference between genders at onset of SLE is the Danish study by Jackobsen *et al*.[81] In this sample of 513 SLE patients, males (11.5%) expressed a greater frequency of serositis, nephropathy and high blood pressure, and less photosensitivity, than women. In this study, the cases were recruited from rheumatology or nephrology clinics, which may overestimate the prevalence of renal disease.[81]

Natural history S. 2-

In contrast, the cohort of 743 incident cases of SLE (7.9% males) in a region of Greece, shows numerous differences in clinical manifestations between men and women. At the time of diagnosis of SLE, males had greater frequency of nephropathy (27.1 v. 16.1% in women, *OR*= 2.81; 95% CI: 1.46-5.38), thrombosis (20.3 v. 4.7%, *OR*= 5.83; 95% CI:2.70-12.61), gastrointestinal symptoms (16.9 v. 9.2%, *OR*= 2.24; 95% CI: 1.04-4.80), ictus (8.5 v. 0.9%, *OR*= 12.29; 95% CI: 3.18-47.55), and APS (8.5 v. 2.43%, *OR*= 3.63; 95% CI: 1.11-11.87), whilst in women, arthralgia was more frequent (63.2 v. 45.8% in men, *OR*= 0.42; 95% CI: 0.24-0.72), as well as photosensitivity (31.6 v. 13.6%, *OR*= 0.30; 95% CI: 0.13-0.68), Raynaud's phenomenon (24.1 v. 11.9%, *OR*= 0.39; 95% CI: 0.16-0.93), and alopecia (16.8 v. 3.4%, *OR*= 0.19; 95% CI: 0,04-0.78). During an average five-year monitoring period of the diagnosis, males had greater accumulated frequency of nephropathy (23.8 v. 12.7%, *OR*= 2.96; 95% CI: 1.31-6.67), myositis (7.1 v. 1.4%, *OR*= 5.26; 95% CI: 1.25-22.11), and tendinitis (9.5 v. 2.2%, *OR*= 5.59; 95% CI: 1.57-19.64), as well as a higher rate of infections (31 v. 16.5%, *OR*= 3.21; 95% CI: 1.51-6.82).[82]

Natural history S. 2-

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

Among the Spanish studies that evaluate the influence of gender on the clinical manifestations of SLE, the longitudinal study of 300 patients of Font *et al*. showed that the only symptomatic differences between males and females are the lower prevalence of arthritis (59 v. 82% $P<0.0005$), and malar rash (29 v. 50%, $P<0.05$), and the greater frequency of discoid cutaneous lesions (18 v. 3%, $P<0.001$) among males during the evolution of the disease, with no significant clinical or serological differences at the onset of SLE.[69] Natural history S. 2+

In contrast, in the one-centre cohort of Alonso *et al*., they found more differential characteristics, in such a way that males (15.3% of the cohort) had significantly more renal disease at the time of diagnosis (39.1% v. 15%, $P=0.05$) and more thrombocytopenia during the evolution of the disease (39.1 v. 16.5% $P=0.01$), as well as less frequency of detection of anti-SSB antibodies (La) (0 v. 17.7%, $P=0.03$), with no significant differences in survival at five and 10 years. Raynaud's phenomenon appears more frequently in women (40.9% v. 3%, $P=0.01$). However, in this cohort, males had a significantly higher average age at diagnosis than women (54 v. 43 years, $P=0.001$).[83] Natural history S. 2+

Males had significantly less prevalence of anti-Ro antibodies at the time of diagnosis with respect to women 818.6% v. 34.6%, $P=0.047$), in the descriptive study conducted in the north of Spain by Lopez *et al*.[84] Prevalence S. 3

In Latin America, in the GLADEL (Latin American Group of Lupus Study) multi-centre cohort, conformed by 1214 people recently diagnosed with SLE (including patients without ACR criteria), of which 123 were men, they found that constitutional symptoms, such as fever or weight loss, were significantly greater in the latter both at onset and during the progression of the disease. There was also a greater prevalence of high blood pressure, proteinuria, cellular cylinders in urine and haemolytic anaemia ($P<0.05$). A tendency towards greater prevalence of glomerulonephritis was observed but with no significant differences between genders. The most frequent among women were: alopecia, photosensitivity, arthralgia and Raynaud's phenomenon. Serologically, only the presence of IgG anticardiolipin antibodies and low levels of C3 were more frequent among males. No differences were found between genders with respect to the activity of the disease, irreversible organ damage or mortality.[85] Natural history S. 2++

Different results are offered by the descriptive study of Molina *et al*., with greater prevalence in males of renal disease (58 v. 44%), vascular thrombosis and anti-dsDNA antibodies ($P=0.002$) and less prevalence of Raynaud's phenomenon ($P<0.03$).[86] Prevalence S. 3

In an Asian population, the descriptive study of Feng *et al*. (n=1,790, 9.8% males), with no significant differences in average onset age of disease between males and women, showed that the accumulated prevalence of serositis, pleurisy and discoid rash was greater among males, who also had less prevalence of malar *rash*, alopecia, mouth ulcers, ANA, anti-Ro and anti-La antibodies. In women, as they got older, there was a decrease in the prevalence of malar *rash*, discoid lupus, photosensitivity, anti-dsDNA, anti-Sm, Anti-La and anti-RNP antibodies, reflecting a probable relationship with sex hormones rather than with age.[87] Prevalence S. 3

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However, in the case and control study of Mok *et al*. on 51 males and 201 Chinese women monitored at rheumatologic or nephrology outpatient clinics, they did not find any significant differences between males and women in any clinical or serological parameter, with the exception of a lower number of flares of the disease in males ($P$=0.04). The presence of anti-Ro antibodies was more frequent among women (62 v. 47%, $P$=0.05), which is at the limit of statistical significance.[88] Natural history S. 2-

Similar results are observed in the case and control study of Koh *et al*., on 61 males compared with 86 Asiatic women diagnosed with SLE, with less frequency of anti-Ro and anti-La antibodies ($P$<0.001), arthritis and leucopoenia ($P$<0.04) among males.[89] Natural history S. 2-

Furthermore, in the study of Chang *et al*., among 71 Chinese males diagnosed and monitored at a hospital in Taiwan, they detected more accumulated frequency of renal disease, malar *rash* and photosensitivity, and less frequency of arthritis and lymphadenopathy with respect to Caucasian men.[90] Natural history S. 2-

In the Thai population, the case and control study of Mongkoltanatus *et al*., on 37 males (7.3%) originating from a population of 508 SLE, paired by age with 74 women, showed that the males have a lower prevalence of arthralgia (2.7 v. 17.6% in women, $P$=0.032), Raynaud's phenomenon (0 v. 12.2%, $P$=0.027), alopecia (13.6 v. 44.6%, $P$=0.001), and psychosis (0 v. 13.5%, $P$<0.0029), and a higher prevalence of thrombocytopenia (32.4 v. 12.2% in women, $P$=0.019), and renal insufficiency (40.5 v. 16.4%, $P$=0.006).[91] Natural history S. 2-

**Summary of evidence**

| | |
|---|---|
| 2++ | SLE is a chronic inflammatory autoimmune disease with a great variety of clinical systemic, cutaneous, musculoskeletal, cardiovascular, renal, neuropsychiatric, haematological, pulmonary and gastrointestinal manifestations, both at onset and during the progression of the disease.[22,46,63] |
| 3 | The prevalent clinical pattern during the first years of SLE tends to prevail later on.[46,67] |
| 2+ | Systemic symptoms, such as fever, asthenia or weight loss are present in half the patients at onset of SLE. Fever related to the activity of SLE is the first manifestation of the disease in up to 36% of the patients.[22] |
| 2++ | Arthritis/arthralgia, mainly located in the hands, is the most frequent symptom at onset of SLE in the different ethnic groups and geographical regions.[22-48-52,54] |
| 2+ | The most prevalent mucocutaneous symptoms at onset of SLE include malar *rash* and on nose (butterfly wings), alopecia and mouth ulcers.[22-48-52,54] |
| 2+ | Raynaud's phenomenon is a frequent symptom at onset of SLE, but with prevalence that varies between regions and ethnic groups.[22] |
| 2+ | Renal disease, with variable severity, may be the predominant clinical pattern on onset of SLE in 16-40% of patients. If it is not present at onset, the development of renal disease is typical during the first years of evolution of SLE.[22,48,49,51,52,54] |

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| 2++ | Neuropsychiatric syndromes are present at onset and during the first years of evolution in 28% of SLE patients, especially headache, depression, thromboembolic cerebrovascular disease, seizures, anxiety and cognitive dysfunction, although this can only be directly attributed to SLE in 12%.[55] |
| 3 | Neuropsychiatric symptoms are present in half the SLE patients, especially depression and cognitive impairment.[92,93] |
| 2+ | Cardiovascular manifestations are more typical of the progression than of the onset of SLE.[22,48-53] |
| 3 | Pleurisy is the most frequent pulmonary manifestation of SLE, but it is the initial symptom in just 2-3% of patients.[46] |
| 4 | Gastrointestinal symptoms are more often secondary to the treatment of SLE, related to taking NSAID ± glucocorticoids, than directly caused by the disease.[47] |
| 2+ | 23% of caucasian SLE patients start with haematological disorders, but these end up being present in 80% during the entire progression. Leucopoenia is the most prevalent.[51,52,59] |
| 2+ | APS associated with SLE is characterised by associating arterial or venous thrombosis, or pregnancy complications, such as repeated miscarriages or preeclampsia, with presence of APL. APS is the only initial manifestation of SLE in 20%.[60] |
| 2+ | APS may be a phase prior to the development of SLE, with a variable interval that may even reach 10 years.[61,62] |
| 2++ | The incidence and prevalence of the majority of clinical manifestations and laboratory findings of SLE show great variability between ethnic groups and geographical regions.[22,48,49,51,52,63,65,82,85.] |
| 2+ | The clinical and serological pattern for the presentation of SLE in European Caucasians is characterised by arthritis, malar *rash*, nephropathy, photosensitivity, fever, neurological impairment, Raynaud's phenomenon and/or serositis, accompanied by ANA and subsequent accumulation of anti-dsDNA and anti-Ro autoantibodies during evolution.[22] |
| 2+ | In Spain and in other countries of the Mediterranean basin, the European clinical pattern of the appearance of SLE is repeated, but with an additional high prevalence of haematological disorders, especially leucopoenia.[51,52,59,79,82,94,95] |
| 2+ | The clinical and laboratory patterns of SLE show differences in agreement with the age at which the disease appears.[69,71-73,96] |
| 2+ | Evidence is consistent with the low prevalence of SLE after the age of 50, which in European countries is situated at 9% and in Spain at around 15%.[65,66,68-70] |
| 2+ | Late onset of SLE is characterised by a decrease in the woman-man ratio and a less severe appearance than in earlier ages.[69,71,73,96] |
| 3 | The appearance of SLE at a late age is clinically associated with a greater prevalence of serositis, pulmonary impairment and dry syndrome, and less frequency of malar *rash*, photosensitivity, alopecia, Raynaud's phenomenon, neuropsychiatric manifestations and nephropathy, with respect to onset at earlier ages. The serological pattern includes greater detection of rheumatoid factor and less detection of anti-dsDNA, anti-Sm, and anti-RNP antibodies, as well as low complement levels in people with late onset SLE.[69,71-73,96] |

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|---|---|
| 2+ | There is a lack of consistent evidence about the less severe evolution of SLE in people with onset at late age with respect to an earlier age. Greater activity of the disease and organ damage at the expense of neurological impairment, thrombotic events, osteoporosis and hypertriglyceridemia in late onset SLE has been described in recent studies.[69,71-74,96] |
| 2++ | The most consistent evidence about the clinical phenotype of SLE according to gender at the time of diagnosis shows less incidence of musculoskeletal symptoms, Raynaud's phenomenon, mouth ulcers, alopecia and photosensitivity and, with less consistency, greater prevalence of serositis and discoid lupus in males compared with women.[65,70,82,83,85,86,89,91] |
| 2++ | Arthritis/arthralgia is consistently less frequent in men than in women with SLE from Caucasian, Chinese and Greek population.[65,70,82,84,89] |
| 2+ | The greater prevalence of early renal impairment in males with SLE, both as an onset manifestation and at the time of diagnosis, as well as thrombosis and gastrointestinal symptoms, is inconsistent between studies.[65,70,82,84,89] |
| 2++ | In Latin America, males can express more constitutional symptoms before and during the diagnosis of SLE than women.[85,86] |
| 3 | At the time of diagnosis, the only differential serological pattern by gender is the greater frequency of anti-Ro antibodies in women with SLE.[84,87,89] |
| 2++ | Evidence is inconsistent about the different clinical-serological profile and worse prognosis, in terms of disease activity and mortality, of males compared with women with SLE, according to regions and countries. In North America, males present a greater prevalence of nephropathy, haematological and serological disorders (lupus anticoagulant, anti-Sm, anti-dsDNA, anti-RNP and C3 hypocomplementinemia), with greater baseline and accumulated organ damage, which determines a worse prognosis, whilst European studies show contradictory results.[86] |
| 2+ | There is an association between some autoantibodies and the expression of a certain clinical phenotype. Anti-dsDNA and anti-Sm antibodies are associated with renal disease, APL with arterial and venous thrombosis, and repeated miscarriages, anti-Ro antibodies with cutaneous and renal disease, and anti-histone antibodies with arthritis.[35,41,63,64,97] |
| 3 | When SLE starts with malar *rash*, pericarditis, pleurisy or spontaneous miscarriage, the diagnostic delay is less with respect to other symptoms.[35] |
| 3 | In the European environment, the clinical and serological pattern as well as the age at onset and diagnosis of SLE have not undergone significant changes over the last three decades, except for an increase in Raynaud's phenomenon and a decrease of mouth ulcers and false positives in the syphilis test as onset symptoms and signs.[79,94] |

**Recommendations**

| | |
|---|---|
| B | We recommend clinically monitoring women under the age of 50 with onset of arthritis or else arthralgias associated with skin lesions, photosensitivity, Raynaud or systemic symptoms, especially if there are haematological alterations (cytopenias), or of the urine sediment, bearing SLE in mind in the differential diagnosis. Determining antinuclear antibodies and, where appropriate, specific antibodies, may be indicated in these women. |

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# 4.2. Diagnostic confirmation

## 4.2.1. Laboratory tests

### 4.2.1.1. Detection of antinuclear antibodies

**Questions to be answered:**

- What is the technique of choice to detect antinuclear antibodies?

CPGs evaluate the clinical and methodological aspects and the basic criterion for the recommendation is diagnostic usefulness.[98-105]

The use of other serum-free culture media cell lines and proteins seems to offer similar results to the HEp-2 cells; however, the evidence is still not very consistent.[106] — Diagnostic S. 3

There are also new technologies based on flow cytometry and antigen microarrays that permit the simultaneous determination of a large number of autoantibodies in the same sample. Although to this day, the expert committees have not been defined and reference is only made in published CPGs to ANAs determined by indirect immunofluorescence (IIF) and immune-enzyme analysis (IEA).[107] — Prevalence S. 3

The results of the IIF technique can be expressed either on a qualitative scale, which reflects the intensity of the fluorescence, although it is not always proportional to the concentration of antibodies, or on a semi-quantitative scale, in the form of indicative titre of the last dilution with which the studied serum shows the antigen-antibody reaction, or, if standard international reference serum is available, in the form of autoantibody concentration in UI/ml. The quantitative method permits establishing the cut-off point that achieves the best equilibrium between sensitivity and specificity, but it presents intra- and inter-laboratory reproducibility problems due to the subjectivity in interpretation. The dilution titres of 1:40 and 1:160 correspond approximately to autoantibody concentrations of 5 and 20 UI/ml, respectively.[100] — Diagnostic S. 2

Despite the fact that this procedure can currently be partially automated, it is a subjective technique and with limitations, requiring qualified personnel to interpret the results. It is also difficult to standardise. The IIF requires an arduous process that consists in a series of dilutions of positive serums, the visual determination of the staining patterns, followed by a second test when the specificity of the antibody is determined. It requires technical experience. Another limitation of the IIF is its lack of specificity; depending on the population studied, the dilution of the serum or the cut-off point used, up to 25% of the serums of apparently healthy individuals may have positive ANAs and there is little likelihood of them developing a systemic autoimmune disease (SAD).[105] — Expert opinion 4

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The HEp-2 or the HEp-2000 cells are the substrate of choice for detecting ANAs. The antigens are found in their native location, they are not denatured and preserve their own structure. These cells have advantages over rodent tissues due to their greater sensitivity, their larger-sized nuclei and nucleoli that improve the visualisation of the structures and of the fluorescence patterns, and due to the ability to express certain antigens present in different phases of the cell cycle. Hence, the requirement for the presence of cells in mitosis in cell preparations. Furthermore, they permit the detection of specific antibodies with respect to human nuclear antigens that are not present in mouse or rat tissues. The determinations in which rodent tissues are used are only able to detect ANA in 80-85% of SLE patients, while with HEp-2 cells, the percentage increases up to 95%.[106]

Diagnostic S. 3

The study of the different specificities of ANAs should be carried out in a well-founded manner, taking the pattern and titre observed on the HEp-2 cells as the basis. The titre and especially the ANA-HEp-2 patterns help discriminate healthy individuals from patients with SAD. Studying ANAs by IIF on HEp-2 cells should include the nuclear patterns in cells in inter-phase and in mitosis, and also in cell cytoplasma, as there are antigens that are only expressed in certain phases of the cell cycle or in the cytoplasm.[108,109]

Diagnostic S. 2

The titre of ANAs determined on HEp-2 cells is a relevant, but limited, parameter to discriminate between ANAs in healthy individuals and people with SAD. Titres under 1/40 will be considered as negative, titres over 1/40 and under 1/160 as low positive, and titres over 1/160 as positive,[100] when the discriminating value is established at 1/160, the diagnostic specificity for SLE increases, although the sensitivity decreases.

Expert opinion 4

ANA dilution tires of 1/80 and 1/160 are adequate for detecting SAD. These results indicate that a negative result of ANA in HEp-2 at a dilution of 1/80 is not very likely in people with SAD, especially in those with SLE and systemic sclerosis. Although carrying out an initial dilution at 1/80 has been recommended until now, currently the titre of 1/160 is recommended as the most acceptable cut-off point, and discriminating between serums of supposedly healthy individuals from possible pathological ones, although the ANA pattern on HEp-2 cells is more solid than the titre to discriminate between healthy individuals and people with SAD.[110-114]

Diagnostic S. 2/3

One of the main problems in detecting ANAs is standardisation. The Foundation for Arthritis in collaboration with the *Center for Disease Control and Prevention* prepared a panel of five serums of reference that included specificities for ANA, dsDNA, La, RNP and Sm.[115]

Expert opinion 4

The results of the ANAs vary depending on multiple factors, including diversity and nature of the substrates, type of conjugate, types of substrate fixation, determination methods, degree of laboratory automation, training and experience of the observer, characteristics of the microscope and interpretation of the results.

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As an alternative to the IIF technique, the ELISA (*enzyme-linked immunoabsorbent assay*) has been incorporated into daily practice. This is a fast, simple and sensitive method that permits detecting specific autoantibodies with respect to different antigens in an objective and automated manner. The use of this method as screening for ANA has increased over the last few years, in order to select serums with positive results, on which the IIF should later be carried out.[111]

Expert opinion 4

However, the experts from the ACR Development Group[116] and from the *European Autoimmunity Standardisation Initiative* (EASI)[117] concluded that immunoassays in solid phase are not an appropriate method to replace IIF for detecting ANAs, and they continue to recommend screening for ANA by IIF in HEp-2, based on the fact that 35% of patients are not diagnosed due to negative screening for ANAs by ELISA[118]. They only admit its use if there is at least 90% agreement with the IIF, having to confirm the positive results by this latter technique, specifying the pattern and fluorescence titre. In any case, if a screening ELISA method is used, this should recognise certain ANAs that are not very common but have clinical relevance, such as directed antibodies with respect to nucleoli or to the nuclear membrane.

Expert opinion 4

ELISA techniques are generally less sensitive than IIF, but they have certain advantages: they are less laborious, they are subject to less subjectivity in their interpretation, and they can be automated. The different ELISA techniques available to detect ANAs have variable sensitivities and specificities to diagnose SLE, due to considerable differences in the antigen content of the reagents used,[119] although the majority currently use dsDNA, SM, RNP, Ro, La antigens, centromere B, Jo-1, Scl-70, ribosomal-P and HEp-2 cell extracts. Conversely, this method does not permit detecting certain atypical ANAs, or obtaining information about the different fluorescence patterns. The results are usually semi-quantitative and they are generally expressed in arbitrary units established by the manufacturer.

Diagnostic S. 3/2

There is great variability in terms of the antigens used in the different ELISAs, some contain mixtures of purified antigens, recombinant antigens, antigen extracts from complete cell preparation or extracts enriched with certain more scarce autoantigens in the cell. False negatives can also be found due to the absence of certain antigens in the antigenic mixtures immobilised in the plate well. Faced with this variability, the impact on the result of using one type of antigenic substrate or another should be evaluated.[111]

Expert opinion 4

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People with systemic autoimmune diseases, including SLE, usually result in a positive ANA test with high titre. However, high or intermediate titres can also be seen in the elderly (10-37% of people over 65),[114,120] pregnant women,[121] acute and chronic infections, neoplasias,[122] relatives of patients with systemic autoimmune diseases (25-30%),[122-124] idiopathic thrombocytopenic purpura (ITP),[125] patients being treated with certain drugs (statins, angiotensin-converting enzyme inhibitors-ACE-Is, betablockers), and even supposedly healthy individuals.

Natural history S. 2-

Risk factor S. 2+

Diagnostic S. 1

Prevalence S. 3

Expert opinion 4

In different grade A studies reviewed in the CPGs, it is observed that healthy individuals present a positivity percentage with a titre of 1/40, of 25-30%, with a titre ≥ 1/80 between 10-20%, 5% present positive ANAs with a titre ≥ 1/160 and only 3% present positivity with titres of over 1/320. The frequency of positive ANAs increases with age, above all in women. 38% of the elderly present positive ANAs, generally with low titres. The presence of ANAs has also been described with a titre ≥ 1/40 in relatives of patients with SAD (25-35% of the cases). Therefore, these situations should be taken into consideration in cases of patients with positive ANAs outside a certain clinical context.[107]

Prevalence S. 3

Diagnostic S. 2

All the CPGs coincide and determine that the clinical use of ANAs will be limited to those clinical processes related to SAD or relevant clinical suspicion according to the diagnostic criteria established for each type of disease. The results will always be evaluated within their specific clinical context, as their detection is not very useful if the patient does not present suggestive signs of SAD. ANAs form part of the diagnostic criteria of SLE, of drug-induced lupus and of mixed connective tissue disease.[98-105] If the ANA result is positive, we recommend determining the anti-dsDNA antibodies only when there is clinical suspicion of SLE.

Anti-dsDNA and anti-Sm antibodies specifically form part of the classification criteria of SLE, together with the IgG and IgM anticardiolipin antibodies and lupus anticoagulant.[38,104,105]

Expert opinion 4

To diagnose SLE, a positive likelihood ratio of ANAs is considered useful, and a negative ratio as very useful. Due to the high sensitivity of the determination of ANAs for SLE patients, we find that almost all SLE patients have positive ANAs during the course of the disease, although at the start, sensitivity may discretely decrease (76%).

Diagnostic S. 2

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Due to the low prevalence of the disease in the general population, the majority of individuals with positive ANAs do not suffer from SLE, as the positive predictive value is very low. A negative result of ANAs would rule out SLE due to its high sensitivity (93-100%) and negative predictive value (94-100%), as well as its low negative likelihood ratio (NLR) (0.1).[98,102] However, 3% of individuals have SLE with negative ANA and they are known as ANA-negative SLE. Some of these patients have other antibodies such as anticardiolipin or anti-Ro antibodies. Despite this limitation, in people with clinical suspicion of the disease, ANAs are the main laboratory test to rule out its presence. Anti-dsDNA and anti-Sm antibodies are generally only found in this group of patients but not in other SADs or in healthy subjects, so they are specific of SLE. High anti-dsDNA are moderately related to the activity of SLE.

Diagnostic S. 1

On the other hand, although the anti-RNP antibodies may be present in 30% of these patients, they are not specific of SLE, so they are not useful to establish its diagnosis.[104]

A cost analysis performed at an immunology laboratory of a hospital in Tenerife (Spain) shows that the detection of ANA with IIF in HEp-2 at initial dilution of 1:160 significantly increase the positive anti-ENA and anti-dsDNA predictive value, compared with the baseline dilution of 1:40. Furthermore, economic benefits are generated as 16.6%, 41.8% and 36.4% fewer determinations of ANA, antiENA and anti-dsDNA respectively, are carried out. This represents an average of 0.87 cost units per serum avoided (1 unit= € 2.06).[112]

Economic assessment

Despite the accepted associations, no pattern is specific of the presence of a specific circulating antibody. Anti-dsDNA antibodies are associated not only with the homogeneous pattern but also with the mottling and nucleolar pattern in the study of Servais *et al*.[126]

Diagnostic S. 3

The application of previously validated CPGs for the use of the ANA test in the diagnosis of SLE significantly reduces the number of second or third-level immunological tests conducted in 685 patients, as shown by the study of Tampoia *et al*.[127,128]

Economic assessment

Available evidence suggests that detecting ANA by means of IIF is the test with greatest validity in diagnostic screening for ANA in SLE, due to its high sensitivity, with greater result consistency between studies.[116]

Expert opinion 4

Requests for ANA detection tests have increased over the last decade and their execution by means of IIF requires qualified personnel to read and interpret the results. So recently, the cost-effectiveness of screening for the presence of ANA by means of ELISA has been suggested, confirming positive results by means of Hep-2 cell substrate IIF. In Copple *et al*. study, four commercial ANA detection kits were validated with ELISA, compared with ANA IIF, and the detection of ANA with ELISA is proposed to be used as a first screening test, and to confirm positive results by IIF, to determine titre or concentration of ANA and fluorescence pattern, as a strategy to increase the performance of the test and the cost-effectiveness ratio of the intervention.[129]

E. diagnóstico 1

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The results of studies that compared the validity of the IIF and ELISA methods to detect ANA show some inconsistencies. The detection of ANA by IFF is more sensitive and effective as an ANA detection screening method in people with clinical suspicion of SLE than detection by ELISA. Diagnostic S. 2

Another disadvantage of starting ANA screening with an ELISA technique is that a negative result is not the equivalent to negative for all nuclear or cytoplasmatic antibodies, as not all commercial brands include all the specific antigens against which autoantibodies are generated in SLE.[130] Diagnostic S. 2

In cases with a high clinical suspicion of SLE and ANA by negative IIF, the determination of ANA can be repeated by ELISA, with a recognised validity technique similar to IIF and that contains the Ro antigen. If it is positive, the second diagnostic step can be used to detect specific autoantibodies of SLE. If this is also negative, the presence of SLE is unlikely, so we would recommend ruling out other autoimmune diseases and clinical monitoring.[98,100,102] The presence of a possible anti-Ro antibody via IIF with HEp-2000 transfected cells can also be evaluated. Diagnostic studies ½ CPG 4

It is also very important for the test to be performed by qualified personnel, experts in morphology, regularly assessing their competency to perform the test and to report results, especially with the IIF technique.[98] CPG 4

To reduce the intra- and inter-laboratory results variability, due to the subjectivity of the interpretation and the low degree of standardisation of the visual microscopy method, automatic ANA detection methods have recently been developed via IIF. Some of the automated systems only discriminate between positive and negative screening ANA detection (Helios®, *Aesku DIagnostics*, Germany; IMage Navigator®, *Immuno Concepts*, USA; Cytospot®, *Autoimmun Diagnostika*, Germany), whilst others also provide identification and classification of fluorescence patterns (Aklides®, Medipan, Germany; Nova View®, Inova, USA; Zenit G Sight®, *Menarini Diagnostics*, Italy; Europattern®, Euroimmun, Germany). When comparing the execution of IIF in HEp-2 cell substrate by manual method and by automatic Aklides® (Medipan, Germany) method, based on capturing images and fluorescence pattern recognition algorithms, in a sample of 1,222 consecutive serums of people with suspected systemic rheumatic disease from one university laboratory and one private laboratory, a very good degree of agreement (kappa=0.83) was obtained in the identification of ANA and differentiation of immune-fluorescence patterns. The percentage of agreement in the positive and negative result between the manual and automated methods was 93% and 90.6% in the university laboratory and in the private laboratory, respectively. The percentage of agreement in the recognition of fluorescence patterns were 90.1% and 92.7% for the university and private laboratories, respectively. 8% discrepancies arise in the classification of serums as positive or negative (weak positive cut-off point 1:160 and positive 1:320) and 15% in the immune-fluorescence patterns, especially in mixed or cytoplasmatic patterns, or with antibodies against the nuclear membrane.[117] Diagnostic S. 2

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

Over the last few years, simultaneous multiple screening techniques for antinuclear autoantibodies have been introduced, based on individualised microspheres marked with specific antigens (MIA-*microsphere based immunoassays*). When this method is compared with the traditional detection using ELISA or radioimmunoassay in SLE patients, more positive results are obtained in the identification of anti-RO, but less in the identification of anti-dsDNA. The sensitivity of the multiple techniques, using the traditional ELISA technique as *gold standard*, varies between 70% (Scl-70) and 91.1% (dsDNA), with a mean of 81% and specificity between 88.9% (Ro) and 98% (centromere B). Compared with IIF, the MIA multiple technique has a similar rate of false positives (7%).[131] Other authors conclude that the validity parameters of the multiple screening technique can improve the value of the ELISA traditional techniques for ANA screening, except for the identification of anti-dsDNA antibodies.[132]

Diagnostic S. 2

Diagnostic S. 3

In the Italian study of Bizzaro *et al*. six automated ANA identification methods were compared via IIF (Aklides®, EIROPattern®, G-Sight® (I-Sight-IFA), Helios®, Image Navigator® y Nova View®) and via the standard manual IIF method. The positive/negative result was obtained by consensus from the six participating laboratories, specifying agreement of at least four of them; and the titre and pattern are selected from the value observed with greatest frequency. The sensitivity and global specificity of the six automated methods was 96.7% and 89.2%, respectively. False negatives occurred more frequently between the cytoplasmatic and nucleolar patterns with low fluorescence level. Correct discrimination of the result in positive/negative occurred in 95% of the serums with automated methods. Automatic methods showed good correlation of the fluorescent light signal with visual method reading (Spearman rho between 0.672 and 0.839, $P<0.0001$). The imprecision varies between 1.99% and 25.2% in automated methods, lower than that observed in the visual method (25.2%). The correct identification capacity of the immunofluorescence pattern is limited for the different automated methods between 52% and 79%.[133]

Diagnostic S. 1

The automated IIF-HEp-2000 method called Zenit G. Sight® (Menarini Diagnostics, Italy) offers a quantified result in positivity likelihood terms according to the intensity of the fluorescence. In Bossuyt *et al*., there was significant correlation between the estimation of the fluorescence intensity and the ANA titre. The positive likelihood ratio (PLR) for SLE is greater insofar as the positivity likelihood is greater: PLR 0.06 (95% CI: 0.02-02), 0.4 (95% CI: 0.2-08), 6.8 (95% CI: 2.6-17.8), 12.1 (95% CI: 6.2-23.6), 43.9 (95% CI: 16.0-120.4) for positivity likelihood of ≤10%, 11-30%, 31-50%, 51-85% and >85%, respectively.[134]

Diagnostic S. 2

More recently, the ICARE® algorithm on recognition and interpretation of ANA-IIF images, which offers a fluorescence index as a result, shows an adequate correlation with the ANA titre obtained by traditional manual technique (Spearman rho: 0.80, $P<0.0001$). The sensitivity and specificity of the automated IIF method and the Kappa index of concordance between methods is 95%, 98% and 0.92, respectively, which permit considering it as a possible faster and better standardised alternative in ANA screening via IIF.[135]

Diagnostic S. 2

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The validity of more recent automated methods that improve the resolution of the images of the autoantibody patterns by three-dimensional reconstruction, and quantify the intensity of fluorescence has still not been proven.[136] Diagnostic S. 3

In any case, the automated ANA screening methods, based on HEp-2 cell tests by means of IIF technique, require improving diagnostic validity and the number of recognised fluorescence patterns, therefore a positive result should be confirmed. Their greater usefulness in ANA screening currently lies in the exclusion of negative samples. A new mixed automated method has recently been introduced that incorporates in one single Aklides® platform (Medipan, Germany) the simultaneous execution of ANA screening by high sensitivity IIF, and the confirmation diagnosis with specific autoantibody analysis by means of simultaneous multiple immunoassay technique based on MIA microspheres, each one marked with a specific antigen (Scl-70, Sm, Ro, La dsDNA, and centromere B). Grossman *et al*. compared this automated system with the results obtained by MIA and traditional MIA, reaching a kappa index of 1 in the identification of antibodies with respect to Scl-70, Sm, La and centromere B, kappa of 0.96 to identify anti-dsDNA and kappa of 0.78 to detect anti-Ro. The sensitivities and specificities in the detection of autoantibodies with respect to all antigens is 100%, except with anti-dsDNA that shows a specificity of 97%.[137] Diagnostic S. 3

Monitoring the titre or concentration of ANA autoantibodies by IIF lacks usefulness in monitoring the course of SLE or the response to the treatment.[98,100,102,138] Diagnostics S. 1 and 2
CPG 4

**Summary of evidence**

| | |
|---|---|
| Ia | The ANA screening test via indirect immunofluorescence (IIF) used in the diagnostic process of SLE presents a sensitivity between 93% and 100%, but it is not specific for this disease, with frequent positive results in other inflammatory connective tissue diseases and even in healthy individuals, and it offers low diagnostic performance in populations with low SLE prevalence.[98,102,109] |
| II | The use of HEp-2 human cell substrate in the detection of ANA by IIF improves the sensitivity of the test.[100,106] |
| Ia | The ANA screening test presents a high negative predictive value, close to 100%, and a low negative likelihood ratio, so a negative result is very useful to practically exclude the diagnosis of SLE.[98] |
| Ia | Given its low specificity and the limited prevalence of SLE in the general population, the ANA screening test only shows adequate diagnostic performance in people with two or more suggestive symptoms or signs of SLE.[98,102] |
| Ib | One third of supposedly healthy individuals have a positive ANA test at titre of 1:40, whilst this only occurs in 13% at titre of 1:80, and in 5% at titre of 1:160, with ethnic and age variations.[107,114] |
| III | The ANA titre rises with age, especially in women, regardless of the presence of a SLE diagnosis.[114,120] |

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| | |
|---|---|
| 2+ | High or moderate ANA titres can occur in pregnant women, patients with neoplasia, infections, or other immune disease and relatives of patients with systemic autoimmune diseases.[121,123,125] |
| Ib | The cut-off point of the greatest sensitivity ANA-IIF titre for ANA screening is 1:40, but with low specificity.[100,114] |
| II | The ANA-IIF titre of 1:80 is observed in 95% of people with clinical diagnosis of SLE, but also in 4% of supposedly healthy individuals.[100] |
| II | In Caucasian population of our environment with clinical suspicion of SLE, the ANA-IIF titre with adequate equilibrium between its diagnostic discrimination capacity, positive predictive value and cost is 1:160.[100,112] |
| II | There is limited evidence about the prognostic value of the ANA-IIF fluorescence pattern in SLE.[138] |
| III | The ANA screening test via IIF has intra- and inter-assay reproducibility problems, both in SLE patients and other connective tissue diseases.[129] |
| II | ANA screening using traditional ELISA techniques or simultaneous multiple detection techniques based on microspheres marked with specific antigens, are generally less sensitive than IIF techniques, with variability between commercial brands depending on the type of antigens they contain and their native or recombinant nature. However, they are also more objective, specific and easier to automate.[118,130-132,137,138] |
| Ib | ANA screening with ELISA and confirmation of positive results via IIF with HEp-2 cell substrate to establish ANA titre and fluorescence pattern could be a cost-effective strategy given the greater complexity of the IIF technique.[129,130] |
| II | There is no consistent evidence available about improvement in validity, precision or reproducibility of traditional IIF or ELISA techniques, when simultaneous ANA multiple screening methods based on microspheres marked with specific antigens or linear immunoassays are used.[131,132] |
| II | To maintain adequate diagnostic validity and reproducibility of the ANA screening test, especially with IIF, the quality parameters of the anti-Ig conjugate should be satisfied, carrying out positive and negative controls in each assay, using standard reference serum (*Center for Disease Control and Prevention*, WHO), maintaining the positive result intervals up to date in healthy people of the population on whom the test is applied, and having personnel who are specialised in performing the test and reporting the results.[1112] |
| Ib | The automated reading and interpretation methods of ANA screening with IIF can reduce the variability of intra- and inter-laboratory results, as they also present diagnostic validity parameters similar to the visual microscopy technique, however they still require greater evidence consistency.[56,49,52-55] |

**Recommendations**

| | |
|---|---|
| A | As a general rule, we do not recommend carrying out the antinuclear antibody detection test if there are not at least two clinical manifestations that suggest SLE (see Annex 7). |
| A | The method of choice to detect antinuclear antibodies in the diagnostic process of SLE is the indirect immunofluorescence due to its high sensitivity. |

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| | |
|---|---|
| B | The antinuclear antibody detection test by indirect immunofluorescence should preferably be carried out with human epithelial cellular (HEp-2) substrate. |
| A | If an ELISA method is used to detect antinuclear antibodies, using a traditional technique or based on antigen microspheres with proven sensitivity similar or higher than indirect immunofluorescence, the positive result should also be confirmed via indirect immunofluorescence. |
| B | To establish the cut-off point and interpret the titre of antinuclear antibodies, we recommend knowing the antinuclear antibodies levels of reference in the general population of application with no antinuclear antibody-related diseases. |
| A | Titres below 1:40 (<5 UI/ml) of antinuclear antibodies detected through indirect immunofluorescence should be considered as negative. |
| B | We recommend considering as clinically relevant a titre of antinuclear antibodies detected by indirect immunofluorescence of 1:160 (≥20 UI/ml) or more in the Caucasian population of our context, and proceeding with the diagnostic confirmation cascade through the detection of specific anti-dsDNA and anti-ENA (mainly anti-Sm) antibodies. |
| A | We recommend interpreting a positive result in the antinuclear antibody detection test in the patient's clinical context since, on its own, it does not establish the diagnosis of SLE at all. |
| C | In people with suggestive symptoms of SLE and antinuclear antibody detection test by indirect immunofluorescence with result persistently negative, we suggest performing the antinuclear antibody detection via an ELISA technique that includes Ro (SSA) antigen reagents or the direct determination of anti-Ro (SSA). |
| B | We recommend assessing the fluorescence pattern obtained in the antinuclear antibody detection test via indirect immunofluorescence to have useful additional information in the differential diagnosis of SLE with other systemic autoimmune diseases. |
| D | We suggest that result report of the antinuclear antibody detection test includes the detection technique used, the positive dilution titre or the concentration of autoantibodies in UI/ml, together with the percentage of healthy individuals or individuals with no diseases associated with antinuclear antibodies that present the same titre in the reference population, as well as the intensity and the nuclear, cytoplasmic and/or mitotic fluorescence patterns identified. |

### 4.2.1.2. Diagnosis Confirmation

**Questions to be answered:**

- What is the validity of laboratory tests to confirm the diagnosis of systemic lupus erythematosus?

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The role of specific immunological tests mainly consists in confirming the diagnosis of SLE, monitoring the activity of the disease and identifying subgroups of patients with different prognosis and therapeutic options. Currently, no test on its own satisfies the adequate discriminatory capacity requirements of SLE given that the increase in its specificity determines an important decrease of its sensitivity. The first step in the diagnosis of patients with specific symptoms or signs of SLE (Annex 7) is circulating ANA screening, identified by ELISA, following by the confirmation of positive results by IIF or directly by IIF, basically, with a sensitivity of 96.5% and specificity of 45.2% (SLICC 2012).[38] According to current international recommendations, the ANA study will be carried out only with the purpose of diagnosing SLE, but not to monitor the disease.[105]

Diagnostic S. ½ CPG

With rare exceptions, only in individuals with symptoms of SLE and positive ANA screening test, the diagnostic confirmation cascade should be pursued by detecting specific autoantibodies, especially anti-dsDNA and anti-ENA. Among these, the one with greatest diagnostic relevance in SLE due to its specificity is anti-Sm, although it has very low sensitivity. These antibodies will be determined by means of more specific techniques such as IIF with *Crithidia luciliae* substrate IIF-CL), radioimmunoassay (RIA), ELISA or immunoblotting (IB).[102] This process in cascade, with serial tests, accelerates the diagnostic confirmation and increases the validity of the tests.[98,100]

Indiscriminate requests for determining specific autoantibodies decreases the validity of the tests and their clinical usefulness, as observed in the study performed by Campos-Gonzalez *et al*., at a hospital in Mexico, with a high prevalence of SLE (33%).[139]

Diagnostic S.3

Identifying the specific subtypes of autoantibodies in people with symptoms of SLE and with positive ANAs at significant titre, should include anti-dsDNA and antibodies to ENA. Antibodies to ENA include anti-Sm, anti-Ro, anti-La and anti-RNP, also called anti-U1RNP, and anti-U1 snRNP. The presence of cytoplasmatic autoantibodies, such as anti-ribosomal proteins (anti-RibP) is also relevant in SLE. The more specific autoantibodies of SLE are the anti-dsDNA, anti-Sm, anti-nucleosome antibodies, and to a lesser extent, anti-RibP (P0, P1, P2) and anti-PCNA (*proliferating cell nuclear antigen*). Anti-RNP antibodies are not specific of SLE but they are associated with anti-Sm antibodies, so almost all serums with anti-Sm are positive anti-RNP.

**Detection of anti-dsDNA antibodies**

Anti-dsDNA antibodies react against antigenic determining factors present in the DNA. They are identified in 60-80% of SLE patients, with no important differences between ethnic groups, but they are not associated with subacute cutaneous lupus or with discoid lupus.[140]

Expert opinion 4

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Their prevalence in healthy controls is very low, less than 2.5%. The presence of anti-dsDNA circulating antibodies is not very frequent in other rheumatic diseases or diseases of another nature (≤ 5%) and if they are present, this is usually at low titres, so the detection of anti-dsDNA antibodies lacks usefulness in the diagnosis of autoimmune diseases other than SLE. The presence of anti-dsDNA antibodies has been described in other autoimmune rheumatic diseases, infections and relatives of SLE patients.[98] Diagnostic S. 1

There are high and low affinity anti-dsDNA antibody subtypes. High affinity anti-dsDNA antibodies are specific of SLE. In contrast, low affinity forms are present in other diseases.[141,142] Diagnostic S. 3

Natural history S. 2-

The most-commonly used techniques today to determine anti-dsDNA include indirect IIF on *Crithida luciliae* substrate (IIF-CL) and ELISA techniques. IIF-CL detects the union of the high affinity anti-dsDNA antibodies to the kinetoplast of a haemoflagelate that contains a high concentration of dsDNA but no histone proteins or single-stranded DNA (ssDNA). The most commonly-used dsDNA ELISA technique in the clinical environment is the one that detects the anti-dsDNA IgG isotype, but its greatest disadvantage is that it identifies both high and low affinity forms of anti-dsDNA. This increases false positives and decreases the specificity for SLE diagnosis. It can also be contaminated by single-stranded DNA and produce a falsely positive result The advantages of the ELISA technique are that the test is easier to develop, it is quantitative and can be automated. To interpret the results of the anti-dsDNA detection test, the identification technique used in the result report should be explained as well as the reference intervals used, both in healthy individuals and in SLE patients.[143] Diagnostic S. 1

Detecting anti-dsDNA autoantibodies is useful for the diagnostic confirmation of SLE. High titres of anti-dsDNA are more specific of SLE than discretely high titres, above the reference level, and the diagnostic validity of the anti-dsDNA test in SLE depends to a great extent on the detection technique selected. Diagnostic S. 1

In the SR of diagnostic studies performed for the ACR CPG, 11 out of the 168 selected studies were considered as high quality. In agreement with the results of these studies, performed with more than 4000 patients and considering the three identification methods together (Farr, IIF-CL and ELISA), the detection of anti-dsDNA presents an average specificity of 97% and a PLR for the diagnosis of SLE of 16.4. Considering the three identification methods together, the detection of anti-dsDNA presents an average sensitivity of 57%, and a NLR to rule out diagnosis of SLE of moderate usefulness (0.49).[143]

On the other hand, between 0 and 0.8% of all individuals have circulating anti-dsDNA autoantibodies despite having a negative ANA-IIF test with HEp-2 cell substrate. Diagnostic S. 1

The detection technique of high affinity anti-dsDNA antibodies with the best specificity and PRL to confirm the diagnosis of SLE is IIF-CL, starting with a dilution of 1:10, followed by Farr and dsDNA ELISA.[143-146] Diagnostic S. 1,2,3

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Furthermore, the IIF-CL test is technically simpler than the Farr RIA and it does not require the use of radioactive substances. Given that the ELISAs to detect anti-dsDNA may present less specificity in the diagnosis of SLE than IIF-CL[147] and Farr,[148] a value of anti-dsDNA is required that is twice as much as the reference value to state that this immunological criterion of the 2012 SLICC group SLE classification is satisfied.[38]

Diagnostic S. 2 and 3

However, in an Italian multicentre study that assessed the validity of the detection of anti-dsDNA to diagnose and monitor SLE, several autoantibody identification methods were tested: IIF-CL (Clift®, Inova, USA), Farr RIA, ELISA (The Binding Site, United Kingdom) and enzyme fluoroimmunoassay (EliA™, Phadia, Germany). IIF-CL showed much greater sensitivity and lower specificity than those observed in other comparative studies, showing the lack of consistency between laboratories and even between countries in the anti-dsDNA detection results. The specificity in the differential diagnosis of SLE with other connective tissue diseases decreases with all techniques except ELISA, which remains at 92%. During follow-up, the anti-dsDNA antibody levels measured by ELISA, IIF-CL and enzyme fluoroimmunoassay are significantly higher in people with active SLE and correlate with the ECLAM (*European Consensus Lupus Activity Measurement*) disease activity index (correlation coefficients between 0.336 and 0.425; $P<0.0001$). The titres are also higher in patients with lupus nephropathy and haematological impairment, and significantly lower in patients with CNS impairment.[149]

Diagnostic S. 1

Another comparative study of the IIF-CL (Kallestad, USA) and ELISA (BioRad, USA) techniques to detect anti-dsDNA antibodies in the early diagnosis of SLE, concluded that the detection of anti-dsDNA by means of IIF-CL was more sensitive and effective than ELISA as a diagnostic method of SLE, in such a way that a positive test confirms the disease, whilst a negative test does not rule it out. In contrast, the serialisation of the anti-dsDNA antibody titre by ELISA, which permits quantifying them, is more useful in monitoring SLE because it shows a good correlation with the BILAG (*British Isles Lupus Assessment Group*) disease activity index, and the titre decreases significantly after treatment ($P=0.010$).[138]

Diagnostic S. 2

Tan *et al*. analysed nine ELISA commercial kits that included specific autoantibody and ANA detection, observing considerable variability between them with important sensitivity and specificity limitations in the detection of anti-dsDNA antibodies.[115,150]

Diagnostic S. 1

There is sufficient evidence to recommend the IIF-CL technique as a method to detect the existence of anti-dsDNA antibodies with diagnostic purposes in positive ANA patients, and with suggestive symptoms or signs of SLE.[143]

Diagnostic S. 1

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**Detection of anti-Sm antibodies (Ac compared with anti-Sm)**

Anti-Sm is comprised of proteins B, D, E, F and G, combined with small fragments of nuclear ARN (U1, U2, U4, U5 and U6). The complexes made up of ARN and nuclear proteins are called small nuclear ribonucleoproteins (snRNP) particles. The anti-Sm antibodies are, therefore, multiple autoantibodies that link to multiple antigenic proteins. Anti-Sm and RNP antibodies are located in the nuclear U1 snRNP particle. Hence, the relationship between the anti-Sm and anti-RNP antibodies, in such a way that serums with anti-Sm antibodies often also present anti-RNP antibodies.[151,152]

Diagnostic S. 3

Expert opinion 4

Anti-Sm antibodies are present in 15-40% of SLE patients, although with ethnic variations. Anti-Sm antibodies are more frequent in Afro-Americans (*OR*= 2.48; *P*<0.05[153] and *OR*= 5.7; *P*<0.05[154], according to studies) and Afro-Caribbeans compared with Caucasians.[155,156,157]

Prevalence S. 3

Natural history S. 2+

The detection of anti-Sm antibodies is very useful to confirm the diagnosis of SLE given that they are specific for this disease, they are practically never found in healthy individuals and they are rarely identified in patients with other rheumatic diseases. The SR of diagnostic studies of SLE based on the detection of anti-Sm antibodies, published between 1996 and 2003, performed by Benito-Garcia *et al*.[104] for the ACR, showed that there are 17 high quality studies that compare the diagnostic discriminatory capacity between SLE patients (n=1569) and healthy control (n=978), and 15 high quality studies that assess the use of anti-Sm antibodies in the diagnosis of SLE (n=1523) compared with other rheumatic diseases (n=2843). The anti-Sm antibody detection techniques vary between studies, and include immunodiffusion (ID), RIA, counter-immunoelectrophoresis (CIE), haemaglutination, ELISA and Western blotting (WB).

Diagnostic S. 1

The detection of anti-Sm antibodies to discriminate SLE patients from healthy controls shows a sensitivity that varies between studies from 7 to 41%, with a weighted mean of 24% (95% CI: 19-30%), and a specificity of between 93 and 100%, with a weighted mean between studies of 98% (95% CI: 96%-99%).

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The variability of results between studies may be explained by the technique used to detect anti-Sm antibodies, as ID and CIE prove to be more specific than ELISA, both to differentiate SLE from healthy controls and for other rheumatic diseases. The PLR for the presence of circulating anti-Sm antibodies is very high both in the diagnostic discrimination of SLE with healthy controls and with respect to other rheumatic diseases (26.5). NLR is variable between studies, from 0.60 to 0.93 with respect to healthy controls, and from 0.48 to 0.97 with respect to controls with other rheumatic diseases. Consequently, the presence of anti-Sm antibodies, especially with high titres, firmly supports the diagnosis of SLE because it rarely identifies healthy people or people with other rheumatic diseases as carriers of SLE, thanks to their high specificity and PLR. In contrast, a negative result in the detection of anti-Sm antibodies does not permit the exclusion of an SLE diagnosis, due to its low sensitivity and inadequate NLR. The detection of anti-Sm antibodies is not useful in diagnosing rheumatic diseases other than SLE, such as mixed connective tissue disease, systemic sclerosis, Sjögren's disease, rheumatoid arthritis (RA), polymyositis/dermatomyositis.[104]

ID has been the standard technique to determine anti-Sm antibodies due to its high specificity for the diagnosis of SLE, although its sensitivity is low.[104] Diagnostic S. 1

The multiple simultaneous detection methods of ENA together with ELISA-based anti-dsDNA, applied to SLE patients, show low consistency between techniques, due to the specific characteristics of each trial.[158] Diagnostic S. 3

Tan *et al*. analysed nine ELISA commercial kits that included specific autoantibody and ANA detection, observing considerable variability between them with important sensitivity and specificity limitations in the detection of anti-dsDNA antibodies.[115,150] Consequently, ID, DIE, linear IB or ELISA techniques can be used to detect anti-Sm antibodies, bearing in mind that ID and IB offer better specificities. Diagnostic S. 1

**Detection of anti-nucleosome antibodies**

A new diagnostic marker of SLE has been proposed over the last few years, even as a replacement for the anti-dsDNA antibodies. These are the anti-nucleosome antibodies, also called anti-chromatin antibodies. The nucleosome is the basic element of chromatin present in the dsDNA. Anti-nucleosome antibodies are directed against the histone epitopes exposed in the chromatin, against the dsDNA and against the conformational epitopes created by the interaction of dsDNA and the cell nucleus histones. Anti-nucleosome antibodies may precede the development of other nuclear antibodies in SLE and play an important role in the pathogenesis of this disease, especially in the development of glomerulonephritis. It can be identified with ELISA methods. Anti-nucleosome antibodies are present in 60-75% of SLE patients.[159] Prevalence S. 3

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A recent SR with MA of studies published until November 2011, which assesses the discriminatory capacity between SLE patients and controls of the determination by quantitative immunoassay of anti-nucleosome antibodies (n=37), shows that the sensitivity of the test is 61% (95% CI: 60%-62%) and the specificity is 94% (95% CI: 94%-95%). The PLR is 13.81 (95% CI: 9.05-21.09) and the NLR is 0.38 (95% CI: 0,33-0,44). The MA encompasses 4,239 SLE patients and 6,667 controls. The joint analysis of the 26 studies that compared the determination of anti-nucleosome antibodies and anti-dsDNA obtained greater sensitivity with anti-nucleosome antibodies (59.9 v. 52.4%), and similar specificity (94.9 v. 94.2%). The likelihood of having SLE with positive nucleosome antibodies is 41 times greater than with negative anti-nucleosomes (*OR*=40.7; 95% CI: 26.2-63.3), whilst for dsDNA the likelihood is 28 times greater. In some studies (n=19) the presence of antinucleosome antibodies ($P<0.0001$) but not anti-dsDNA ($P=0.256$) is significantly associated with the activity of SLE. The authors conclude that the detection of antinucleosome antibodies by means of ELISA techniques was greater than that of anti-dsDNA antibodies for the diagnosis of SLE, due to its similar specificity but greater sensitivity and PLR. The value of the anti-nucleosome antibodies in the diagnosis of SLE could be relevant in people with clinical criteria of this disease but not having identified other specific autoantibodies such as anti-dsDNA or anti-Sm.[133]

Diagnostic S. 2

**Antiribosomal protein antibodies**

Anti-RibP antibodies are directed against the ribosomal proteins P0, P1 and P2 of the cell cytoplasm and they are identified in 6-46% of SLE patients. Prevalence varies depending on the ethnic group and on the activity of SLE. They are more frequent in Chinese patients (36%) than in Caucasians (6-20%). In some studies, they are associated with the appearance of SLE at earlier ages. Anti-RibP antibodies are specific of SLE and are rarely found in other autoimmune diseases. Anti-RibP antibodies are not often detected in isolation, as they are usually associated with other specific autoantibodies of SLE, mainly anti-dsDNA, anti-Sm and anti-cardiolipin, although this may be due, partly, to crossed reactivity. In the diagnostic validity study of Carmona-Fernandes *et al*., the determination of anti-RibP antibodies by enzyme fluoroimmunoassay (Elia Rib-P™ , Phadia, Switzerland) in 127 SLE patients, 100 with RA, 99 with ankylising spondylitis, 34 with juvenile idiopathic arthritis, 23 with psoriatic arthritis and 100 healthy controls, showed high specificity, and PLR was very useful in confirming the diagnosis of SLE when anti-RibP antibodies were identified, but its low sensitivity and inadequate NLR prevented excluding the diagnosis of SLE when the anti-RibP antibodies were negative. The prevalence of anti-RibP antibodies in SLE patients of this study was 14.2%, whilst they were detected in only 0.8% of controls with other autoimmune diseases and they were not identified in healthy controls. The Caucasian ethnic group is the only independent factor associated with the presence of anti-RibP antibodies ($\beta= -0.19$, $P=0.034$).[160]

Diagnostic S. 2

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In another study, the identification of autoantibodies against recombinant ribosomal proteins P0, P1 and P2 by means of ELISA (Euroimmun, Germany) in 163 SLE patients, 66 with scleroderma, 54 with Sjögren's syndrome, 90 with RA and 100 healthy blood donors, offered a specificity of 99%, with sensitivity in the diagnosis of SLE of 22% for anti-RibP0, 10.7% for anti-RibP1 and 14.9% for anti-RibP2. In SLE patients and negative anti-dsDNA and anti-Sm antibodies, anti-RibP0 antibodies were detected in 10%. Anti-RibP0, anti-RibP1 and anti-RibP2 antibodies were significantly associated with high levels of anti-Sm antibodies and an increase in anti-dsDNA antibodies. Anti-RibP2 antibodies were associated with an increase in anti-nucleosome antibodies and anti-RibP1 antibodies with an increase in anti-La antibodies.[161]

Diagnostic S. 2

In the study of Girardello *et al*., they compared the anti-RibP antibody detection technique by IB with ELISA in a sample of 60 unselected caucasian SLE patients, 100 patients with other rheumatic inflammatory diseases and 100 healthy controls. The detection of anti-RibP antibodies was slightly higher with IB than with ELISA, 20% and 16.7%, respectively. For the diagnosis of SLE, the specificity of both techniques was 100%, both with healthy controls and with patients. As in other studies, anti-RibP antibodies were significantly associated with the presence of anti-cardiolipin antibodies.[162]

Diagnostic S. 2

**Determination of other autoantibodies**

**Anti-RNP antibodies** are antibodies against small RNA component nuclear riboproteins that are components of ARN and have structural similarities with anti-Sm antibodies, so the majority of serums with anti-Sm antibodies also have anti-RNP antibodies. Anti-RNP antibodies are present in 30-40% of SLE patients, although with ethnic variations. As occurs with anti-Sm antibodies, anti-RNP antibodies are more frequent in Afro-Americans (*OR*= 1.79; *P*<0.05 (Ward 1990) and *OR*= 15; *P*<0.05, according to studies)[158] and Afro-Caribbeans,[155] compared with Caucasians.

Prevalence S. 3

Natural history S. 2+

Anti-RNP antibodies are not specific of SLE as they may also be present in other systemic diseases such as Sjögren's syndrome, RA, polymyositis, systemic sclerosis and mixed connective tissue disease.[104]

Diagnostic S. 1

In the diagnostic discrimination between SLE patients and people with other rheumatic or connective tissue diseases, the specificity decreases considerably to 82% (95% CI: 58-91%), with similar sensitivity (27%; 95% CI: 20-37%). The low sensitivity and moderate specificity with a low PLR indicate that obtaining a positive result in the anti-RNP antibody detection test in people with clinical suspicion of SLE has limited usefulness in the SLE differential diagnosis with other systemic diseases.[104]

Diagnostic S. 1

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

**Anti-histone antibodies** are detected in 35-70% of SLE patients and in more than 95% of patients with drug-induced lupus. Unlike what occurs in SLE, in drug-associated lupus, anti-histone autoantibodies are exclusively detected. 50% of patients treated with lupus-associated drugs, especially procainamide, develop anti-histone antibodies, although only half of them present clinical manifestations of lupus. Anti-histone antibodies are not specific of SLE, as they are also detected in other SADs (RA, Sjögren's syndrome, polymyositis, mixed connective tissue disease) and in up to 5% of healthy individuals, so they lack usefulness in diagnosing SLE. In the sample of Půtová *et al*. the prevalence of anti-histone antibodies was 54% in SLE patients, compared with 5% in patients with sclerodermia and 3% in Sjögren's syndrome.[159]

Prevalence S. 3

**Anti-Ro and anti-La antibodies** are antibodies against ribonucleoproteins involved in the transcription and translation processes of proteins. Anti-La antibodies are rarely detected without anti-Ro. Anti-Ro antibodies are not specific of SLE as they are detected in 35-50% of SLE patients but also in more than 90% of patients with Sjögren's syndrome, and around 60% of patients with subacute cutaneous lupus. Anti-La antibodies are not specific of SLE, either, as, apart from this disease (10-15%) they are present in type B Sjögren's syndrome, RA and polymyositis, so they lack A diagnostic value in SLE. Anti-La antibodies are of the first to occur in SLE patients, appearing on average 2.83 ± 0.43 years before the onset of symptoms and 3.61 ± 0.38 years before the diagnosis.[40]

Natural history S. 2+

The most commonly used anti-Ro and anti-La antibody identification methods today are ELISA and linear IB, which have improved the sensitivity of the test to diagnose SLE. The ELISA method is more sensitive than IB to detect Ro and La antigen antibodies.

In the validation study on the determination of anti-La antibodies by linear IB (Imtec Inmunodiagnostika GmhH, Germany), performed by Rao *et al*., they used a Chinese population sample conformed by 74 selected patients, diagnosed with SLE, and 30 controls conformed by people with varying rheumatic diseases. The sensitivity of the anti-La to differentiate SLE patients from other rheumatic diseases was 25.7% and specificity was 96.7%. These results indicated good specificity of the anti-La to help in the diagnosis of SLE, but they did not confirm the presence of this disease as 3.3% of other rheumatic diseases also present these antibodies. On the other hand, a negative result in the detection of anti-La does not exclude the diagnosis of SLE.[163]

Diagnostic S. 3

**Summary of evidence**

| | |
|---|---|
| II | In the diagnostic process of SLE, the request for serial autoantibodies increases the validity of the immunological tests.[98,100] |
| Ia | The most specific autoantibodies to diagnose SLE are anti-dsDNA, anti-Sm, anti-RibP and anti-nucleosome.[98,104,133] |
| Ia | The detection of anti-dsDNA antibodies by means of IIF with *Crithidia luciliae* substrate is more specific than Farr RIA and ELISA for the diagnostic discrimination between SLE patients and other connective tissue diseases, or healthy individuals.[138,143,149] |

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|---|---|
| Ib | The sensitivity and specificity of the different ELISA commercial brands for the detection of anti-dsDNA antibodies for the differential diagnosis of SLE with other autoimmune diseases show great variability, with a considerable improvement of specificity in those of recent generation, especially those that use human recombinant DNA and nucleosome complexes to establish dsDNA.[115,149,150] |
| Ia | A positive test for the detection of anti-dsDNA antibodies by means of IIF with *Crithidia luciliae* substrate or Farr radioimmunoassay with high titre or concentration in people with suggestive symptoms of SLE and positive ANA test, confirms the highly likely diagnosis of SLE, due to its high specificity (97%) and PLR (16.4).[143] |
| Ia | A negative test for the detection of anti-dsDNA antibodies by means of IIF with *Crithidia luciliae* substrate or Farr radioimmunoassay in people with suggestive symptoms of SLE and positive ANA test, does not rule out the diagnosis of SLE, given its low sensitivity (57%) and inadequate PLR (0.49).[143] |
| Ia | High anti-dsDNA antibody titres are more specific of SLE than discretely higher titres at reference level.[143] |
| II | There is variability in the diagnostic and prognostic validity and in the consistency of the different simultaneous multiple identification techniques of autoantibodies, including anti-dsDNA antibodies (linear immunoassay, multiple microspheres), which in general, do not exceed the sensitivity of traditional ELISA, although the recent automation of these methods has improved their specificity and reproducibility.[137] |
| 3 | The prevalence of anti-Sm antibodies in SLE patients shows ethnic variations, being higher in Afro-American and Afro-Caribbean patients than in Caucasians.[155,156] |
| Ia | Detecting anti-Sm antibodies has clinical usefulness in the confirmation diagnosis of SLE because a positive test with high titre or concentration in people with suggestive symptoms of this disease and positive ANA test, confirms the diagnosis with high likelihood, differentiating it from other rheumatic diseases due to its high specificity (96%) and PLR (26.5).[104] |
| Ia | A negative test for the detection of anti-dsDNA antibodies lacks clinical usefulness for excluding SLE diagnosis in people with suggestive symptoms of this disease and positive ANA test, as it does not rule out the diagnosis due to its low sensitivity (30%) and inadequate PLR (0.7).[104] |
| II | The different identification techniques for anti-SM, ID, CIE, ELISA, linear IB or multiple antigenic microspheres, show similar sensitivities and specificities in the diagnosis of SLE, although the different ELISA commercial brands show variability in their diagnostic validity and consistency, and the ID and the IB offer better specificities.[115,150,158] |
| Ia | Anti-RNP antibodies are not specific of SLE and their usefulness in the differential diagnosis of lupus with other systemic diseases is limited.[104] |
| 3 | Anti-nucleosome antibodies are present in 60-75% of SLE patients and although their association with anti-dsDNA antibodies is frequent, 21% of patients only express this autoantibody.[159] |
| II | Anti-nucleosome antibodies quantified by ELISA have a sensitivity and specificity for SLE diagnosis of 61% and 94%, respectively.[133] |

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| | |
|---|---|
| II | Anti-RibP antibodies are specific of SLE and their high specificity (98-99%) and PLR (23.7) makes them useful for supporting the SLE diagnosis, but not to exclude it if they are negative due to their low sensitivity (14-23) and inadequate NLR (0.86).[149,160-162] |
| III | Anti-histone antibodies are detected in 35%-70% of people with SLE and in more than 95% of people with drug-induced lupus. They are usually the only antibodies present in the latter patients. |
| III/3 | Anti-Ro and anti-La antibodies are not specific of SLE in adults, so they lack diagnostic usefulness in this disease, except for patients with suggestive symptoms and negative ANAs.[163] |

**Recommendations**

| | |
|---|---|
| A | In people with symptoms or signs related to SLE and a positive ANA test, we recommend determining specific high affinity IgG type anti-dsDNA antibodies and anti-Sm antibodies to confirm the diagnosis of SLE. |
| A | For the differential diagnosis of SLE with other connective tissue diseases in patients with positive ANA test, we recommend determining anti-dsDNA antibodies via indirect immunofluorescence with *Crithidia luciliae* substrate. |
| A | SLE should be considered as first diagnostic option in patients with suggestive symptoms, a positive ANA test and a high titre of anti-dsDNA antibodies. |
| B | For the differential diagnosis of SLE with other connective tissue diseases in patients with positive ANA test, we recommend determining anti-Sm antibodies with ID, IB, CIE, ELISA or multiple simultaneous immunoassays with antigen microspheres. |
| A | We do not recommend determining anti-RNP antibodies with diagnostic purposes in people with symptoms that are suggestive of SLE. |
| B | In people with symptoms or signs related to SLE, a positive ANA test and negative high affinity specific anti-dsDNA, anti-Sm and anti-nucleosome antibodies, determining specific anti-RibP antibodies could be useful to diagnose SLE. |
| C | We do not recommend determining anti-Ro and anti-La antibodies in order to diagnose SLE, unless there is an absence of other autoantibodies in people with suggestive symptoms. |
| C | We recommend determining anti-histone antibodies only when people are suspected of having drug-induced SLE. |

## 4.2.2. Diagnostic and classification criteria

**Questions to be answered:**

- What are the classification criteria for systemic lupus erythematosus? Should the new classification criteria proposed by the SLICC 2012 group be used as diagnostic criteria?

The classification criteria of SLE are not diagnostic criteria. The classification criteria have been developed in order to make the definition of SLE operative, and consequently, have homogeneous criteria to select individuals in the research studies, that will permit establishing comparisons

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between them. They are not validated for application to individual cases in clinical practice. Compliance or not with the SLE classification criteria does not permit confirming or ruling out the disease with total certainty, as diagnostic errors can occur.[164]

The first SLE classification criteria were published in 1971. The objective was to differentiate SLE from other rheumatic diseases. It was constructed based on the description of 74 manifestations of SLE in a group of 245 patients who unmistakeably presented this disease according to the 52 participating rheumatologists, coming from 59 hospitals and clinics in the US and Canada. The patients with SLE were compared with 234 patients diagnosed with RA and 217 with different diagnoses, excluding rheumatic disease. The result was 14 criteria. For a patient to be classified as a carrier of SLE, the presence of four of the 14 criteria was required, either simultaneous or in series, during any observation period.[165,166]

Two updates have been carried out by the ACR at later dates (1982[39] and 1997[37]), which have been regularly used in the different research studies.

The ACR criteria were reviewed in 1982.[39] The construction process was carried out based on SLE cases, originating from the North American hospital environment, provided by 18 researchers acknowledged as experts, with their relative controls, paired by age, gender and ethnic group, carriers of non-traumatic or degenerative connective tissue diseases. From 30 potential combinations, obtained from 177 cases of SLE and 162 controls, the analysis of *clusters* established 11 criteria as the best grouping to distinguish between people with and without SLE. The criteria of Raynaud's phenomenon and alopecia, belonging to the 1971 classification, were eliminated, and the detection of autoantibodies, such as antinuclear (ANA), anti-DNA and anti-Sm was incorporated. The selected criteria were tested on one third of the sample used to create aggregations and, later on, on a new sample conformed by 172 SLE patients, 299 with sclerodermia and 119 with dermatomyositis, according to the opinion of rheumatologists. For a patient to be classified as a patient with SLE, the presence of four of the 11 criteria was required, either simultaneous or in series, during any observation period. In this process, the 1982 ACR criteria reached a sensitivity and specificity of 96%.

Diagnostic S. 2

In 1997, the 1982 ACR criteria were updated again with a minor review, which included new immunological aspects such as the presence of APL (criterion 10.d of 1982) and eliminated an out-of-use test such as the LE cells (criterion 10.1 of 1982) (Annex 3).[37] However, these criteria were not validated later on.

Diagnostic S. 3

The main limitations in the ACR classification criteria refer to the over-representation of severe forms and the longer evolution time of SLE; to the excessive relative weight of cutaneous manifestations; the absence of many manifestations of cutaneous lupus (such as subacute lupus or lupus panniculitis, for example); the omission of many neurological manifestations of SLE; and the lack of inclusion of some immunological criteria, such as low complement levels and the failure to update new knowledge about APL. Indeed, as a combination of any four criteria is required, patients without immunological criteria may be classified as SLE, despite this being a disease mediated by autoantibodies.

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Furthermore, the almost universal use of these criteria as an inclusion method for patients into research studies determines that those patients who do not satisfy them are not represented in these studies, even though they have been diagnosed with SLE according to clinical criterion, and paradoxically, patients who satisfy four or more classification criteria may be included, who may not have SLE, or who really have another rheumatic disease.[167]

Diagnostic S. 2

*The Boston weighted criteria* were developed in 2002.[36] They are based on the 1982 ACR classification with a review of some of its criteria, for example arthritis, that is defined as objective synovitis. The Bayesian nomogram of Clough *et al*. was used in its construction, which, with the cut-off point of ≥2 points, classified SLE with a sensitivity of 92%, and the absence of SLE with a specificity of 96%, calculated in a population of 87 SLE and 73 controls with other rheumatologic processes.[168] The Boston classification assigned a value to each criterion so that the final score was the sum of the values of the criteria presented by the patient. The *gold standards* used to validate the Boston criteria were the 1982 ACR classification and the SLE diagnosis carried out by expert rheumatologists on 271 patients (70% Caucasians, 16-84 years old) randomly selected among those examined at a university rheumatology clinic in Boston with suspected SLE. Other connective tissue diseases or other different diagnoses were not represented in the sample, and there were few patients with less than two years' clinical evolution. 63% of the sample satisfied the 1982 ACR criteria, 66% had been clinically diagnosed with SLE by a rheumatologist, and 70% satisfied the Boston weighted criteria. The optimal cut-off point was calculated for each criterion, with better relationship between sensitivity and specificity in order to differentiate between SLE and non-SLE. When the *gold standard* was compliance with the 1982 ACR criteria, the two-point cut-off was the one that offered the best classification validity for SLE, with a sensitivity of 93%, specificity of 69%, positive predictive value of 84%, and negative predictive value of 85%. If the *gold standard* was the clinical diagnosis by the rheumatologist, the validity parameters were 88%, 65%, 83% and 74%, respectively. Once again, it was a classification to select SLE cases in research studies, and its diagnostic validity has not been verified in the application to individual cases in clinical practice. The weightings obtained were based on certain prevalence both of SLE and of its different clinical manifestations, which vary between countries and clinical environments, thus limiting its generalisation and applicability. These criteria have, in fact, been little used.

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Diagnostic S. 2

To try to overcome the limitations of the ACR criteria in use, the SLE validation and classification proposal carried out by the SLICC was published.[169] The construction of the SLICC classification criteria of SLE was carried out with 702 out of 716 patients originating from 25 centres, diagnosed by experts, rheumatologists and dermatologists, with SLE (293), RA (199), myositis (55), chronic cutaneous lupus (50), undifferentiated connective tissue disease (44), vasculitis (37), primary APS (33), sclerodermia (28), fibromyalgia (25), Sjögren's syndrome (15), rosacea (8), psoriasis (7), sarcoidosis (1) and juvenile idiopathic arthritis (1). The rheumatologists of the development group reached a consensus about the diagnosis of SLE, with respect to other diseases, in 98% of the patients. 17 criteria were selected by means of logistic regression and the application of decision trees, and they were divided into two clinical and immunological criteria groups. For a patient to be classified as SLE, four of the 17 criteria had to be satisfied, providing that at least one of the criteria was clinical and one immunological, with simultaneous or serial presentation, or there was LN confirmed by biopsy, in presence of ANA with or without anti-dsDNA antibodies. Using the diagnostic opinion agreed by experts as the reference pattern, the sensitivity of the 2012 SLICC classification criteria in construction phase was greater than that of the 1982-1997 ACR classification (94 v. 86%, $P$=0.001), with similar specificity (92 v. 93%, $P$=0.39). There were fewer classification errors when the 2012 SLICC classification was used ($P$=0.0082).

The new classification was validated in another sample of 690 patients, originating from 15 centres, which included 337 diagnosed with SLE, and other patients with similar rheumatic diseases to the construction sample. Once again, the 2012 SLICC classification was more sensitive than the 1982-1997 ACR (97 v. 83%, $P$=0.0001), but less specific (84 v. 96%, $P$<0.0001), although with no significant differences in the classification errors ($P$=0.24). The reproducibility or agreement among experts in the application of the criteria was greater with the 2012 SLICC classification (Kappa= 0.82) than with the 1982-1977 ACR (Kappa= 0.79). When the sample was restricted to the 615 patients with respect to whom there was no diagnostic agreement among the rheumatologists who developed the classification and the clinics that referred the patients, the sensitivity and specificity of the new SLICC criteria increased to 98% and 91%, respectively, whilst the ACR criteria obtained a sensitivity and specificity of 88% and 98%, respectively. It is noteworthy that this study was the first formal validation of the 1982-1997 ACR criteria.

Despite the limited differences found in the validation studies and the lower specificity with respect to the 1982-1977 ACR criteria, the 2012 SLICC criteria represented progress due to their more clinical nature, to the inclusion of parameters normally used in daily practice, such as complement levels, to a better distribution of the relative weights of each one of the organs and systems, and to the need to satisfy both clinical and immunological criteria to complete the classification. However, once again, they were not constructed or validated with diagnostic purposes, but rather for use in the selection of homogeneous patients in epidemiological and clinical studies.

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With the evidence that exists today, the diagnosis of SLE continues to be clinical, based on the presence of a history of multisystemic impairment disease, mainly of skin, joints, kidneys, serum, blood, CNS or lungs, associated with the presence of significant titres of circulating autoantibodies, after ruling out other diagnostic possibilities.

**Summary of evidence**

| | |
|---|---|
| III | The 1982 ACR SLE classification criteria have not been validated for application to individual cases in clinical practice for diagnostic purposes.[167] |
| II | In the original validation sample, the reviewed 1982 ACR SLE classification criteria presented a specificity of 96% with respect to other rheumatic diseases such as RA, sclerodermia, dermatomyositis and polymyositis, when the clinical diagnostic opinion of the rheumatologist was used as reference pattern.[39] |
| III | The inclusion in 1997 of APL among the SLE classification criteria of the ACR was not validated at the time. However, they were validated later on in their comparison with the 2012 SLICC criteria.[37,169] |
| III | The Boston weighted criteria for the classification of SLE for research purposes with two-point cut-off presented sensitivity, specificity, positive predictive value and negative predictive values of 93%, 69%, 84% and 85%, respectively, when the reference pattern was the 1982 ACR classification, and 88%, 65%, 83% and 74%, respectively when the comparison pattern was the clinical diagnosis of the rheumatologist.[36,168] |
| II | The SLE classification of the 2012 SLICC group was validated in a representative sample of different ethnic groups and clinical environments, including patients diagnosed by rheumatologists and dermatologists.[169] |
| II | The SLE classification criteria of the 2012 SLICC group present greater construction validity and criterion, with similar discriminatory capacity to the 1982 ACR classification.[169] |
| II | The SLE classification of the 2012 SLICC group presents a sensitivity of 94% and specificity of 92% in the construction sample, when the comparison pattern is the diagnostic opinion agreed among experts.[169] |
| II | The SLE classification of the 2012 SLICC group shows greater sensitivity (97 v. 83%), and less specificity (84 v. 96%) than the 1982-1997 ACR classification in the validation sample, but with no significant differences in the classification errors.[169] |
| | The diagnosis of SLE continues to be clinical, based on the presence of compatible manifestations (skin, joint, kidney, etc.) and analytical disorders (autoantibodies, hypocomplementemia). |

**Recommendations**

| | |
|---|---|
| √ | We recommend basing the diagnosis of SLE on expert clinical opinion, combining suggestive clinical characteristics with the relative serological confirmation. |
| √ | The classification criteria should not be used with a diagnostic purpose; however, the SLICC classification criteria may provide useful guidance for the diagnosis. |

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| | |
|---|---|
| B | We recommend using the SLE classification criteria of the ACR 1982-1977 and/or those of SLICC 2012 to select homogeneous patients in clinical research and epidemiological studies. |

## 4.2.3. Initial evaluation tests after diagnosis

**Questions to be answered:**

- After confirming the diagnosis, what tests should be carried out to make an initial evaluation of any patient with systemic lupus erythematosus?

After confirming the diagnosis of SLE, it is important to assess and monitor the activity of the disease, the organs affected and the accumulated organ damage, identifying subgroups of patients with different prognosis and therapy options. With respect to these aspects, laboratory tests, especially immunological tests, are of great value.

EULAR proposes a series of recommendations in the initial assessment and when monitoring the progress of SLE. These are related to the study of the disease activity, organ damage, HRQoL, cardiovascular risk factors, comorbidities (osteoporosis and cancer), risk of infections, mucocutaneous impairment, renal impairment, neuropsychiatric manifestations, eye examination in patients with glucocorticoids or antimalarial drugs, and assessment of laboratory tests.[10] — CPG

We advise carrying out the assessment of the general activity of the disease and the organ damage with standardised indices validated for SLE patients, and from the time of diagnosis to guide the therapeutic decisions as objectively as possible (see monitoring chapter). Indices are available to measure the global activity of the disease (ECLAM, the reviewed *Systemic Lupus Activity Measure* –SLAM-R, *Systemic Lupus Erythematosus Disease Activity Measure* –SLEDAI, *Systemic Lupus Erythematosus Disease Activity Index 2000* –SLEDAI-2K, *Lupus Activity Index* –LAI, *Systemic Lupus Activity Questionnaire* –SLAQ) and individualised activity indices by organs (BILAG). All of these have proven their ability to measure the disease activity and its response or sensitivity to change (improvement/stabilisation/worsening). All the indices include some haematology and biochemistry parameters, but only some contain immunological disorder criteria. For example, the anti-dsDNA antibodies and the complement are used in the SLEDAI index and its variants, but not in the SLAM-R or BILAG.[170] We recommend using assessment indices for the activity of SLE, as well as the HRQoL, in each medical visit, and organ damage once a year.[10] — Expert opinion and CPG

Screening for osteoporosis is carried out in agreement with the existing recommendations for post-menopausal women or for patients receiving treatment with glucocortidoids or any other medication that might reduce bone mineral density (BMD). Cancer screening is carried out in agreement with the existing recommendations for the general population.[10] — CPG

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We also recommend screening for the human immunodeficiency virus (HIV) in patients with risk factors, and for hepatitis B, C[171] and tuberculosis[172] in patients treated with immunosuppressants or glucocortidoids at high doses if they have risks factors for these infections.

Prevalence S. 3

Prognostic S. 2-

During the initial assessment of SLE, EULAR recommends studying the presence of anti-dsDNA and anti-Sm antibodies, which already form part of the confirmation diagnostic tests, as well as anti-RNP, anti-Ro, anti-La and antiphospholipid antibodies. During the progress of SLE, EULAR recommends monitoring anti-dsDNA, in association with the levels of complements C3 and C4, and in previously negative patients it recommends determining the APL before planned pregnancy, surgery, organ transplant or treatment with oestrogens, or when there is a presence of new neurological or vascular events, as well as anti-Ro and anti-La antibodies before a planned pregnancy or early on during pregnancy if this had not been planned.[10]

CPG

The presence and monitoring of anti-dsDNA antibody levels in SLE patients has prognostic usefulness. It can provide information, both when the diagnosis is confirmed and during follow-up, about the existence of SLE activity, the presence of renal disease and the activity or lack of activity of nephropathy. In the SR of Kavanaugh *et al*. on 31 studies published until 2002, which assessed the association between anti-dsDNA antibodies and prognostic factors, 18 studies were considered of high methodological quality, although it was not possible to observe the potential confounder effect of the treatment with glucocorticoids and/or immunomodulators in any of them. In general lines, the studies showed an association between the presence of anti-dsDNA antibodies and the increase in SLE activity. However, there were considerable differences in term of sensitivity and specificity between studies. When IIF-FL was used as an anti-dsDNA identification method, the sensitivity to detect the SLE activity varied between 14 and 100%, and the specificity between 13 and 97%. When the technique used was Farr radioimmunoassay, sensitivity varied between 41 and 98%, and specificity between 25 and 97%. Finally, with ELISA, the sensitivity was between 32 and 92%, and the specificity between 35 and 77%.[143]

Diagnostic S. 1

The PLR were extremely variable between studies, going from zero prognostic value (0.88) to clearly useful to confirm the activity of SLE. The weighted mean between studies offers a PLR of 4.14, of limited usefulness in predicting the disease activity. Therefore, the presence of anti-dsDNA antibodies only affords value in the prognostic assessment if accompanied by clinical (clinical history and physical examination) and laboratory parameters that are suggestive of SLE activity, which increase the pre-test likelihood to 10% or more, except in those patients who present high anti-dsDNA titres, that are strongly associated with SLE activity in different studies. In contrast, the mean weighted negative likelihood ratio between studies for the association between dsDNA and SLE activity is 0.51, which means that a negative result in the anti-dsDNA detection test does not exclude the existence of active disease.[143]

Prognosis S. 2+

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The detection of anti-dsDNA antibodies and their titre or concentration may be of some usefulness in predicting the existing of renal disease. In the SR of Kavanaugh & Solomon, the studies that assessed the association between the presence of anti-dsDNA antibodies and the existence of renal disease showed an average sensitivity of 65%, specificity of 41%, PLR of 1.7 and NLR of 0.76, meaning that the request for anti-dsDNA antibodies to assess the presence of renal disease only has a limited value in patients with high previous suspicion of renal impairment.[143] Diagnostic S. 1

In the association of anti-dsDNA antibodies with the presence of membranous lupus nephritis, type IV of the World Health Organisation (WHO), the sensitivity of determination via IIF-CL and ELISA is 93% and 100%, respectively, with PLR of 2.3 and 1.04, respectively, indicating the limited prognostic value of the mere presence of anti-dsDNA antibodies.[173] Diagnostic S. 3

In the study of Hanly *et al*., the detection of anti-dsDNA antibodies by multiple simultaneous immunoassay with anti-ENA antibodies (BioPlex 2200®, USA) was significantly associated with the accumulated risk of active LN ($P$=0.047).[174] Diagnostic S. 2

The high concentrations or titres of anti-dsDNA antibodies are useful for the prognosis of active lupus renal disease. In the SR of Kavanaugh & Solomon, the studies that assessed the association between the titre of anti-dsDNA antibodies and the activity of lupus nephropathy showed a sensitivity of 86%, specificity of 45%, PLR of 1.7 and negative likelihood ratio of 0.3, indicating a greater capacity for exclusion than for confirmation of active renal impairment. However, high titres of anti-dsDNA are considerably correlated both with the existence of renal disease and a greater activity of nephropathy. Due to the specificity limitations of the test, the interpretation of a high titre of anti-dsDNA antibodies in SLE patients, as a prognostic factor of nephropathy and its activity, should be done in combination with other clinical aspects and renal disease measurements. The combination of high anti-dsDNA titres and low complement levels may be more predictive of active LN.[143] Diagnostic S. 1

There is little and not very consistent evidence about the prognostic value of the detection and monitoring of the anti-Sm antibody titre in SLE. One SR showed that the diagnostic capacity of the presence of anti-Sm antibodies on LN presented a sensitivity, specificity and PLR of 25%, 8% and 1.3, respectively. Therefore, the absence of anti-Sm antibodies did not indicate the absence of renal disease, due to the large number of false negatives that it may cause. In contrast, the presence of anti-Sm antibodies is associated with the existence of lupus nephropathy, but this is a prediction with limited clinical usefulness because 15% of SLE patients can be erroneously classified as carriers of renal disease.[104] Evidence is also inconsistent in studies that analyse the association between anti-SM antibodies and LN, given that three studies do not show any statistically significant correlation between the detection of anti-SM antibodies by ID, haemaglutination or ELISA, and the existence of renal disease,[175-177] whilst in another, lower quality, study, membranous glomerulonephritis significantly correlated with anti-Sm antibodies.[157] Consequently, the limited and inconsistent evidence leads to the conclusion that anti-SM antibodies, alone, have no prognostic usefulness for LN. Diagnostic S. 1

Prognosis S. 2+/2-

Diagnostic S. 3

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There is not sufficient evidence about the prediction capacity of anti-SM antibodies on the impairment of the CNS or other systemic manifestations of lupus. In the SR of Benito-Garcia *et al*., only six studies assessed this association, two of high quality and four of moderate quality. The sensitivity, specificity and PLR obtained in the two high quality studies varied considerably (sensitivity 0 and 77%, specificity 90% and 80%, and PLR 0 and 3.85). Of the six moderate quality studies, only one observed a statistically significant correlation between anti-Sm antibodies and impairment of the CNS. Evidence about the prognostic value of anti-Sm antibodies on other systemic lupus manifestations (pleuropulmonary, haematological, cardiac, cutaneous, joint, vasculitis and thrombosis) is even more limited and inconsistent.[104]

Diagnostic S. 1

Correlation of anti-Sm antibodies with the activity or severity of SLE is uncertain. Available evidence comes from moderate quality methodological studies with different result measurements. Some find no correlation between anti-Sm antibodies and cutaneous lesion, arthritis or serositis.[157] Another study concluded that the haematological disorders seemed to be less frequent in patients who only had anti-Sm autoantibodies, but with no statistical significance.[176] In the studies that used standardised cross-sectional measurement SLE severity indices, some found no association between anti anti-Sm antibodies and organ damage (SLICC/ACR DI index)[178] and others showed that the presence of anti-Sm is less frequent in mild forms of SLE 12.5%) compared with moderate and severe forms of the disease (47.5%; $P<0.01$).[179]

Diagnostic studies 2

Prospective studies that assess the association between anti-Sm antibodies and longitudinal measurements of SLE activity are limited and of moderate quality as they present variability in the definition used for the activity or flare of SLE, selection biases of the populations studied, and lack of control of the effects of treatment on the disease activity or on the test result.

Barada *et al*. carried out an average follow-up of 2.5 years of 30 SLE patients, classified according to the presence or absence of anti-Sm antibodies. They found a significant correlation (r= 0.06) between the titre of anti-Sm antibodies requested throughout the follow-up period and the SLE activity, with an average titre of 3.6 UI/ml during flare-up and 1.0 UI/ml during remission ($P<0.05$). Given that they only considered the most serious flare-up episode, a second analysis of 29 flares was performed, in which the average titre of anti-Sm antibodies was 3.2 UI/ml, whilst during the remission period it was 1.8 UI/ml ($P<0.001$). In half the patients, the increase in anti-Sm antibody titre predicted the flare of SLE.[175] Other available studies confirm this association, but they do not provide sufficient quality information about the prediction of future lupus flares.[180,181] Consequently, and in order to monitor SLE patients, the presence of anti-SM antibodies does not predict the appearance of new disease activity flares.

Prognosis S. 2+

Prognostic s. 2-

The presence of anti-RNP antibodies lacks diagnostic value of LN. The eight high methodological quality studies of the SR of Benito-Garcia *et al*. assessed this aspect, showing that the combined measurement of sensitivity, specificity and PLR for the diagnosis of LN is 28%, 74% and 1.1, respectively, so many patients will be wrongly classified.[104]

Diagnostic S. 1

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The limited evidence available suggests that the presence of anti-RNP antibodies in SLE patients has no prognostic value for identifying organ damage (SLICC/ACR ID),[178] impairment of the CNS[176,182,183] or other systemic manifestations of the disease.[178,182-184] Changes in levels of anti-RNP antibodies do not predict flares of SLE, although the number of available studies is limited, so we do not recommend monitoring anti-RNP antibodies in SLE patients to assess the disease activity over time.[177,185]

Diagnostics S. 1/2/3

Prognostic s. 2-

The presence of anti-nucleosome antibodies is significantly associated with the activity of SLE. In the study of Su *et al*., 66% of patients with active disease had anti-nucleosome antibodies compared with 45.7% of those with inactive SLE (P=0.010). The anti-nucleosome antibody levels significantly but moderately correlated with the SLEDAI index of SLE activity (r=0.385, *P*<0.001). In this sample, patients with anti-nucleosome antibodies had significantly more fever, skin *rash*, arthralgias, leucopoenia, increase in erythrocyte sedimentation rate" (ESR) and C-reactive protein C (CRP), and decrease in C3/C4 levels and proteinuria.186 In the sample of 107 Hungarian patients with SLE originating from a specialised university centre, the anti-nucleosome antibodies, as well as the anti-dsDNA antibodies correlated with the disease activity measured through the SLEDAI index (r= 0.35; *P*=0.0002 anti-nucleosome, r= 0.37; *P*<0.0001 anti-dsDNA). Furthermore, patients with anti-nucleosome antibodies had four times more risk of LN than patients without these autoantibodies (*OR*= 4.4; 95% CI: 1.8-10.3). Patients with anti-dsDNA antibodies had almost twice as much risk of LN than patients without these autoantibodies (*OR*= 1.91; 95% CI: 0.8-4.5).[187] In contrast, in the study of Carins *et al*. they did not observe any significant correlation between anti-nucleosome antibodies and SLE activity measured through the SLAM index. However, in this sample there was a prevalence of patients with a relative low activity of SLE.[188]

Diagnostic S. 2

Prevalence S. 3

Diagnostic S. 3

Diagnostic S. 2

Diagnostic S. 3

More than 5 years have passed since the publication of this Clinical practice Guideline and its validity has not been reviewed

The association of anti-chromatin antibodies with lupus nephropathy is also observed in other studies such as in the study of Cervera *et al*., where the detection of anti-chromatin antibodies by means of ELISA (Inova Diagnostics, USA) was performed on 100 consecutively recruited SLE patients, 100 people with Sjögren's syndrome, 30 people with primary APS, 10 with sclerodermia and 100 healthy blood donors. Sensitivity and specificity for the diagnosis of lupus nephropathy was 81% and 39%, respectively. SLE patients and anti-chromatin antibodies had three times more risk of presenting renal disease than those that with negative anti-chromatin (58% v. 29%, *OR*= 3.4; 95% CI: 1.3-9.3), whilst patients with anti-dsDNA antibodies had five times more risk of presenting nephropathy compared with those who did not have these autoantibodies (*OR*= 5.4; 95% CI: 2-14.8). The anti-chromatin antibody levels significantly correlated with the SLE activity measured through the ECLAM index (*P*=0.011).[189] In contrast, in another study, no association was observed between anti-chromatin antibodies and lupus nephritis or with the presence of anti-dsDNA antibodies. However, this study presented an important selection bias, as only the presence of anti-chromatine antibodies in positive ENA patients was explored.[190] In prospective studies, anti-nucleosome antibodies are more sensitive than anti-dsDNA antibodies to identify the activity of SLE. In the cohort of Gutierrez-Adrianzen *et al*., the 87 patients diagnosed with SLE and monitored for 12 months had a lupus activity prevalence of 50.6%, according to the SLEDAI index, and nephropathy prevalence of 49.4%. The prevalence of anti-nucleosome antibodies at start and end of monitoring was 40% and 58.6%, respectively. The prevalence of anti-dsDNA antibodies at start and end of monitoring was 10.9% and 21.8%, respectively. The sensitivity of the anti-nucleosome antibodies to identify active SLE, in both periods, was 72.7% and 100%, respectively. The sensitivity of the anti-dsDNA antibodies to identify the activity of SLE, in both periods, was 31.3% and 54.8%, respectively. The specificity of the anti-nucleosome and anti-dsDNA antibodies to identify active SLE at the start of monitoring were 66.7% and 88.7%, respectively, whilst at the end of monitoring they were 83.7% and 100% respectively. The sensitivity and specificity of the anti-nucleosome antibodies to diagnose active nephropathy at the start of monitoring were 32% and 67.5%, respectively, opposed to 46.2% and 67.3% at the end of monitoring, respectively. The sensitivity and specificity of the anti-dsDNA antibodies to diagnose active nephropathy at the start of monitoring were 16% and 85.1%, respectively, and at the end of monitoring they were 35.4% and 97.5%, respectively. Consequently, anti-nucleosome antibodies are more sensitive than anti-dsDNA antibodies for identifying the activity of SLE and active nephropathy.[191]

Prognosis S. 2+

More than 5 years have passed since the publication of this clinical practice guideline, and its validity has not been reviewed

The first observation of the association between high levels of anti-RibP antibodies and the presence of a psychotic flare, with decrease when the acute symptoms are overcome, corresponds to Bonfa *et al*. in 1987.[192] From then on, results of the studies are inconsistent. In prospective studies, the presence of anti-RibP antibodies in SLE patients increases the future risk of psychosis. The international multi-centre cohort of Hanly *et al*. was conformed by 1047 people recently diagnosed with SLE (mean duration 5.4 ± 4.2 months), and monitoring of 3.5 ± 2.6 years, during which time they developed 917 neuropsychiatric events (47.3%), of which 15-28% could be attributed to SLE, according to the predictor model used. At the start of monitoring, 9.2% and 13.4% of the patients had anti-RibP and anti-cardiolipin antibodies, respectively. The presence of anti-RibP antibodies increased the subsequent risk of psychosis (multivariate HR = 3.92; 95% CI: 1.23-12.5; *P*=0.02).[193] In a cross-sectional analysis of this same cohort, relating to the moment SLE was diagnosed, the frequency of anti-RibP antibodies in patients with neuropsychiatric events of the CNS was 20% opposed to 8.5% in patients without this type of events (*P*=0.04). Association was observed between the presence of anti-RibP antibodies and psychosis attributed to SLE (*P*=0.02).[194] Other lower quality methodological prospective studies found no association between anti-RibP antibodies and the neuropsychiatric manifestations of SLE after an average monitoring period from diagnosis of 5.11 ± 2.9 years.[195] In cross-sectional analysis studies, the association between anti-RibP antibodies and neurolupus, or lupus psychosis was inconsistent. Some of them did not observe this association[160,196] whilst others do describe it.[197-199]

Prevalence S. 3

Prognosis S. 2++

Nested prevalence S. in cohort 3

Prognostic s. 2-

Diagnostics S. 2/3

The MA of diagnosis studies of Karassa *et al*, which combined standardised data from 1,537 SLE patients –European, Asians and South Americans–, originating from 14 research teams until the year 2006, showed that the sensitivity and specificity of anti-RibP antibodies for the diagnosis of neuropsychiatric lupus (SLE-NP) was 26% (95% CI: 15%-42%), and 80% (95% CI: 74%-85%), respectively. For the diagnosis of psychosis, mood disorders or both, sensitivity and specificity was 27% (95% CI: 14%-47%), and 80% (95% CI: 74%-85%), respectively. For other neuropsychiatric manifestations, sensitivity was 24% (95% CI: 12%-42%) and specificity 80% (95% CI: 73%-85%).[200] These results indicated little diagnostic usefulness of anti-RibP antibodies in the identification of SLE-NP and to discriminate between its different syndromes, given its low sensitivity because few patients with neuropsychiatric syndromes associated with SLE present anti-RibP antibodies. Furthermore, there are patients who have anti-RibP antibodies but do not have SLE-NP. In the study of West *et al*., the highest diagnostic value of anti-RibP antibodies occurred in patients with diffuse SLE-NO characterised by primary psychiatric disease.[201]

Diagnostic S. 2

Diagnostic S. 3

Evidence about the correlation of anti-RibP antibodies with the global activity of SLE and their disappearance during the remission of the flare are inconsistent. Anti-RibP antibodies correlated with standardised indices of SLE activity in some studies.[195,196,198,199] Others, however, did not observe this association.[160,161,202] There is no consistency, either, between studies in terms of the relationship between the presence of anti-RibP antibodies and lupus gomerulonephritis or hepatitis.

Diagnostics S. 2/3

Prognosis S. 2-

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Both anti-Ro and Anti-La antibodies are associated with neonatal lupus (95%) and with cutaneous manifestations of subacute cutaneous lupus. In SLE patients, anti-Ro and anti-La antibodies are associated with pneumonitis and photosensitive rash without severe renal disease, which is known as subacute cutaneous lupus (70%). Anti-Ro and anti-La antibodies cross the placenta and can produce heart block in the foetus (2%-5%, which increases to 16%-25% in women with past history of foetal heart block in previous pregnancies), normally between gestation weeks 16 and 24, as well as photosensitive *rash* (16%) and haematological (27%) and hepatic (26%) disorders, in the newly born. Thus, we recommend its determination in women with SLE who are planning a pregnancy, or in those who are already pregnant in order to carry out a strict foetal control of the PR interval by echocardiography on a weekly basis during gestation weeks 16 to 26 and every two weeks from 26 to 32.[203] Anti-Ro antibodies are also associated with leucopoenia, neutropenia, thrombocytopenia, vasculitis, renal disease and a high incidence of concomitant anti-dsDNA antibodies. Anti-La antibodies are associated with a lower risk of LN. However, there is not sufficient evidence to support the prognostic value of anti-Ro or anti-La antibodies on the activity of the disease or the development of nephropathy during the progress of SLE.[163] In a sample of Chinese population, anti-La antibodies were associated with erythema, alopecia, serositis, secondary Sjögren's syndrome, leucopoenia, increase in IgG and presence of anti-Ro antibodies.[52-60] The levels of anti-La antibodies were correlated with the activity of SLE measured with the SLEDAI index.[163]

CPG 4

Diagnostic S. 2

Diagnostic S. 3

The APLs are a heterogeneous group of autoantibodies directed against phospholipids integrating the cell membranes, and they are present in 30%-50% of SLE patients. Anti-cardiolipin antibodies, lupus anticoagulant and anti-β2-glyoprotein I antibodies are APLs. The most frequent in SLE are anti-cardiolipin, with prevalences of 16-60%. Lupus anticoagulant is detected in 20% of SLE patients. The APLs are not specific of SLE given that they can also be observed in other autoimmune diseases such as sclerodermia, vasculitis and RA, as well as in infectious diseases, such as hepatitis C, HIV, leprosy, Lyme's disease, Q fever, varicella zoster virus and tuberculosis, leukaemia and solid tumours, although in these cases, they are not associated with clinical manifestations of APS and the anti-β2-glycoprotein I antibodies are usually negative. Anti-cardiolipin antibodies and lupus anticoagulant can be detected in 5% and 3.6% of health individuals, respectively.[204]

Prevalence S. 3

The most characteristics manifestations of APS are frequently recurrent arterial and venous thrombosis, repeated miscarriages, foetal deaths, other pregnancy complications such as preeclampsia, preterm birth or delay in intrauterine growth, livedo reticularis and thrombocytopenia.[60] Evidence about the increase in risk during pregnancy in women with SLE, who are APL carriers, is consistent between studies. Other less frequent associations of APL are valvulopathies, avascular nechrosis (osteonechrosis), epilepsy, migraine and retinal vascular disorders.

Natural history S. 2+

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

The prognostic value of thrombosis of the presence and high persistent titre of anti-cardiolipin antibodies type IgG and IgM, lupus anticoagulant or anti-β2-glycoprotein I is observed in many prospective and cross-sectional studies.[255-267] The presence of lupus anticoagulant is the most powerful independent risk factor of APS in SLE patients. In SLE patients, persistently positive anticardiolipin antibodies have also shown association with thrombosis.[261] In a cohort of 237 patients with an average of 10 years' follow-up, 12.6% and 9.7% presented arterial and venous thrombotic events, respectively. The adjusted risk of arterial thrombosis is greater in patients with lupus anticoagulant (*OR*= 15.69; 95% CI: 4.79-51.42) or persistent anticardiolopin antibodies (*OR*= 7.63; 95% CI: 2.0-29.08) with respect to negative patients for these antibodies. Patients with temporary positive anticardiolipin antibodies and without lupus anticoagulant do not present a significant increase in risk of arterial thrombosis (*OR*= 1.08; 95% CI: 0.22-5.26).[205] Patients with APS and triple positivity to anticardiolipin antibodies, lupus anticoagulant and anti-β2-glycoprotein I have a high risk of developing thromboembolic events[267]. The antiphospholipid index constructed by Otomo *et al*., in groups of patients with APS and autoimmune diseases, with or without APS, showed that the cut-off point ≥30 behaves as an independent risk factor of thrombosis, tripling the risk of patients with lower indices (multivariate *OR*= 3.14; 95% CI: 1.38-7.15).[206]

Prognosis S. 2+ /2-

Prevalence S. 3

Prevalence S. 3

The presence of anticardiolipin antibodies is a risk factor of pregnancy complications both for mother and foetus. In one study, the levels of anti-dsDNA antibodies correlated with the risks of flare-up of SLE and premature birth (*P*=0.003). The increase in the titre of anti-dsDNA and anti-cardiolipin antibodies may suggest an increase in risk of foetal loss, although this relationship is not statistically significant.[207] For these reasons, in women diagnosed with SLE who are planning a pregnancy, the European and American CPGs recommend the previous determination of APL to assess the risk of miscarriage, foetal death and pregnancy complications, which will permit giving pre-conception advise, appropriately monitoring the pregnancy and providing preventive treatment with heparin associated with aspirin in women with APS.[10,208-210]

Prognosis S. 2+

CPG

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In the study of Sciascia *et al*. a representative sample of 230 consecutive SLE patients was used, with an average age of 42.7 ± 11.9 years, with average duration of the disease of 12.2 ± 8.7 years, carrying out determinations of APL on them with ELISA techniques. The prevalences of lupus anticoagulant, IgG/IgM anticardiolipin, IgG/IgM anti-β2GPI, IgG/IgM anti-phosphatildylserine/prothrombin (APL/PT) and IgG/IgM antiprothrombin were 25%, 56%, 21%, 30% and 30%, respectively. The greater discriminatory capacity of APS and its manifestations of thrombosis and repeated miscarriages was obtained with the combination of positive results in lupus anticoagulant, anti-β2GPI and anti-phosphatildylserine/prothrombin (aPS/PT) antibodies. This association increases the risk of APS (*OR*= 3.73; 95% CI: 1.82-5.38) thrombosis (*OR*= 3.75; 95% CI: 2.13-6.62) and repeated miscarriage (*OR*= 4.82; 95% CI: 2.17-10.72). Triple positivity obtained sensitivity, specificity, positive and negative predictive values for the diagnosis of APS of 57%, 75%, 63% and 64%, respectively, higher than the specificity shown by the combined positivity of anticardiolipin antibodies and lupus anticoagulant (44%), although with less sensitivity (80%). To identify thrombosis, sensitivity, specificity, positive and negative predictive values of triple positivity were 68%, 69%, 52% and 77%, respectively, and for repeated miscarriage, 77%, 61%, 29% and 91%, respectively. Triple positivity was strongly associated with thrombosis or repeated miscarriages (*OR*= 23.2; 95% CI: 2.57-46.2 lupus anticoagulant, positive aPS/PT and anti-β2GPI) when compared with double positivities (*OR*= 13.78; 95% CI: 2.04-16.33 lupus anticoagulant and positive β2GPI; *OR*= 9.13; 95% CI: 2.17-15.62 aPS/PT and positive β2GPI) or single positivities (*OR*= 7.3; 95% CI: 2.21-25.97) positive lupus anticoagulant; *OR*= 5.7; 95% CI: 2.12-17.1 aPS/PT; *OR*= 3.11; 95% CI: 1.56-7.8 anti-β2GPI).[211]

Diagnostic S. 1

SLE patients often present a decrease in complement levels, especially a decrease of C3, C4 and CH50, which are associated with the activity of the disease. Fraction decreases of the complement were observed in 9% of SLE patients controlled for an average period of 4.25 years by Sullivan *et al*.[212] Detecting low levels of C3 and C4 in other autoimmune diseases is not very frequent, but they can be observed in RA with vasculitis. The most frequent complement deficiency in SLE patients is that of C4, and although the isolated decrease of C4 levels does not necessarily indicate consumption of the complement, it is also related to SLE activity.[213]

Prognosis S. 2+

Prognosis S. 2-

Prevalence S. 3

In the cross-sectional descriptive study of Amezcuoa-Guerra *et al*., when 115 SLE patients and 26 healthy controls were recruited, it was observed that the levels of complements C3 and C4 were lower in SLE patients than in controls ($P<0.0001$). The activity of SLE measured with the SLEDAI-2k index inversely correlated with C3 ($P=0.004$), C4 ($P=0.04$) and CH50 ($P=0.02$). Patients with active nephritis showed lower levels of C3, C4 and CH50 than patients with SLE but without nephritis.[214]

Prevalence S. 3

Persistent low levels of C3 in SLE patients were associated with chronic renal disease.[212,215] The high levels of anti-C1q antibodies, associated or not with the decrease in complements C3 and C4, were associated with proliferative glomerulonephritis.[216-218]

Prognosis S. 2+/2-

Prevalence S. 3

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Other laboratory studies that should be performed on SLE patients, both at the time of diagnosis and during its follow-up, are haemograms, especially to detect anaemia, leucopoenia, lymphopenia, and/or thrombocytopenia, ESR, C-reactive protein, albumina, creatinine, urinary sediment, and protein/creatinine ratio in 24-hour urine or proteinuria. The consensus between experts establishes that in people with inactive SLE their execution at intervals of 6-12 months is sufficient.[10]

CPG 4

A rise in CRP can be observed in SLE patients. High levels of CRP can distinguish between bacterial infection and active SLE, as normally CRP is low in lupus activity flares. However, CRP may evolve into severe lupus serositis.[219] In studies that jointly assess the association between different acute phase proteins (C3, C4, CH50, CRP, alpha-1antitripsin), ESR and SLE activity, it was observed that acute phase proteins behaved differently depending on the organ that showed the SLE activity. In the cross-sectional descriptive study of 115 SLE patients and 26 healthy controls carried out by Amezcua-Guerra *et al*., the CRP was higher in SLE patients than in the controls ($P$=0.005). The activity of SLE measured with the SLEDAI-2K index positively correlated with CRP ($P$=0.04). Patients with arthritis showed higher levels of CRP than patients without arthritis.[214] Although the consensus documents and CPGs recommend its determination every 6-12 months if the SLE is inactive or during each visit if disease activity is suspended, the degree of evidence/level of recommendation is 5D.[10]

Prognosis S. 2+, 2-

Prevalence S. 3

CPG

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The rise of ESR is frequent in SLE. In a North American prevalence study, 56% of the SLE patients presented a rise of ESR at some moment during its evolution.[34] Evidence about the usefulness of ESR in the assessment and follow-up of the SLE activity is limited and low quality. More recent evidence based on longitudinal studies suggests that ESR may be an activity marker of SLE but that its lacks prognostic value. In the *Hopkins Lupus Cohort*, which assessed predictor factors of activity flares, arteriosclerosis and state of health in SLE, the levels of ESR were associated with the disease activity, measured through standardised indices such as SELENA-SLEDAI (*Safety of Estrogens in Lupus Erythematosus National Assessment- Systemic Lupus Erythematosus Disease Activity Measure*) and PGA (*Physician Global Assessment*), and with the organ-specific activity of renal, joint, haematological location, *rash* and serositis. Changes in ESR levels between two visits significantly correlated with real changes in the PGA index and in the analogical visual scales of renal and joint impairment, and fatigue. In contrast, changes in ESR between two visits do not predict future activity of SLE. In the subgroup of patients who had no anti-dsDNA antibodies or low complement, the ESR was associated with the SLEDAI index, PGA and the analogical visual scales of renal and joint impairment. Therefore, the seriation of the ESR from the diagnosis and during the follow-up of SLE patients may be quite useful as a disease activity marker.[220] In the North American multi-ethnic cohort, LUMINA, the rise in ESR was also significantly associated with the current global activity of SLE measured with the SLAM index.[221] In the German cohort of 120 Caucasian SLE patients, the ESR, at the time of diagnosis, did not predict future changes in the SLEDAI index of the disease activity.[222] In studies that jointly assess the association between different acute phase proteins (C3, C4, CH50, CRP, alpha-1-antitripsin), ESR and the SLE activity, it is observed that the disease activity measured with the SLEDAI-2K index positive correlated with ESR ($P$=0.01).[214] As occurs with the CRP, the CPGs of the EULAR recommend its execution at the time of diagnosis and later, every 6-12 months if the disease remains inactive, or during each visit if SLE activity is suspected, again with level 5D.[10]

Prevalence S. 3

Prognostic studies 2++/2+

Prevalence S. 3

CPG

Severe leucopoenia and lymphopenia (<500 cells/mm$^3$) are associated with infections in SLE patients (hr = 4.7; 95% CI: 1.6-13.7; $P$=0.005), as shown by a retrospective study on the Chinese population.[223] Severe anaemia and thrombocytopenia are associated with organ impairment, progression of SLE and worse prognosis.[10]

CPG 4

Anomalies in urine sediment, albumin/creatinine ratio in urine and/or serum creatinine have an important predictive value of renal condition in SLE. [10,224-227]

CPG 4

Prognosis S. 2+

**Summary of evidence**

| | |
|---|---|
| Ia | A high titre of anti-dsDNA antibodies, especially type IgG, obtained by means of IIF-*Crithidia luciliae*, Farr radioimmunoassay or ELISA, is significantly associated with SLE activity but not with the presence of irreversible organ damage.[143] |

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| | |
|---|---|
| 2++ | The rise of the titre of anti-dsDNA antibodies, especially type IgG, during the progression of SLE may predict flare-ups of the disease.[143] |
| Ia/2+ | High titres of anti-dsDNA antibodies in SLE patients significantly correlate with the presence of nephropathy, but they have low specificity.[143,173,174] |
| Ia/2+ | Evidence about the association of the presence of anti-Sm antibodies with the general activity of SLE of lupus nephropathy are inconsistent.[104,175,176,178-181] |
| Ia | Anti-RNP antibodies lack usefulness in identifying nephropathy, CNS impairment or organ damage associated with SLE.[104,178,182-184] |
| II | The rise of anti-RNP antibodies during the progression of SLE does not predict a flare of the disease activity.[177,185,228] |
| II | The association between the presence of anti-nucleosome antibodies with the activity and presence of nephropathy is inconsistent.[187,189,190,229] |
| 2+ | In prospective controls, anti-nucleosome antibodies are more sensitive than anti-dsDNA antibodies for identifying the general activity of the disease and lupus nephropathy.[191] |
| II/2++ | The association between anti-RibP antibodies and neuropsychiatric manifestations of SLE, including psychosis, is inconsistent, both in prospective and cross-sectional analyses, and its diagnostic usefulness of neuropsychiatric episodes is limited given its low sensitivity and specificity.[160,192-199] |
| II/2- | Evidence about the correlation of anti-RibP antibodies with the global activity of SLE is inconsistent, which means that it has a limited diagnostic and prognostic value.[161,195,196,198,199,202] |
| II | Anti-Ro and anti-La antibodies cross the maternal-foetal barrier of the placenta and are associated with heart block in the foetus, and with SLE manifestations in the newly born, generally temporary.[203] |
| III | There is not sufficient evidence to back the prognostic value of anti-Ro and anti-La antibodies on SLE activity or the development of lupus nephropathy, although anti-La antibodies have been associated with a lower risk of nephropathy.[163] |
| 2+ | People with SLE and APL have a greater risk of recurrent arterial and venous thrombosis, repeated miscarriages, foetal deaths, pregnancy complications, livedo reticularis and thrombocytopenia.[60] |
| III/2- | The presence of lupus anticoagulant, anticardiolipin antibodies, anti-β2-glycoprotein I antibodies or anti-prothrombin antibodies in SLE patients are risk factors of thrombotic events.[230-238] |
| 2+ | Triple (anticardiolipin(lupus anticoagulant/anti-β2-glycoprotein I) or quadruple (anticardiolipin/lupus anticoagulant/anti-β2-glycoprotein/anti-prothrombin) positivity increases the risk of thrombotic events in SLE patients.[229,231] |
| I | Triple positivity (lupus anticoagulant/anti-β2-glycoprotein I/antiphosphatildylserine/prothrombin) improves specificity but decreases sensitivity to identify APS in SLE patients, compared with double positivity (anticardiolipin/lupus anticoagulant).[211] |
| 2+ | C3, C4 and CH50 levels correlate inversely with SLE activity, and persistent low levels are associated with LN.[212-216,218] |

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| | |
|---|---|
| 2+ | C-reactive protein may be high in patients with lupus with infection and in joint or serositis flares of SLE. [214,219,239,240] |
| 2++ | The rise of ESR is associated with general and organ-specific activity (renal, haematological, joint and cutaneous, as well as with cutaneous activity and serositis of SLE).[214,220-222] |
| 2+ | The rise in serum creatinine, abnormal urine sediment, proteinuria and high blood pressure have a predictive value of the presence of lupus nephropathy.[224-227] |

**Recommendations**

| | |
|---|---|
| B | For the initial evaluation of patients diagnosed with SLE, we recommend quantifying the different specific antibodies as activity markers and disease prognosis. |
| A | We do not recommend the isolated use of anti-dsDNA antibodies to diagnose a flare of SLE. |
| C | We recommend the joint assessment of the anti-dsDNA antibodies titre and the C3 and C4 complement levels as support to assess activity. |
| A | We do not recommend the isolated determination or monitoring of anti-Sm or anti-RNP antibody levels to evaluate the global activity or risk of nephropathy of SLE. |
| B | We do not recommend determining anti-ribosomal P antibodies as prognostic markers of neuropsychiatric episodes or of general activity of SLE, or in the initial assessment of patients diagnosed with SLE or during its evolution. |
| B | We recommend determining anti-Ro and anti-La antibodies in all women with SLE before planning pregnancy or as soon as an unplanned pregnancy is acknowledged. |
| C | Due to its thrombosis and obstetric complication predictive value, we suggest the periodic combined determination of antiphospholipid (anticardiolipin, lupus anticoagulant and anti-β2-glycoprotein I) antibodies in order to determine their persistence (if positive) or their positivisation with the course of the diseases (if negative). |
| B | We do not recommend using the erythrocyte sedimentation rate as an SLE activity marker. |
| C | We suggest carrying out urine sediment, protein/creatinine quotient in an early morning urine sample, proteinuria in 24-hour urine and serum creatinine, both at the time of diagnosis of SLE and during successive medical visits, to predict the presence and evolution of lupus nephropathy. |
| D | We suggest performing complete routine blood tests to evaluate the existence of anaemia, leucopoenia, lymphocytopenia and thrombocytopenia, both at the time of diagnosis of SLE and during successive medical visits. |

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# 5. General management of systemic lupus erythematosus

## 5.1. Monitoring

### 5.1.1. Clinical monitoring protocol and complementary tests

**Questions to be answered:**

- What is the most recommendable clinical monitoring protocol for people with systemic lupus erythematosus?
- What complementary tests should be carried out on people with systemic lupus erythematosus, and how often, in monitoring and control consultations? Which are the most effective and cost-effective disease activity biomarkers for monitoring systemic lupus erythematosus? Should the 25 (OH) vitamin D levels be monitored as a systemic lupus erythematosus activity marker?

No original studies have been found that assess clinical monitoring protocols in SLE patients. Available recommendations respond to expert consensus.[10,241,242] In the monitoring of SLE patients, apart from the recommended care for the general population, experts recommend including the assessment of the disease activity during each visit, using a validated index, organ damage, comorbidities, possible toxicity of the treatment and HRQoL. The presence of general symptoms and specific signs of the disease activity should be monitored through directed anamnesis and physical examination.[10,241,242]

Experts opinion 4

The symptoms and signs to be compiled, the laboratory data and other additional examinations to be carried out are set out below according to modified table of the EULAR manual, and in agreement with the SLE monitoring EULAR guidelines:[243,244]

**Monitoring of symptoms and signs in SLE**

| |
|---|
| **Anamnesis (patient history):**<br>Joint pain or swelling, Raynaud's phenomenon<br>Photosensitivity, rash, alopecia, mouth ulcers<br>Shortness of breath, pleuritic pain, oedemas<br>General symptoms (depression, fatigue, fever, or weight change) |
| **Physical examination:**<br>Blood pressure*, skin lesions, alopecia, mouth or nasal ulcers<br>Lymphadenopathy, splenomegaly, pericardial or pleural effusions<br>Other features as suggested by clinical history |

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|---|
| **Image/Laboratory:**<br>Haematology with ESR*<br>Biochemistry with lipid profile** and albumin<br>PT/PTT. APL<br>Urine analysis**<br>Serology (anti-DNA*** and complement**)<br>Other tests as suggested by clinical history/symptoms |
| Disease activity index* |
| Side effects of treatment and comorbidities |
| Organ damage index (SLICC/ACR DI): Every year |

Note:* Assess during every medical visit;**: Assess every 3-6 months, if the disease is stable; ***: assess every 3-6 months in patients with active renal disease; ESR: erythrocyte sedimentation rate; PT: Prothrombin time: PTT: Partial thromboplastin time; APL: Antiphospholipid antibodies; SLICC/ACR DI: *Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index.*

The prevalence of CVD increases in SLE patients, not explained by classical cardiovascular factors, although they also present an increase in prevalence of high blood pressure and dyslipemia (variable according to the different studies). Therefore, we recommend assessing smoking habits, the presence of vascular events, physical activity, intake of oral contraceptives or hormone therapies, and family history of CVD at least once a year. Likewise, we recommend examining the blood pressure, the body mass index (BMI) and/or abdomen perimeter once a year, determining cholesterol, (HDL and LDL) and glucose.[245,246] The prevalence of osteoporosis also increases, so we recommend assessing the intake of calcium and vitamin D, the appearance of fractures and practice of regular weight-bearing exercises. The recommendations for osteoporosis screening should be carried out according to the guidelines for post-menopausal women or patients who take glucocorticoids.[10]

Cohort S. 2-

There are few data in literature that permit establishing an optimum frequency for the clinical and analytical monitoring of SLE patients. Apart from four cohort studies that provide certain information about this question,[247-250] we have the recommendations established by consensus among experts in the United States[251] and Europe.[13]

Cohort S. 2+

Gladman *et al*.[247] performed a study on the cohort of the University of Toronto of SLE patients (*Toronto Lupus Cohort*, n=515), with two-year follow-up, in order to establish the optimum frequency of the follow-up visits in these patients. More specifically, information was provided in this study about the frequency of clinical examinations in patients with an average activity index of 2.1 (SLEDAI-2K), in whom new silent isolated findings were detected (proteinuria, haematuria, piuria, low haemoglobin, leucopoenia, thrombocytopenia, high creatinine, positivity for anti-dsDNA antibodies and low complement). In general, new silent isolated characteristics were observed in 5.6% of the visits. These new characteristics were recorded in 24.5% of the patients, over the two-years' follow-up. It was concluded that the interval between the examinations (clinical and laboratory) to detect new silent findings in people with mild or inactive SLE is close to 3-4 months.[247]

Cohort S. 2+

More than 5 years have passed since the publication of this clinical practice guideline, and its validity has not been reviewed

Another study on the same cohort was performed to identify the frequency and the characteristics of the clinical activity with serological quiescence in a large cohort of SLE patients (n=541).[252] Of the 514 patients, 62 (12.05%) presented an episode of clinical activity with serological quiescence, lasting on average for 9.8±6.5 months. Of the 62 patients who presented an episode of clinical activity with serological quiescence, 58 were monitored. Of these 58 patients, nine remained quiescent for 39±23 months. And of the remaining 49, 23 patients became active again, 21 became clinically and serological activity, and the remaining five serologically active but clinically inactive.

Cohort S. 2+

A longitudinal study was carried out on 609 SLE patients in order to determine the frequency of the serologically active clinical remission.[249] Eighty-one patients (13.3%) presented at least one serologically active clinical remission (180 episodes). Of the 106 patients who presented episodes of serologically active clinical remission, 46 (43.4%) presented a clinical flare within one year.

Cohort S. 2+

Along the same line, Steiman *et al*.[250] performed a study with a cohort of 924 SLE patients. 6.1% (56) presented serologically active clinical remission. Of the patients with serologically active clinical remission, 58.9% presented one flare (after 155 weeks on average), 30.4 maintained the serologically active clinical remission (159 weeks), and 10.7% became clinically and serologically inactive.

Cohort S. 2+

According to the recommendations of groups of experts, the frequency of the follow-up visits should be based on the activity and severity of SLE, its complications and evolution. The ACR has recommended a clinical examination frequency of 3-6 months for patients with mild or stable SLE;[251] whilst the EULAR recommends that clinical and laboratory examinations should be carried out on patients without active disease or damage and without comorbidity, every 6-12 months.[13] Patients with active or more severe disease, or with complications related to the treatment, as well as pregnant women will need controls more frequently. More frequent controls may also be required when the immunosuppressant treatment starts to be reduced.[251]

Expert consensus 4

There are some studies that correlate different analytical parameters with the degree of activity of the disease and whose determination could facilitate the monitoring of SLE patients. Even so, the interpretation of many of them in the clinical context, and their relative contribution respect to the traditional parameters, is not clear, and prospective studies are required to assess their usefulness for the diagnosis and monitoring of SLE patients.

Although different cross-sectional studies suggest a correlation between the levels of CRP and the disease activity, its role in the monitoring of SLE is controversial. In two case-control studies performed by Gheita *et al*. with 45 women with SLE compared with 30 healthy women, and by Barnes *et al*. with 213 SLE patients and 134 healthy controls, the former found a significant relationship between the levels of CRP and the disease activity assessed with SLEDAI ($r = 0.67$; $P<0.001$)[253] whilst the latter did not find any correlation ($r= 0.0056$; $P=0.11$).[254]

Case-control study 2+

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In seven cross-sectional studies, that included a total of 1537 different SLE patients, they concluded that there was a significant correlation between the C-reactive protein and different indices, clinical and laboratory measurements that measure the disease activity.[255-261]

Cross-sectional s. 3

The determination of serum parameters of the complement such as CH50, C3 and C4 has limited usefulness to evaluate the degree of the disease activity in SLE patients. Although low levels of CH50 and C3 are associated with a higher degree of activity, the same levels can also be obtained in patients who do not present any clinical activity. Low levels of C3 presented specificity values of 94%, but sensitivity values of 20% in one study.[262]

Cohort S. 3

Ng *et al*., in order to determine the differential predictive capacity of anti-dsDNA and anti-nucleosome antibodies of flares in patients with clinical remission and serological activity, retrospectively analysed a group of 37 SLE patients. The result was that the presence of anti-nucleosome (r= 0.57; *P*=0.007) is a better predictor of future flares than anti-dsDNA, which was not associated in this case (r= 0.13; *P*=0.58).[263] However, the heterogeneity of these autoantibodies and their lack of standardisation does not permit generalising these results, making them difficult to apply in daily clinical practice.[264]

Observational S. 2++

There are some data about the association of the deficit of 25-HO vitamin D in SLE patients and the disease activity. In the study of Thudi *et al*., the eight patients with 25-OH vitamin D deficiency had a worse functional state, with a higher combined index than the 29 patients without 25-OH vitamin D deficiency: 44.7±5.4 nmol/L (13.4-67.4) vs. 25.6 ± 3.2 nmol/L (5.0-55). However, patients with positive ANA test and 25-OH vitamin D deficiency (n=3) had lower levels of anti-dsDNA than the 22 patients with positive ANA test and normal 25-OH vitamin D: 33±14 vs. 365±110 IU; *P*=0.0069).[265]

Cross-sectional S. 3

In the study of Yeap *et al*. on 38 patients, the average levels of 25-OH vitamin D were higher in patients with low disease activity (SLEDAI < or = 10), compared with those of high disease activity (SLEDAI > or = 11): 23,09±4,54 ng/mL *vs*. 19.95±4.10 ng/mL.[266]

Cross-sectional S. 2-

Likewise, Petri *et al*., in a longitudinal study on 1006 patients from the *Hopkins Lupus Cohort*, followed-up for 128 weeks, observed that an increase of 20 ng/ml in the level of 25-HO vitamin D was associated with a decrease of 21% in the likelihood of having a high activity score in the disease index, and a decrease of 15% in the likelihood of having clinically important proteinuria.[267] However, the magnitude of the associations was not so clinically relevant (reduction of 0.22 points in the SELENA-SLEDAI score and of 25% in the protein/creatinine ratio in urine).

Observational S. 2+

**Summary of evidence**

| | |
|---|---|
| 4 | No original studies have been found that assess clinical monitoring protocols in SLE patients. The majority of the recommendations respond to expert consensus.[10,241,242] |

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| | |
|---|---|
| 4 | Experts recommend assessing smoking habits, the presence of vascular events, physical activity, intake of oral contraceptives or hormone therapies, and the family history of CVD at least once a year. Likewise, they also recommended examining blood pressure, BMI, and/or abdomen perimeter once a year, and determining lipids and glucose.[245,246] |
| 4 | Among the complementary tests, there is expert consensus about requesting a haemogram, biochemistry with renal profile and urine analysis during the monitoring, together with another series of biomarkers.[10] |
| 2+ | The interval between the examinations (clinical and laboratory) to detect new silent analytical changes in patients with mild or inactive SLE could be close to 3-4 months.[247] |
| 2+ | Clinically quiescent and serologically active patients have a risk of around 50% of presenting a clinical flare during the following months.[249,250] |
| 4 | The recommendations of ACR and EULAR experts place the frequency of examinations in stable patients at between three and 12 months, although they recommend shorter intervals for patients with active disease or patients in whom the immunosuppressant treatment has started to be withdrawn.[13,251] |
| 3 | The value of CRP in the monitoring of SLE patients is controversial, but studies indicate that it could be useful to assess the disease activity in SLE.[253,255-216,268,269] |
| 3 | Serum parameters such as CH50, C3 and C4, although routinely used in clinical practice, provide controversial results in their association with the activity in SLE patients.[262] |
| 3 | The relationship between the levels of 25-OH vitamin D and the SLE activity is clinically little relevant.[265,266] |
| 2+ | In 6-13% of SLE patients, the disease is clinically quiescent but serologically active, with between 43 and 59% of the cases developing a flare after one year.[249,250] |
| 2+ | The correlation between clinical manifestations and laboratory tests is heterogeneous. These findings explain the need to monitor both the clinical and the serological aspects in SLE patients.[248] |

**Recommendations**

| | |
|---|---|
| √ | We suggest performing a comprehensive, clinical and analytical assessment at the time the diagnosis of SLE is confirmed. |
| √ | In the monitoring protocol of patients with SLE, we suggest monitoring the activity of the disease, organ damage, comorbidities (including the presence of vascular risk factors) and the possible toxicity of the pharmacological treatment. To this end, the clinical interview, physical examination, blood pressure testing will be used, as well as basic analytical determinations that will include complete blood test, biochemical analysis with renal profile and urine analysis, complement and determination of anti-dsDNA antibodies. |
| √ | In patients with active SLE, the monitoring intervals should be adapted to the clinical situation and they are, therefore, variable. |
| √ | If the disease is in clinical and analytical remission, we suggest monitoring every 6-12 months, depending on the disease evolution time and the treatment intensity. |

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| | |
|---|---|
| C | In clinical quiescent patients with maintained activity analytical criteria, we suggest closer monitoring, every 3-4 months, at least during the first years. |
| D | We suggest periodically determining the levels of 25 (OH) vitamin D in SLE patients, above all if there is a presence of osteoporotic fracture risk factors. |
| D | We suggest the regular use of activity biomarkers such as levels of C3 and C4 and of anti-dsDNA in SLE patients, above all in those with renal involvement. |

## 5.1.2. Disease assessment tools

**Questions to be answered:**

- Are the available standardised tools effective to assess the disease in clinical practice? Should they be used in normal clinical practice?

SLE is a very heterogeneous disease, its activity fluctuates over time and irreversible damage may appear during the course of the disease. This variability means that pateints with SLE require standardised and objective monitoring of the disease, with validated instruments to determine the degree of activity and the degree of damage. We recommend assessing the activity of SLE between every 15 days and six months, depending on the previous clinical-analytical data, the risk of flare and changes in the treatment, evaluating the accumulated damage every year.[270]

Meticulous monitoring of all the aspects of the disease and the use of validated and reliable instruments to measure the activity and damage associated with the disease become even more necessary, if in addition to this situation of the patient with SLE, we add the current and future availability of new drugs, both immunosuppressants and biological therapies to treat the disease.[270]

**Disease assessment tools:**

The simplest tool to evaluate the activity in daily clinical practice is the physician global assessment.[271] However, this is subject to considerable intra –and inter– observer variability.[272]

Over the last few years, some activity indices have been developed in SLE, and validated and translated into different languages. The aim of their development has been to serve as objective tools for cohort studies of SLE patients.[273] They also help standardise the monitoring of SLE and allow a more accurate evaluation of the disease, facilitating therapeutic decision-making, although their usefulness in daily clinical practice is less established.[270]

A list of tools developed to evaluate the activity of SLE is given below:

– *European Consensus Lupus Activity Measurement* (ECLAM)[271]
– *Systemic Lupus Activity Measure* (SLAM)[78]
– Reviewed SLAM (SLAM-R)[274]
– *Systemic Lupus Erythematosus Disease Activity Measure* (SLEDAI)[78,275]
– *Mexican Systemic Lupus Erythematosus Disease Activity Index* (MEX-SLEDAI)[275,276]
– Modified SLEDAI (SLEDAI-2K)[276]

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- *Safety of Estrogens in Lupus Erythematosus National Assessment* (SELENA)-SLEDAI[277]
- *British Isles Lupus Assessment Group* (BILAG)[78,278]
- Revised BILAG (BILAG-2004)[279,280]
- *Systemic Lupus Activity Questionnaire* (SLAQ)[281]
- *Lupus Activity Index* (LAI)[282]

All of these scales and indices have proven to be valid to measure the activity of SLE. It is known that they are also able to predict damage and mortality.[283] There are studies that compare some of these tools:

Gladman *et al*.[284] compared (n=8) the capacity of the SLEDAI, SLAM and BILAG indices to assess changes in disease activity. The results showed that the three indices detected differences between the patients ($P$=0.0001) and that they can be considered comparable, although SLEDAI seems to be more sensitive to change in activity between visits ($P$=0.04). — Cohort S. 2+

In another study with 23 patients and 40-week follow-up, Ward *et al*.[153] compared the validity and sensitivity of five SLE activity indices: SLAM, SLEDAI, LAI, BILAG, ECLAM. It was concluded that all the instruments were valid to measure activity, that the ECLAM detected recovery better than the other indices and that the SLEDAI was the least sensitive to change. The authors emphasised that, despite the BILAG being the only activity index by organ systems, the limited availability of the computer tool required for it to be used correctly, and the need for specific training for its correct application, make its implementation in daily practice little feasible. — Cohort S. 2+

Along the same line, Fortin *et al*.[274] recruited 96 SLE patients to assess the capacity of the SLAM-R and SLEDAI indices to detect clinically meaningful changes. Results showed that, although both are sensitive to change, SLAM-R is more sensitive than SLEDAI. — Cohort S. 2+

There is currently no agreement on the use of one single activity index. According to expert consensus of biological therapies in SLE of the SER (Spanish Rheumatology Society), the SLEDAI in its updated versions, SLEDAI-2K or SELENA-SLEDAI, which is a numerical, brief and easy to apply index even for non-experts, can be the instrument of choice. Other numerical global indices, such as ECLAM or SLAM-R can also be valid.[270] — Expert consensus 4

Castrejon *et al*. performed a SR with the purpose of determining the most appropriate indices to assess the disease activity and damage. They concluded that, despite the many validated indices to assess SLE patients, there is not sufficient evidence to determine which was the most appropriate. So, it appears that BILAG and SLEDAI are the two indices with the most complete validation and also the ones most commonly used; however, they present moderate reliability and little sensitivity to change.[285] — SR 2+

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**Structural damage indices:**

Damage in SLE refers to irreversible and clinically relevant lesions, attributable to SLE, to the treatments used or to the associated complications. It is, thus, an index that aims to measure sequelae.

The only available instrument to measure damage is the SLICC/ACR DI, which was developed and validated[286] after consensus reached among an extensive group of rheumatologists concerning which characteristics of SLE should be considered to assess permanent damage.[285]

This index has been used in morbidity and mortality studies in different population groups. Different studies have shown that early damage in SLE measured with SLICC/ACR DI has a prognostic value, and high scores in SLICC/ACR DI have been associated with mortality in the majority of studies.[284]

Rahman *et al*., in a prospective study with 263 patients and at least 10 years' follow-up, showed that early damage measured at the onset by means of SLICC/ACR DI, was associated with a higher mortality rate. 25% of patients who showed damage in SLICC/ACR DI in their initial assessment died during the first 10 years of their disease, compared with just 7.3% of those who had no early damage ($P$=0.0002). Furthermore, they showed that these patients had more likelihood of having kidney damage ($P$=0.013) and a tendency to more CVDs ($P$=0.056) compared with patients who were alive.[287] Cohort S. 2+

Another study was performed on 80 SLE patients (70 women, 10 men), with at least five years' follow-up, to determine the predictive capacity of SLICC/ACR DI on survival.[288] At the start of the study, 37 patients did not present any damage (SLILCC/ACR ID = 0). Of the remaining 43, 25 had a score of one (SLICC/ACR DI= 1) and 18 had a score of more than one (SLICC/ACR DI > 1). Fourteen patients died within seven years following the start of the study. Seven of them formed part of the group of 18 patients with a score of more than one in SLICC/ACR DI, with respect to the seven who died out of the 62 patients who presented less or no damage ($P$<0.01). The mortality RR with SLICC/ACR DI ≥ 2 was 3.4 (95% CI: 1.5-14.4) with a predictive value of 38%. Only one of the 37 patients who did not present damage at the start of the study died during the observation period, opposed to the 13 patients who died out of the 43 cases with initially registered damage ($P$<0.001). Cohort S. 2++

The SLICC/ACR DI is an instrument that has proved to be valid, reliable and reproducible and that has little inter-observer variability,[289] which allows it to be used in multi-centre clinical research. Two instruments derived from it, the questionnaires Lupus *Damage Index Questionnaire* (LDIQ) and *Brief Index of Lupus Damage* (BILD), have been developed over the last few years and they are being validated. These are self-administered to the patient so that they can be used normally in daily clinical practice.[290-292] It should, however, be taken into account that the measurements of SLICC/ACR DI cannot be alternated with the self-administration instruments.

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**Summary of evidence**

| | |
|---|---|
| 2+ | Studies that analyse different activity indices show that all the instruments are valid to measure activity and that they are comparable, although some present greater sensitivity to change than others.[274] |
| 4 | There is currently no agreement about the use of one single activity index.[285] According to the expert consensus of the SER on biological therapies in SLE, SLEDAI in its updated versions, SLEDAI-2K or SELENA-SLEDAI, which is a numerical, brief and easy to apply index even for non-experts, can be the instrument of choice. Other numerical global indices, such as ECLAM or SLAM-R can also be valid.[10,270] |
| 2++/2+/2- | The SLICC/ACR DI is a validated instrument to measure accumulated damage in patients with SLE, which has also proven to be predictive of survival in the long term.[287,288] |
| 2+ | The patient self-administered questionnaires, LDIQ and SLILD, could be useful and reliable alternatives to SLICC/ACR DI in assessing damage related to SLE but they cannot be used alternatively with SLICC/ACR DI.[290-292] |

**Recommendations**

| | |
|---|---|
| √ | SLE patients require the highest standardised and objective monitoring of their disease as possible, so we suggest the use of validated instruments to quantify the degree of activity, accumulated damage and quality of life. |

## 5.1.3. Predictive factors of flare or increase in disease activity

**Questions to be answered:**

- What are the analytical or biological markers that can predict a lupus flare or which factors have been associated with an increase in activity of systemic lupus erythematosus?

The response for predictive factors of flares or associated with an increase in activity ofSLE (of those that are normally used in daily clinical practice), is based on seven cohort studies and on one post-hoc analysis of a clinical trial. Two cohort studies have been included for patients with LN.

| | |
|---|---|
| One study assessed flares in SLE for 12 months as well as predictive clinical changes of the disease activity, with monthly clinical and analytical monitoring. A significant increase of flares in asymptomatic patients was obtained in those with high titres of anti-dsDNA (OR= 3.2; 95% CI: 1.7-5.7) and low levels of C3 (OR= 1.8; 95% CI: 1.3-4.5).[293] | Observational S. 2++ |
| In order to identify the prevalence of both the sociodemographic and serological risk factors of flares, another study (n=299) found that low titres of C3 (OR= 2.57; 95% CI: 1.45-4.55; *P*=0.0019) and of C4 (OR= 2.75; 95% CI: 1.54-4.90; *P*=0.0009) and high titres of anti-dsDNA (OR= 2.24; 95% CI: 1.28-3.92*)*; *P*=0.070) were predictive factors of flares.[294] | Observational S. 2++ |

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A *post hoc* analysis[295] to identify the predictive factors of flares (moderate to severe) in 502 SLE patients included in two phase III RCTs, which compared standard therapy (immunosuppressant and anti-malarial drugs) plus placebo or belimumab,[296,297] found that low levels of C3 (<90 mg/dl, *P*<0.001) and C4 (<16 mg/dl, *P*<0.01), and high titres of anti-dsDNA (≥200 UI/ml, *P*<0.001) are predictors of flares. High values of C-reactive protein (>3 mg/l, *P*<0.01), proteinuria (≥0.5 g/24 h, *P*<0.001) and B lymphocyte stimulator (Blys) (≥2 ng/ml, *P*<0.001) also seem to predict flares in SLE.

Another one-year follow-up study (n=53) also showed that a reduction of C3 and C4 is associated with flares, measured by modified LAI (OR 1.9; *P*=0.01) and SLAM (OR 1.9; *P*=0.03), C4 defined by SLAM (OR 2.2; *P*=0.007). Likewise, an increase in renal activity measured through the LAI subscale [C3 (OR 2.2; 95% CI:1.4-3.5; *P*=0.001); C4 (OR= 1.9; 95% CI:1.1-3.4; *P*=0.02)] and haematological activity [C3, white cell count (OR= 2.2; *P*=0.002), platelet count (OR= 2.5; P=0,0006), or haematocrit count (OR= 4.6; *P*=0.003)] [C4, haematocrit (OR= 3.2; P=0.009)] were also related to flares.[215]

Observational
S.
2++

In the LUMINA multi-centre cohort study,[298] the factors listed below were found to be sociodemographic predictors of high activity: being young (OR= 0.986; 95% CI: 1.094-2.938; *P*=0.0046), being Hispanic or Afro-American (OR= 1.793; 95% CI: 1.094-2.938); *P*=0.0204 and OR = 2.310; 95% CI: 1.507-3.540; *P*=0.0001, respectively), lacking health insurance (OR= 1.609; 95% CI: 1.167-2.205; *P*=0.0001), abnormal health-related behaviour (*P*=0.0001), low social support (OR= 1.065; 95% CI: 1.000-1.205, *P*=0.0481), feeling unprotected (*P*=0.0001) and a high previous SLAM-R score (*P*=0.0001). On the other hand, a high level of anti-dsDNA was found to be a serological flare marker (OR = 2.248; 95% CI: 1.638-3.085; *P*=0.0001).

Observational
S.
2++

In contrast to the above, a prospective study performed in Canada with people with quiescent SLE (n=609) did not find any association of the development of flares with complement levels or with the anti-dsDNA level. They only observed association was with higher doses of glucocorticoids and immunosuppressants (*P*=0.01) and with the presence of vasculitis (*P*=0.04).[249]

Observational
S.
2++

Ng *et al*., in order to determine the differential predictive capacity of anti-dsDNA and anti-nucleosome antibodies of flares in patients with clinical remission and serological activity, retrospectively analysed a group of 37 SLE patients. The result was that the presence of anti-nucleosome (r= 0.57; *P*=0.007) is a better predictor of future flares than anti-dsDNA, which was not associated in this case (r= 0.13; *P*=0.58).[263] However, the heterogeneity of these autoantibodies and their lack of standardisation does not permit generalising these results, making them difficult to apply in daily clinical practice.[264]

Observational
S.
2++

In patients with LN, two studies identified predictive factors related to flares or increase of renal activity:

To assess the relationship between levels of C3 or C4 in serum and renal flares in SLE, Birmingham *et al*. performed a prospective study on a cohort of patents with LN (n=71). The result was that the reduction in the C4 levels (*P*=0.002) was associated with flares in the following two months, and the reduction in C3 levels marked the presence of renal flare (*P*<0.001).[299]

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Moroni *et al*. performed a six-year follow-up prospective study on patients with LN in remission (n=228) to assess the role of immunological tests in monitoring LN activity. It was observed that the best renal flare predictor was the anti-C1q antibody (OR= 12.7; 95% CI: 6.3-25; *P*=0.0005), above all in the proliferative form. On the other hand, the multivariate analysis showed that the best prediction of renal flares was obtained by the combination of anti-C1q (OR= 11.8; 95% CI: 4.9-8.1; *P*=0.0005) with C3 (OR= 2.99; 95% CI: 1.5-5.8; *P*=0.0005) and C4 (OR= 3.3; 95% CI: 1.7-6.5; *P*=0.0005).[300] However, the EULAR 2012 guidelines on management of LN advise against its use due to a lack of standardisation.[12]

Observational S. 2++

The urine levels of certain proteins have been correlated with the appearance of renal flare in observational studies, as is the case of RANTES and M-CSF[301], TWEAK (*TNF-like weak inducer of apoptosis*),[302] with neutrophil gelatinase-associated lipocalin[303] or urine monocyte chemoattractant protein-1.[304]

Observational S. 2++/2+

Likewise, a longitudinal study found association between the level of urinary T-bet expression of ARNm and of GATA-3 in clinically quiescent SLE patients, and the risk of flare-up of the disease.[305]

In another one-year follow-up study on SLE patients (n=267) it was observed that the high levels of two chemokines in serum (IP-10 and MIP-3B) were able to predict flares in the following year, and were correlated with the disease activity.[306]

Observational S. 2++

All these new biomarkers are still being researched and at the present time, they do not satisfy sufficient conditions to be used as such as in daily clinical practice.

**Summary of evidence**

| | |
|---|---|
| 2++ | Low C3 and C4 levels and high anti-dsDNA titres are predictive factors of flare and are associated with an increase in activity in patients with SLE.[293-295,298] |
| 2++ | Reduction in C3 and C4 is associated with flares and an increase in renal and haematological activity.[215] |
| 2++ | Antinucleosome antibodies seem to predict future flares in patients with SLE better than the levels of anti-dsDNA antibodies.[263] |
| 2++ | In patients with LN, the reduction of C4 and C3 is associated with flares in the following two months299 and anti-C1q is a predictor of renal flare.[300] |
| 2++ | Six markers not used in clinical practice have been identified as predictors of renal flares or associated with an increase in activity in patients with LN[304]: high urinary level of RANTES and M-CSF[301], high urinary level of urine monocyte chemoattractant protein-1, of renal flare; high urinary level of TWEAK of LN and severity of renal impairment (Schwartz, 2099); high urinary level of T-bet ARNm (*type 1 T-helper cell transcription factor*), of lupus flare[305]; high levels of IP-10 and MIP-3B chemokines in serum, of flares in the following year, and they with the disease activity[306]; and neutrophil gelatinase-associated lipocalin of renal flare and impairment.[303] |

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**Recommendations**

| | |
|---|---|
| B | When following-up SLE patients, we recommend using periodic determinations of C3, C4 and anti-dsDNA as predictors of active disease. |
| C | Although anti-C1q and antinucleosome antibodies are probably more sensitive and specific as lupus nephritis markers, the current lack of standardisation advises against their routine use for this purpose. |

# 5.2. General therapeutic approach

## 5.2.1. Therapeutic objectives

**Questions to be answered:**

- What are the therapeutic objectives in people with systemic lupus erythematosus?

SLE is a disease with unknown aetiology, variable course and prognosis, characterised by periods of relative quiescence and others when the symptoms flare up, possibly involving one or several organs.[251] The actual complexity of the disease leads to the need to develop therapeutic objectives and general guidelines to increase the disease care quality.

Mortality in SLE patients is greater with respect to what can be expected in the general population of a similar age and gender.[307] There are a series of factors related to the bad prognosis of SLE, so it can be inferred that actions that manage to minimise them will have a favourable prognostic impact. Unfortunately, this impact has not been verified in clinical studies.

A recent MA (12 studies, n=27,123) has confirmed a risk of death that is three times greater in the population with SLE compared with the general population. Among the specific causes of mortality, significant increases in the risk of death were observed in cardiovascular-caused events (meta–*standardised mortality ratio* [SMR] = 2,62; 95%; 95% CI: 1.83-4.04), infections (meta–SMR= 4.98 (95% CI: 3.92-6.32), and renal disease (SMR= 7.90 (95% CI: 5.50-11.00). It is noteworthy, however, that the last two associations were based on two and one studies, respectively.[307]

MA of observational S.
1+

In different observational studies, the development of irreversible organ damage was associated with greater mortality in SLE patients.[28,288,308] A recent MA of observational studies published between 1950 and 2010 concluded that renal and neuropsychiatric damage are the main determining factors of damage on the mortality of SLE patients.[309]

Cohort S.
2+

MA of observational S.
1+

A recent SR of 50 observational studies has identified several damage predictors,[310] noteworthy among which are lupus activity, above all renal and neuropsychiatric condition.

SR of observational S.
2++

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In the recent GLADEL cohort study, an increase in irreversible damage was observed, associated both with mild-moderate flares (OR= 1.91; 95% CI: 1.28-2.83; *P*=0.001), and severe flares (OR= 2.62; 95% CI: 1.32-5.24; P=0006).[311] The effect on the damage of high blood pressure,[312] of APL[308] and of APS[29] also stands out. Cohort S. 2+

In Sutton's SR, treatment with cyclophosphamide (CPM), azathioprine (AZA) and glucocorticoids was associated with an increase in the risk of damage, whilst the protective effect of anti-malarial drugs should be highlighted.326 With respect to treatments, there is plenty of evidence regarding the damage caused by prednisone, although average daily doses of less than 7.5 mg/day were not associated with damage during the first five years of the disease.[310] For more information, see question 5.2.2.3. Glucocorticoids of section 5.2.2. Treatment Indications

Steiman *et al*. analysed the clinical evolution of 165 patients from the *Toronto Lupus Cohort*, 55 with serological activity (high anti-DNS and/or hypocomplementemia) in clinical remission for two years, compared with 110 controls that did not satisfy the previous criteria. In the subsequent follow-up, the accumulated damage (measured by SLICC/ACR ID) was less in clinically quiescent/serologically active patients than in the controls after three, five, seven and 10 years (*P*<0.001 in all the comparisons). The authors concluded that these results do not support the active treatment of patients with serological activity without clinical activity.[313] Case-control study 2+

Recently, a group of international experts proposed a series of specific objectives in the treatment of SLE.[314] Worthy of note among the basic principles of the recommendations is that the decisions should be taken together by the properly informed patient and his/her physician, with the main objectives of ensuring long-term survival, preventing organ damage and optimising HRQoL by controlling the disease activity, minimising comorbidities and medication toxicity. CPG 4

On the other hand, the SER group, in the consensus document on the use of biological therapies in SLE, highlights, as objectives of the treatment, complete clinical response, understood as the absence of perceived or noticeable clinical activity, stabilisation of the disease, and suspension, or failing this, reduction to minimum doses, of the immunosuppressant and steroid treatment.[270] CPG 4

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**Summary of evidence**

| | |
|---|---|
| 1+ | The risk of death is three times greater in SLE patients compared with the general population, mainly due to infectious and renal cardiovascular causes.[307] |
| 2++/2+ | Irreversible organ damage is the main predictor of mortality in SLE patients,[28,288,308] especially damage that occurs at renal and neuropsychiatric level.[309] |
| 2++/2+ | Lupus flares,[310,311] renal and neurological conditions,[310] high blood pressure,[312] APL[308] and APS[29] are associated with greater damage. |
| 2++ | Treatment with CPM and AZA, and above all, with glucocorticoids increases the risk of damage. Conversely, anti-malarial drugs are a protective factor.[310] |
| 2+ | Serologically active patients in prolonged clinical remission present a favourable evolution and do not require active pharmacological treatment aimed at improving the analytical parameters.[313] |
| 4 | Groups of experts point out that the main objectives of treating lupus are to ensure long-term survival, to prevent organ damage and to optimise HRQoL by controlling the disease activity, minimising comorbidities and drug toxicity.[314] Other objectives are complete clinical response, disease stabilisation and suspension of the immunosuppressant and steroid treatment.[270] |

**Recommendations**

| | |
|---|---|
| B | As the main therapeutic objective in SLE patients, we recommend establishing, the control of perceived or verifiable clinical lupus activity, avoiding secondary irreversible damage both to the actual disease (particularly renal and neurological damage, and cardiovascular events) and to its treatment, above all glucocorticoids (osteonecrosis, osteoporotic fractures, diabetes mellitus, cataracts, etc.), minimising the impact on the patients' quality of life and survival. |
| B | We recommend minimising the risk of infections. |

## 5.2.2. Treatment indications

### 5.2.2.1. Non-biological immunosuppressive treatments

**Questions to be answered:**

- What non-biological immunosuppressive treatments are effective in extrarenal lupus?

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One SR analysed the efficacy and safety of non-biological immunosuppressants in the treatment of extrarenal SLE.[315] The article inclusion criteria were: a) population: adult patients with SLE, b) intervention: treatment with non-biological immunosuppressant, c) comparator: placebo and active comparator, and d) outcome measurement that assesses efficacy and/or safety. The review selected 158 articles for detailed analysis, 65 of which satisfied the inclusion criteria. The conclusions reached were: a) several immunosuppressants have proven their safety and efficacy in extrarenal SLE, b) no specific immunosuppressant can be recommended for each individual manifestation, although CPM should be taken into account for more severe cases, and methotrexate (MTX) could be the first option in the majority of people with moderately active extrarenal SLE, c) myocophenolate mofetil (MMF) has improved extrarenal manifestations in patients with LN, treated with this drug, and d) higher quality RCTs with a larger number of patients are required. SR of RCT and cohort study, 1++

One open RCT analysed the effect of CPM after six months in patients with NPSLE.[316] It compared 37 patients treated with intravenous CPM (200-400 mg/month for six months) and prednisone with 23 patients treated only with prednisone. Clinical improvement, relapses, electroencephalographic improvement and improvement in evoked potentials, were measured. Patients treated with CPM presented statistically significant improvement in all the parameters mentioned compared with the control group ($P$=0.005, $P$=0.005, $P$=0.003 and $P$=0.003, respectively). RCT 1-

Another open RCT analysed the effect of CPM after 24 months in patients with recently established NPSLE.[317] Patients with APS and infections or metabolic disorders were excluded. This RCT compared 19 patients treated with intravenous methyl-prednisolone (MPred) (1 g/day for three days) followed by prednisone (1 mg/Kg/day with posterior reduction of dose) and intravenous CPM (0.75 g/m$^2$/month for 12 months, and afterwards, every three months for one year), with 13 patients treated with intravenous Mpred (3 g/month for four months, followed by 3 g every two months for six months, followed by 3 g every month for 12 months). The response to treatment was measured (improvement ≥ 20% in clinical, serological and neurological parameters). Patients treated with CPM presented a significantly higher response rate than patients from the control group ($P$<0.03). RCT 1+

Another open RCT analysed the effect of CPM after six months on patients with pulmonary hypertension associated with SLE.[318] Patients with pulmonary embolism, pulmonary fibrosis, asthma and chronic obstructive pulmonary disease (COPD) were excluded. This RCT compared 16 patients treated with intravenous CPM (0.5 g/m$^2$/month for six months) with 18 patients treated with enalapril (10 mg/day) The clinical improvement (reduction of limitations caused by cardiac symptoms, assessed by means of the NYHA scale) and the reduction of systolic pulmonary pressure were assessed. Patients treated with CPM presented a statistically significant improvement in both parameters compared with the control group ($P$=0.02, and $P$=0.04, respectively). This study has important limitations noteworthy among them is that the pulmonary hypertension diagnosis was only carried out by echocardiography, the follow–up was short–term, and no final robust variables were used such as mortality. RCT 1-

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Another open RCT analysed the effect after 30 months of two different CPM regimes in people with moderate-severe SLE and lack of response to moderate-high doses of glucocorticoids or immunosuppressants.[319] 26 patients treated with intravenous CPM (0.75g/m$^2$/month for six months and then, every three months for two years) were compared with 21 patients treated with high doses of intravenous CPM (50 mg/kg for four days). The response to the treatment (complete or partial response, without changes or worsening) was measured with the RIFLE index (*Responder Index for Lupus Erythematosus*), not observing significant differences between both groups, in all the main systems affected, or taking each one individually. RCT 1+

One open RCT analysed the effect of AZA after 24 months on people with active life-threatening lupus who had not received > 20 mg/day of prednisone or immunosuppressants during the previous six months.[320] It compared 11 patients treated with AZA (3-4 mg/kg/day) and prednisone (60 mg/day with subsequent modification of dose according to response) with 13 patients treated only with prednisone (60 mg/day with subsequent modification of dose according to response). The clinical improvement and the average daily dose of prednisone were assessed. There were no significant differences between the two groups in any of the parameters mentioned. RCT 1+

Another open RCT compared the effect after 12 months of cyclosporine A (CsA) with the effect of AZA on people with severe lupus who required doses of prednisone ≥15 mg/day and a new immunosuppressant.[321] It compared 47 patients treated with Cs A (1 mg/kg/day with subsequent increase to 2.5-3.5 kg/kg/day) compared with 42 patients treated with AZA (0.5 m/kg/day with subsequent increase to 2-2.5 mg/kg/day). Co-medication was allowed with stable doses of NSAID, anti-malarial drugs and prednisone. The main final outcome measure was the average change in the prednisone dose. The appearance of flares of SLE was also evaluated. Patients from both groups significantly reduced the daily dose of prednisone at the end of the study ($P$<0.001) without there being any significant difference in this reduction when the two groups were compared. There were no differences in the reduction of SLE flares between both groups. RCT 1+

A double-blinded controlled RCT with placebo analysed the effect of MTX after six months on people with lupus with mild-moderate activity, and little renal compromise, who were receiving < 0.5 mg/kg/day of prednisone, and had not received immunosuppressants during the previous four months.[322] It compared 20 patients treated with oral MTX (15-20 mg/week) with 21 patients treated with placebo. Co-medication with prednisone was allowed. The disease activity (SLEDAI), joint pain (analogical visual scale), improvement of arthritis, improvement of skin lesions and reduction in the daily dose of prednisone were assessed. Patients treated with MTX presented a statistically significant improvement in all the parameters mentioned compared with the placebo group ($P$=0.05, $P$=0.05, $P$=0.001, $P$<0.001 and $P$<0.001, respectively). RCT 1++

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Another double-blinded controlled RCT with placebo analysed the effect of MTX after 12 months on people with lupus with mild-moderate activity (SLAM-R ≥8), without renal impairment and who had not received CPM or AZA during the previous four weeks.[323] It compared 41 patients treated with oral MTX (7.5-20 mg/week) with 45 patients treated with placebo. Co-medication was allowed with NSAID, anti-malarial drugs and prednisone. The disease activity (SLAM–R) and reduction of the daily dose of prednisone were assessed. Patients treated with MTX presented a statistically significant improvement in both parameters compared with the placebo group ($P$=0.03, and $P$=0.01, respectively). RCT 1++

A double-blinded controlled RCT with placebo analysed the effect of lefluonomide (LEF) after 24 weeks on people with active lupus (SLEDAI ≥6), prednisone doses of under 0.5 mg/kg/day and without having to receive CPM or AZA.[324] It compared six patients treated with LEF (100 mg/day for three days, and then 20 mg/day) with six patients treated with placebo. Co-medication was allowed with NSAID, HCQ and prednisone (15 mg/day). The disease activity (SLEDAI) was measured, finding a significantly greater reduction in the group treated with LEF compared with the placebo group ($P$=0.02). The levels of proteinuria, anti-dsDNA levels and the daily doses of prednisone were also assessed, finding similar changes between both groups. RCT 1-

One open RCT analysed the effect of CsA after 12 months on patients with moderately active lupus.[325] It compared 10 patients treated with intravenous MPred (1 g/day for three days) followed by prednisone (0.5-1 mg/kg/day with subsequent reduction of dose) and CsA (< 5 mg/kg/day) with eight patients treated only with the same glucocorticoid pattern. The disease activity (SLEDAI) and the average accumulated dose of prednisone were assessed. Patients treated with CsA presented a statistically significant improvement in both parameters compared with the control group ($P$=0.05, and $P$=0.005, respectively). RCT 1-

**Summary of evidence**

| | |
|---|---|
| 1-/1+ | Intravenous CPM with prednisone and MPred is better than glucocorticoids alone in the short and long-term treatment of neuropsychiatric SLE and in the reduction of relapses.[316,317] |
| 1- | CPM improves the functional class of NYHA and reduces systolic pulmonary pressure in patients with pulmonary hypertension associated with SLE.[318] |
| 1+ | The association of AZA with prednisone could reduce the rate of flares in people with severe SLE.[321] |
| 1++ | In people with extrarenal lupus activity, despite traditional treatment, the association of MTX (7.5-20 mg/week) reduces global, joint and cutaneous activity of the disease in the short to medium term (6-12 months) with a glucocorticoid-saving effect.[322,323] |
| 1- | In people with SLE and mild-moderate activity despite prednisone, LEF is more effective than placebo in reducing the disease activity in the short term (six months).[324] |

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| | |
|---|---|
| 1+ | In people with SLE and renal and/or non-renal activity refractory to glucocorticoids, the addition of CsA may reduce the activity or induce remission of the disease in the short term. In this context, CsA is not less effective than AZA in reducing the renal and/or non-renal activity, and both drugs have a glucocorticoid-saving effect in the medium term.[321] |
| 1- | In people with SLE and renal and/or non-renal activity refractory to glucocorticoids, the addition of CsA may reduce the activity and have a glucocorticoid-saving effect in the long term.[325] |

**Recommendations**

| | |
|---|---|
| B | We recommend intravenous cyclophosphamide as first immunosuppressive drug in the treatment of SLE and of severe non-renal manifestations. |
| A | We recommend methotrexate as first immunosuppressive drug in the treatment of non-renal SLE with moderate activity, specially in those cases with cutaneous and joint manifestations. |
| √ | As an alternative, we suggest using other immunosuppressive drugs such as azathioprine, cyclosporine A, leflunomide or mycophenolate for the treatment of non-renal SLE. |

## 5.2.2.2. Anti-malarial drugs

**Questions to be answered:**

- Is the use of anti-malarial drugs indicated in all people with systemic lupus erythematosus? What is the effectiveness, cost-effectiveness and safety of these drugs in preventing flares? Have they got other additional beneficial effects that may justify their generalised use?

Anti-malarial drugs have been used in lupus since the 40s. However, recognition of their broad therapeutic possibilities in patients with lupus, beyond the specific treatment of concrete manifestations, only came about in the last decade. Its basic action mechanism is the increase in intralysosomal pH, which causes an interference with the processing of low-affinity antigens, not affecting the immune response to high-affinity peptides such as bacterial antigens. They are, therefore, able to produce a considerable immunomodulation without immunosuppression.[326] There are three anti-malarial drugs used in patients with lupus: HCQ, chloroquine (CQ) and quinacrine (or mepacrine), the latter not marketed in Spain.

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**Efficacy**

Most of the information published about the effects of HCQ or CQ on SLE patients has been compiled and analysed in the SR of Ruiz-Irastorza *et al*.[327] The few available RCTs were selected, as well as a large number of well-designed observational studies with consistent results, which, in many of the analysed aspects, permitted assessing the degree of evidence, using the MPM system, as high or moderate. More specifically, a high degree of evidence was obtained for reducing the activity in SLE patients, both inside and outside pregnancy, and, very surprisingly, for increasing survival in patients treated with HCQ and/or CQ. Furthermore, the evidence that supports a protective effect against thrombosis and against the appearance of irreversible damage was categorised as moderate. Other possible favourable actions, such as the adjutant effect in the treatment of LN, protection against osteonechrosis, neoplasia or atherosclerosis and the evolution to oligosymptomatic autoantibody-carrier SLE, are supported by a lower degree of evidence, in the majority of the cases due to having been identified in single observational studies.

SR
2++

A multi-centre observational study published after the SR of Ruiz-Irastorza *et al*., confirmed the data related to the increase in survival of SLE patients treated with anti-malarial drugs.[328] Of 1480 patients from the GLADEL cohort, 77% were treated with anti-malarial drugs. Mortality was reduced by 38% in patients treated with anti-malarial drugs,a similar figure to that of previous studies. This study, with its large number of patients, also afforded an additional analysis with highly consistent results that reinforce its validity, as the mortality rate (per thousand patients-month) was progressively reduced with the treatment time with anti-malarial drugs: 3.07 in the non-treated, 3.85 in those treated for less than 11 months, 2.70 in those treated between 12 and 23 months, and 0.54 in those treated for more than two years ($P<0.001$). This study therefore supports the prolonged use of anti-malarial drugs in SLE patients.

Cohort S.
2++

Two studies published in 2009 and 2010 also afford new data about the effect of anti-malarial drugs on protecting against thrombosis in SLE patients.

In the study of Tektonidou *et al*., the variables associated with thrombosis were analysed in 144 SLE patients, asymptomatic APL carriers, and 144 controls with lupus without APL. During the subsequent follow-up (average of 104 months), the months when treatment was received with HCQ were inversely associated with the risk of thrombosis, both in patients with APL (HR=0.99; 95% CI: 0.98-1.00; $P$=0.05) and without APL (HR= 0.98; 95% CI: 0.95-0.99; $P$=0.04).[329]

Cohort S.
2+

In the study of Jun et al, the effect of anti-malarial drugs on thrombosis was specifically analysed in SLE patients. With a study design of cases (n=58 patients with SLE and thrombosis) and controls (n=108 patients with SLE without thrombosis). The use of anti-malarial drugs was independently associated with a reduction in the risk of suffering thrombosis (OR= 0.32; 95% CI: 0.14-0.74). This effect was the same for arterial thrombosis (OR= 0.34, 95% CI: 0.12-0.99) and venous thrombosis (OR= 0.26; 95% CI: 0.07-1.02).[330]

Case and control s.
2+

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Observational studies have also found a protective effect of HCQ against the metabolic syndrome. The cross-sectional study of Sabio *et al*., found a 20% prevalence of metabolic syndrome in 160 SLE patients from the Granada cohort, with less frequency of treatment with HCQ in this subgroup compared with that of patients with SLE without metabolic syndrome (53 v. 74%; p = 0.035).[331] — Cohort S. 2+

The study of Parker *et al*. in the SLICC initial cohort observed a prevalence of metabolic syndrome of 38.2%, 34.8% and 35.4% at the time of entry into the cohort, after one year and after two years, respectively. In the multi-variate analysis, treatment with HCQ during the follow-up period significantly and clinically reduced the risk of suffering metabolic syndrome in a highly relevant manner (OR= 0.27, 95% CI: 0.14 to 0.54).[332] — Cohort S. 2++

In a nested case-control study of 249 patients, Ruiz-Irastorza *et al*. studied the variables associated with serious infections in SLE patients. Treatment with anti-malarial drugs independently reduced the risk of serious infections (OR= 0.06; 95% CI: 0.02-0.18).[333] — Case-control study 2+

In a series of six cases with active SLE (SLEDAI > 5), despite traditional treatment, Toubi *et al*. observed that the addition of mepacrine to the baseline treatment (including HCQ) resulted in a significant reduction of SLEDAI and of the prednisone dose. All of them had joint impairment and 4/6 also had skin impairment. Similar results have been obtained in larger series, but in cutaneous lupus.[334,336] — Case series 3

**Adverse effects**

In the SR of Ruiz-Iraztorza *et al*.[327] the data referring to the global adverse effects show that the toxicity rate by anti-malarial drugs is low and not at all serious, mainly at gastrointestinal and cutaneous level. The suspension rate of anti-malarial treatment due to adverse effects was calculated at 15%, with less likelihood of suspension of the treatment with HCQ than with CQ (HR= 0.62; 95% CI: 0.40-0.96). The level of evidence about the safety of the anti-malarial treatment was qualified as high, in agreement with the MPM scale, with a moderate level of evidence related to the greater global safety of the HCQ compared with CQ. — SR 2++

With respect to retinal toxicity, the increase in the risk of definite maculopathy in patients treated with CQ (2.5%) compared with those treated with HCQ (0.1%) was significant (OR= 25.88; 95% CI: 6.05-232.28; *P*=0.001). Mepacrine has no ocular toxicity.[336]

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A later study of Wolfe & Marmor[337] analysed the database of the *National Data Bank for Rheumatic Diseases* to estimate the risk of retinal toxicity in 3995 patients with SLE and AR treated with HCQ. A risk of 2% was calculated after 15 years' treatment, with a sudden increase in the rate of maculopathy after reaching an accumulated dose of 1000 g of HCQ. However, the generalisation of these data to SLE patients is questionable due to several factors related to the study methodology: 1.- the toxicity data could not be validated individually by expert ophthalmologists; 2.- only 17% of the patients analysed had SLE; 3.- the prevalence of retinopathy in the subgroup of patients with lupus was very low, detecting one single case of retinal toxicity, which represents 0.15%, that is, within the range calculated in the SR of Ruiz-Irastorza *et al*.[327]. Therefore, due to a series of non-identified factors, the risk of retinopathy caused by HCQ is possibly less in patients with SLE than in patients with AR. The actual authors acknowledge that these numbers are not sufficient to specifically analyse the risks of retinal toxicity in SLE patients. Cohort S. 2-

The more recent recommendations of the *American College of Ophthalmology* established a baseline eye examination during the first year of treatment, and every year after five years' treatment, although the control should be started much earlier in patients with maculopathy of another origin or with additional risk factors. With regards to screening techniques, we recommend including sensitive techniques (at least one) such as the spectral domain optical coherence tomography (SD-OCT), retinal autofluorescence or the multifocal electroretinography, together with a 10-2 automated visual field.[238] CPG 4

**Summary of evidence**

| | |
|---|---|
| 2++ | Treatment with anti-malarial drugs decreases the risk of flares in SLE patients.[327] |
| 2++ | Treatment with anti-malarial drugs decreases the risk of irreversible organ damage in SLE patients.[327] |
| 2++/2+ | Treatment with anti-malarial drugs decreases the arterial and venous thrombosis risk in SLE patients, both carriers and non carriers of APL.[327,329,330] |
| 2++/2+ | Treatment with HCQ decreases the risk of developing metabolic syndrome in SLE patients.[331,332] |
| 2+ | Treatment with anti-malarial drugs decreases the risk of serious infections in SLE patients.[333] |
| 2++ | Treatment with anti-malarial drugs increases survival in SLE patients, with a more marked effect as the treatment time increases.[327,328] |
| 2++ | Anti-malarial drugs have low frequency and severity of adverse effects.[327] |
| 2++ | Toxicity of CQ is greater than toxicity of HCQ, specially at retinal level.[327] |
| 2- | The risk of retinal toxicity due to HCQ seems to increase considerably from an accumulated dose of 1000 g.[337] |
| 2++ | Mepacrine has no retinal toxicity.[336] |

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**Recommendations**

| | |
|---|---|
| B | We recommend using anti-malarial drugs as the basic treatment for all SLE patients who have no contraindications for its administration. |
| B | We recommend maintaining indefinite treatment with anti-malarial drugs due to their effects on activity, damage, thrombosis, infections and long-term survival. |
| B | For its greater safety, we recommend hydroxychloroquine instead of chloroquine as the anti-malarial drug of choice. |
| D | We suggest combining anti-malarial treatment with mepacrine and hydroxychloroquine in patients with refractory lupus activity, specially cutaneous, as this may produce synergic effects. |
| D | In patients with retinal toxicity caused by anti-malarial drugs, we suggest replacing hydroxychloroquine or chloroquine by mepacrine (not sold in Spain). |
| D | We suggest active monitoring of retinal toxicity in patients treated with hydroxychloroquine or chloroquine. |
| D | We suggest at least a baseline eye examination during the first year of treatment, and every year after five year treatment, although the control should be started much earlier in patients with maculopathy of another origin or with additional risk factors. |
| D | We suggest including at least one of the most sensitive techniques: Spectral domain optical coherence tomography (SD-OCT), retinal autofluorescence or mutifocal electroretinogram, together with automated visual field 10-2. |

## 5.2.2.3. Glucocorticoids

**Questions to be answered:**

- What is the recommended dose of glucocorticoids to keep the disease controlled with an assumable risk of adverse effects?

Glucocorticoids, more specifically prednisone and MPred, are commonly-used drugs in SLE patients. They are used both in acute flare situations and in remission maintenance. Surprisingly, and despite SLE figuring as an indication on the technical datasheet, and the generalised prescription of glucocorticoids throughout more than 40 years, there are no quality studies that enable us to establish with certainty the relationship between the different doses, efficacy and safety. In other words, the majority of the recommendations about the use of glucocorticoids in SLE are based on experience and above all, on normal practice.[339] Unfortunately, the short and long-term toxic potential of glucocorticoids is enormous, and this may highly significantly condition the evolution of SLE patients, often as much or even more than the actual disease.[339]

Recent pharmacological studies have shown that glucocorticoids exercise their actions through two different types of pathways, genomic and non-genomic. In the genomic pathways, the immunomodulating effects are inevitably accompanied by undesired actions on the bone, lipid and glycaemic metabolism, among others, which are responsible for complications such as osteoporosis, osteonecrosis, diabetes or Cushingoid appearance, for example.[340] In contrast, non-genomic pathways are free from this type of adverse effects, with a much more intense and faster anti-inflammatory action.

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Recent pharmacological studies show that the activation of one pathway or another is mainly the consequence of the administered dose.[341] Depending on the degree of saturation of the relative receptors, the doses of prednisone have been divided into low (up to 7.5 mg/day), medium (up to 30 mg/day) and high (more than 30 mg/day). The saturation of the genomic pathway is close to 100% with doses of prednisone of over 30 mg/day, which suggests that as from this dose, there is already a high degree of toxicity but without a substantial increase in its anti-inflammatory effect with additional increases. The activation of non-genomic pathways starts to be noticed as from 100 mg/day, with a maximum effect at more than 250 mg/day, which would also point to greater efficacy and less toxicity of the pulse therapy above 100-250 mg/day. In addition, the non-genomic activity of MPred is several times greater at the same dose as the dose of prednisone.[341] Another aspect that the basic studies do not support is the use of prednisone doses adapted to weight (mg/kg/day). It still has to be elucidated if the available clinical studies corroborate or not these pharmacological research data.

**Efficacy**

| | |
|---|---|
| In one 24-week non-inferiority RCT, Zeher *et al*.[342] compared the effect of MMF combined with two different patterns of prednisone in patients with proliferative LN. All of them received three initial pulses of MPred followed by MMF. This pattern was combined in 42 patients with prednisone at initial doses of 1 mg/kg/day (varying between 45 and 70 mg/day), whilst this dose was reduced to half in 39 patients. In both groups, prednisone was reduced gradually, until a maintenance dose of 5 and 10 mg/day, and 5 and 2.5 mg/day were reached, respectively. Outside protocol, around half the patients in both groups received HCQ and IECA. The full remission rate after 24 weeks was 19% and 20.5% (P=0.098 for non-inferiority). Similar partial remission rates and reduction of SLEDAI and BILAG were seen in both groups. The main limitation of this study is the small sample number, with the subsequent loss of power, preventing full statistical significance from being reached in the main objective of the study (remission at 24 weeks). | RCT<br>1- |
| The RCT of Yee *et al*.[343] compared two groups of 16 patients with LN, one treated with CPM and MPred pulses (initially intravenous and later oral), every 3-4 weeks, and another with continuous oral therapy with CPM followed by AZA. The first group received reduced doses of oral prednisone (initial of 0.3 mg/kg/day with progressive reduction to 0.05-0.1 mg/kg/day), whereas the second group was treated with initial prednisone of 0.85 mg/kg/day (maximum of 60 mg/day) with reduction up to 0.11 mg/kg/day in week 52. No significant differences were found between the two groups in terms of mortality or evolution to terminal renal insufficiency. Regarding the evaluation of the efficacy of the different doses of pred, this study has the important limitations of its small sample size and of the different administration method of the other drugs. | RCT<br>1- |

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The observational study of Fischer-Betz *et al*.[344] analysed the clinical course of 40 patients with first episode of LN treated with 12 intravenous CPM pulses, and who did not receive prednisone on a routine basis but rather depending on the extrarenal manifestations of lupus (that is, not depending on the severity of the nephritis). 37.5% of the patients received HCQ. The initial average dose of prednisone was 23.9 mg/day. After 24 months, full remission was reached in 62.5% of the patients, with an additional 20% of partial responses. When comparing the evolution of patients who received an initial dose of prednisone ≥ 20 mg/day compared with < 20 mg/day, the full response rate was 52.5% and 71.4%, respectively (*P*=0.37). The infection frequency was similar in both subgroups. In the long term, the risk of relapses was similar (dose < 20 mg/day v. ≥ 20 mg/day, HR= 0.73 (95% CI: 0.25-2.12, *P*=0.57). The greatest limitation of this study was that the patients in the high-dose group had a greater frequency of class IV LN, although the sum of the patients with classes III and intravenous was identical.

Cohort S. 2+

The observational study of Ruiz-Irastorza *et al*.[345] compared a group of 15 patients with biopsied LN treated with initial medium doses of prednisone (mean 20 mg/day) with 30 historical controls, paired for age, gender and type of LN, who received high doses (mean 50 mg/day). The majority of patients in both groups (86%) were treated with CPM. 100% of the patients in the group of medium doses also received HCQ opposed to 33% in the high dose group. The pulse MPred dose was also greater in the group of medium doses. Likewise, prednisone was reduced much more quickly in the group of medium doses, with average until reduction to 5 mg/day of 16 weeks v. 87, *P*<0.001). Consequently, the average daily dose of prednisone calculated during the first six weeks of treatment was 9 mg/day v. 25 mg/day, respectively (*P*<0.001). The full or partial response rate after six months was 87 v. 63%, respectively (*P*=0.055). In the long term, full remission was reached in 100% of the patients with medium doses, v. 70% in the group with high doses (*P*=0.013). The number of renal re-flare was also less in the group treated with medium doses (13 v. 47%, *P*=0.008). Nine patients in the high-dose group suffered long-term renal complications (four kidney transplants, three haemodialysis, two deaths due to active nephritis) opposed to none in the medium dose group (*P*=0.02). The authors highlight that the combined treatment with HCQ and MPred, in addition to the immunosuppressants, permits reducing the dose of oral prednisone without losing efficacy in the medium or long term.

Cohort S. 2+

The RCT of Illei *et al*.[346] compared the efficacy of a pattern of intravenous CPM (N=27), intravenous MPred (n=27), or the combination of both (n=28), together with prednisone at initial doses of 0.5 mg/kg/day with reduction as from four weeks in patients with class EV LN. The response rate was greater in the combined therapy group: 81 v. 63% in the CPM group (*P*=0.24) v. 33% in the MPred group (*P*=0.002).

RCT 1+

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The RCT of Mackworth-Young *et al*.[347] included 25 people with severe active SLE in agreement with the opinion of the responsible physicians. 1 g intravenous MPred (n=12) was administered for three consecutive days, or placebo (n=13) followed by prednisone at doses of 40-60 mg/day, and at the discretion of the responsible physician, HCQ, mepacrine, AZA and/or CPM. Results showed a tendency towards a better evolution of patients treated with MPred after 14 days (improvement of 100% v. 70%), which was not maintained in subsequent follow-ups, up to six months. There were no differences between either group in terms of the dose of prednisone, use of other immunodulators/ immunosuppressants or adverse effects. The authors highlight the initial efficacy of MPred in severe cases without a greater frequency of undesired effects.

RCT
1-

The SR of Badsha and Edwards[348] included case series and RCTs of patients treated with pulses of MPred, published between 1966 and 2002. Their results showed greater efficacy of the combined MPred/CPM therapy than both drugs in monotherapy in patients with LN. In case series, the efficacy of the MPred pulses in different manifestations of SLE has been communicated, such as arthritis, rash, pleurisy, thrombocytopenia, NPSLE, alveolar haemorrhage and transverse myelitis, among others. The efficacy of doses of 1 g for three days does not seem to be greater than that of smaller doses of 500, 400 or even 100 mg.

SR
1-

**Toxicity**

In the 24-week non-inferiority RCT of Zeher *et al*.[342] the frequency of adverse effects attributable to the study medication was 19% vs. 10.3%, respectively ($P$=0.26). The infection rate was 57.1% in the standard dose group v. 35.9% in the group with reduced dose ($P$=0.056).

ECA
1-

In the observational study of Ruiz-Irastorza *et al*.[345] on patients with NL also commented in the previous section, the respective rate of adverse effects attributable to glucocorticoids in the groups treated with medium and high doses of prednisone was 7 v. 67% ($P$<0.0001). Statistically significant associations were found between global toxicity by glucocorticoids and adverse metabolic effects, and the accumulated dose of prednisone after six months (HR= 1.4; 95% CI: 1.17-1.65 and HR= 1.38; 95% CI: 1.14-1.66, respectively; between osteonecrosis and the daily initial dose of prednisone (HR= 1.03; 95% CI: 1.01-1.3); and between osteoporotic fractures and the weeks receiving doses of prednisone of over 5 mg/day (HR= 0.1; 95% CI: 1,00-1,02). The MPred pulses were not associated with the presence of toxicity attributable to glucocorticoids.

Cohort S.
2+

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

Gladman *et al*.[248] studied the impact of damage attributable to glucocorticoids on an initial cohort of 73 patients with at least 15 years of follow-up. The damage was quantified by means of the validated scale, SLICC/ACR DI, and the association with glucocorticoids was classified as definite (ocular and musculoskeletal items), possibly (cardiovascular, peripheral arterial, neuropsychiatric and diabetes items), or independently (renal, pulmonary, gastrointestinal and cutaneous items, premature gonadal failure and cancer). 87.7% of the patients received glucocorticoids, at a maximum average dose of 37.7 mg/day. The average score of SLICC/ACR DI increased from 0.33 after six months to 1.99 after 15. 49% of the new accumulated damage after 15 years was considered to be definitely secondary to glucocorticoids, with an additional 31% that was probably associated.

Cohort S. 2-

The *Hopkins Lupus Cohort* study of Zonana–Nacach *et al*.[349] analysed the influence of glucocorticoids on the appearance of new damage in 539 patients. 85% of the patients had been treated with prednisone, 21% with high doses. The accumulated dose of glucocorticoids was significantly associated with an increase in the risk of osteoporotic fractures, osteonecrosis, cataracts, diabetes mellitus, coronary artery disease, pulmonary fibrosis and cognitive impairment/psychosis. The accumulated dose of prednisone increases the risk of osteoporotic fractures, cataracts and coronary artery disease between 1.7 and 2.5 for every 10 mg/day for 10 years). High doses of prednisone, defined as ≥ 60 mg/day for two months, increased the risk of osteonecrosis and cerebral vascular disease by 20%. The MPred pulses were only associated with a greater frequency of psychosis.

Cohort S. 2++

In a second study from the same cohort the appearance of first damage was analysed, measured by SLICC/ACR DI, in 525 people recently diagnosed with SLE.[350] The main independent variable was the accumulated dose of prednisone, categorised into five levels: 0 mg/month, >0-180 mg/months, > 180-360 mg/month, > 360-540 mg/month and > 540 mg/month. The appearance of damage, adjusted for confusion variable including SLE activity, was significantly associated with higher doses of prednisone than 180 mg/month, or the equivalent to 6 mg/day. Specific damage subtypes were not analysed in this study.

Cohort S. 2+

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

In the observational study of Ruiz-Arruza *et al*.[351] they have recently analysed the relationship between treatment with glucocorticoids and both general and specific damage after five years, in 230 SLE patients. The total accumulated dose of prednisone during the first four years was calculated, and a categorical variable was created with three levels depending on the average daily dose calculated: 0 mg/day, ≤ 7.5 mg/day and > 7.5 mg/day, that is, no steroid treatment, low doses and medium-high doses according to the classification of Butgereit *et al*.[341] The analyses were adapted for variables such as age, gender and disease activity (SLEDAI) and presence of LN. Association was found between the accumulated dose of prednisone and the total score of SLICC/ACR DI after the fifth year (*P*=0.001), as well as with the increase of SLICC/ACR DI from baseline to the fifth year (P=0.02). Patients with higher doses of prednisone than 7.5 mg/day had a greater risk of suffering damage than those not treated with prednisone (OR= 5.39; 95% CI: 1.59-18.27), whilst the risk was not greater in those treated with doses ≤ 7.5 mg/day (OR= 1.65; 95% CI: 0.53-5.10). Similar results were obtained in relation to the risk of suffering damage attributable to glucocorticoids (cataracts, diabetes, osteoporotic fractures, osteonecrosis) in patients treated with > 7.5 mg/day v. those not treated (OR= 9.9; 95% CI: 1.1-84) whilst no differences were found between those treated with ≤ 7.5 mg/day and those not treated (OR= 1.7; 95% CI: 0.17-17). No relationship was found between damage and treatment with MPred.

Cohort S.
2++

In a nested case-control study of 249 patients, Ruiz-Irastorza *et al*. analysed the variables associated with serious infections in SLE patients.[333] Prednisone was the only immunosuppressant treatment with a significant statistic. The average dose in patients with infection was 7.5 mg/day, opposed to 2.5 mg/day in those without infections (*P*< 0.01). The daily dose of prednisone (in mg/day) was an independent factor of greater risk of serious infections (OR= 1.12; 95% CI: 1.04-1.19).

Case-control study
2++

Finally, the retrospective study of Badsh *et al*.[352] compared the efficacy and safety of two MPred pulse patterns, one consisting in 3-5 g administered in three days (n=29) and another in which a dose of less than 1-1.5 g was administered (n=26). Around half of the patients had LN. Neuropsychiatric impairment and alveolar haemorrhage were the other two most frequent indications. The efficacy of both patterns was similar in terms of reducing the score of SLEDAI and the doses of oral prednisone. However, the high dose pattern was associated with a higher risk of suffering severe infections (OR= 3.34; 95% CI: 1.29-8.65).

Cohort S.
2-

**Summary of evidence**

| | |
|---|---|
| 1-/2+ | Treatment with medium doses of prednisone (≤ 30 mg/day) obtains a response rate that is similar, at least, to treatment with high doses in patients with LN.[342-345] |
| 2+ | Long-term renal prognosis seems to be better in patients with LN treated with medium doses of prednisone (≤30 mg/day), MPred pulses, HCQ and CPM compared to patients treated with high doses of prednisone and CPM.[345] |

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| | |
|---|---|
| 1+ | The combination of PMred pulses and CPM in the induction treatment of LN improves the efficacy of both drugs separately.[346] |
| 1+/1- | MPred pulses improve the short-term response in patients with lupus activity.[347,348] |
| 2++/2+/2- | Treatment with glucocorticoids is associated with irreversible damage.[248,349-351] |
| 2++/2+ | Doses of prednisone below 6 mg/day do not cause clinically relevant irreversible damage.[350,351] |
| 1-/2++ | Treatment with glucocorticoids increases the risk of infections in a dose-dependent manner.[333,342] |
| 2++ | MPred pulses do not produce serious adverse effects or irreversible damage.[349,351] |
| 1-/2- | MPred pulses at reduced dose (< 1g x three days) have a similar effect with a reduced risk of infections.[348,352] |

**Recommendations**

| | |
|---|---|
| B | We suggest not exceeding a dose of 30 mg/day of prednisone in the treatment of patients with lupus nephritis. However, the dose should be personalised. |
| √ | In general, we recommend not exceeding a dose of 30 mg/day of prednisone in other SLE manifestations. However, the dose should be individually assessed for each patient. |
| B | In serious flares, we recommend coadjuvant treatment with methylprednisolone pulses. |
| C | We suggest a rapid reduction of glucocorticoid doses (prednisone) in order to reach 5 mg/day, within six months at the very latest, trying to complete withdraw as soon as possible. |
| B | If necessary in maintenance treatments, we recommend that the prednisone dose does not exceed 5 mg/day. |
| √ | We suggest the use of methylprednisolone pulses below 1000 mg, although we cannot recommend a specific dose. |

## 5.2.2.4. Biological therapies

**Questions to be answered:**

- Which biological therapies are effective and safe in people with systemic lupus erythematosus?

Belimumab was the first biological agent to be specifically approved for use in SLE. Its approval was based on two RCTs.[296,297] Patients with severe kidney and CNS impairments were excluded from this study. The main variable in both trials was the percentage of patients who responded based on the SLE *Responder Index* (SRI), a compound index created for these studies and defined by a reduction of the initial value ≥ 4 points in the SELENA-SLEDAI scale; with no worsening of the disease, measured by the PGA; and no new BILAG A score of major organs and no more than one new BILAG B.

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In the first pivotal RCT published (BLISS 52), 867 SLE patients were assigned to the three treatment groups: belimumab 10 mg/kg (n=288), 1 mg/kg (n=290) or placebo (n=287).[296] The response rates of belimumab (dose of 1 and 10 mg/kg) were significantly greater than placebo after week 52 (51 and 58% v. 44%, O = 1.55; 95% CI: 1.10-2.19); *P*=0.0129 and OR= 1.83; 95% CI: 1.30-2.59; *P*=0.0006 respectively). Compared with patients assigned to the placebo group, those who received belimumab 1 mg/kg presented a significant reduction of the disease activity in week 52, measured using the SLEDAI scale (53 v. 46%, OR= 1.51; 95% CI: 1.07-2.14; *P*=0.0189). Reduction in the 10 mg belimumab group was 58% (OR= 1.71; 95% CI: 1.21-2.41). RCT 1++

The second of the pivotal RCTs (BLISS 76) was performed on 819 SLE patients to determine the efficacy of belimumab (1 mg/kg, n=275 and 10 mg/kg, n=271) compared with placebo (n=273) on the activity of SLE.[297] The response rate after 52 weeks of belimumab (doses of 10 mg/kg) was significantly greater than placebo (43.2 v. 33.5%, *P*=0.017). The response rate in the group that used the dose of 1 mg/kg was 40.6% (*P*=0.089). Likewise, compared with patients assigned to the placebo group, those who received belimumab 10 mg/kg presented a significant reduction of the disease activity in week 52, measured using the SLEDAI scale (46.5 v. 35.3%, *P*=0.006). However, in week 76, no significant differences were found respect to placebo when SRI was evaluated. RCT 1++

In both studies (BLISS 52 and BLISS 76),[296,297] the basic treatment may be a limitation of practical applicability, due to their considerable variability: 42 v. 5% with immunosuppressants, medium dose of prednisone of 13 mg/day v. 9 mg/day, 70 v. 46% of patients with more than 7.5 mg/day of prednisone, 64 v. 61% with anti-malarial drugs. The percentage of patients who received combined treatment with prednisone, HCQ and immunosuppressants is not specified in either of the two trials. Noteworthy is the high percentage of participants without anti-malarial drugs and, above all, without immunosuppressants, considering that these are patients with SELENA-SLEDAI ≥6, which reflects at least a moderate lupus activity. We can say, therefore, that many patients included in both studies, were receiving suboptimal treatment when they were randomised.

Although both trials achieved a higher response rate with 10 mg/kg of belimumab, in general, the results of BLISS 76 are less convincing, and the differences in results between belimumab and placebo in BLISS 52 are more robust. In any case, the low response rate in week 52 is surprising; under 60 in all the branches of both studies, that is, at least 40% of the patients treated with different combinations of prednisone, HCQ, immunosuppressants and belimumab, continued to be active after one year's treatment.

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Three *post-hoc* analyses of the aforementioned pivotal studies obtained the following: RCT 1+

- Belimumab seems to have an especially beneficial effect with a statistically significant difference in contrast to placebo in cutaneous manifestations (10 mg/kg, $P<0.001$) and joint manifestations (1 mg/kg, $P=0.02$).[353]

- Belimumab presents greater therapeutic benefits than standard therapy in serologically active patients or with a high activity level (S-SLEDAI≥10).[354]

- The safety profile of belimumab was good in the RCTs without a significant increase in the adverse effects compared with placebo and this was corroborated in long-term follow-up without having observed an increase in side effects.[355]

In agreement with the results of these pivotal studies, the specific indication for the use of this agent, which is included in technical datasheet and for which the approval of the different international agencies has been achieved, is of lupus with moderate or severe activity that does not respond to standard treatment and that is not primarily due to a LN or to a complication of the CNS. This type of not so well-defined indication has created certain problems when transferring it to daily clinical practice. For a better definition of the indications of belimumab in Spain, consensus documents have been published by the Spanish Rheumatology Society (SER)[270] and by the Systemic Autoimmune Disease Development Group (GEAS) of the Spanish Internal Medicine Society.[356] CPG 2++

In the recommendations of the SER, the panel recommends the use of belimumab in adult patients with active SLE, with positive auto-antibodies, and a high degree of activity of the disease despite standard treatment. It is considered that patients with non-major refractory clinical manifestations (such as arthritis and cutaneous impairment) and with analytical activity data seems to be the most adequate clinical scenario for the use of belimumab. The use of belimumab cannot be recommended in people with SLE and severe impairment of the CNS and/or severe LN.

The concept of standard treatment required before considering the addition of belimumab is described in somewhat more detail in the GEAS recommendations.356 The recommendation for use is in people with clinically active SLE and with sustained positivity to ANA, especially if they also have positive anti-nDNA antibodies and/or hypocomplementemia with:

1. Lack of response after at least three months' treatment including an anti-malarial drug, prednisone and at least one immunosuppressant at an adequate dose, or

2. Need for prednisone at a dose of 7.5 mg/day or more in order to maintain the remission, despite anti-malarial drugs and at least one immunosuppressant, or

3. Contraindication for the use of the clinically indicated immunosuppressants due to toxicity or having surpassed the recommended accumulated dose.

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RTX, although not approved for use in SLE, is the biological agent regarding which more experience has been accumulated. Numerous observational studies with more than 800 patients have shown positive effects of RTX both on controlling lupus activity, assessed with standardised activity indices, and on the response of many different types of clinical manifestations such as arthritis, cutaneous impairment, nephritis, nervous system disorder, or haematological disorders. More specifically, the best-founded organ-specific indications are about arthritis and thrombotyopenia.[357]

Observational
S.
2+

With some variations between studies, the response percentage in all cases varied between 60 and 90%, it being noteworthy that in the immense majority of the cases these were patients who had been refractory to treatment with normal immunosuppressants in these cases. Some studies even showed that RTX can be effective at lower doses that those normally used. Thus, one study showed a good clinical response of thrombocytopenia, using RTX doses of 100 mg358 and in another study a good control of global disease activity assessed by BILAG was obtained, with a treatment protocol that included a single infusion of RTX of 500 mg.[359]

Of all the clinical manifestations, the cutaneous ones have had the poorest response rates. However, in the Spanish cohort, LESIMAB, with 132 refractory patients, a high response rate was achieved in patients with cutaneous impairment (90%)[360] In another two studies, a compilation of cases from literature with 162 patients, and a Mexican cohort with 56 patients, response rates of around 30% were reported.[361,362] However, a work has been published very recently with longitudinal follow-up of 17 patients with cutaneous manifestation that did not respond to normal treatment, in which case a response rate was achieved in 53% of the cases, although this figure is still below the figures commonly reported for other types of manifestations.[363]

In any case, all these studies have been uncontrolled, with different methodological designs (cohorts, historical on record data, etc) and very heterogeneous in terms of the characteristics of the patients included. All this considerably limits their scientific evidence level.

Two RCTs with RTX treatment in SLE have been performed. One focused on SLE without renal impairment (*Exploratory Phase II/III SLE Evaluation of Rituximab study* –EXPLORER)[364] and another on LN (*Lupus Nephritis Assessment with Rituximab study* –LUNAR).[365] No statistically significant differences were observed in either case between the patients in terms of the different objectives proposed.

The EXPLORER study[264] was conducted in order to determine the efficacy and safety of RTX versus placebo in patients with moderate to severe extrarenal activity of SLE (n=257). No differences were observed between placebo and RTX in terms of the primary efficacy evaluation criteria, including the BILAG response.

RCT
1++

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The LUNAR study[365] was also conducted in order to determine the efficacy and safety of RTX versus placebo, but on this occasion, in patients with class III or ev LN (n=144). No differences were observed, either, between placebo and RTX in terms of the primary efficacy evaluation criteria. The serious adverse events rates, including infections, were similar in both groups. Neutropenia, leucopoenia and low blood pressure occurred more frequently in the RTX group. RCT 1+

However, it is important to point out that in both trials, the comparison group received active treatment with proven efficacy for the different manifestations that were treated, and that this made it more complicated to establish significant differences, with respect to the group in which the treatment targeted by the trial was added, unless very large samples of patients were used, or especially refractory people were selected. These conditions are very difficult to achieve in SLE. If, in addition to this, we add the well-known clinical heterogeneity of the disease and the limitations of the different assessment methods in this disease, we can explain the failure of these RCTs, at least to a certain extent.[366] However, different sub-analyses of the LUNAR study show data in favour of the efficacy of this drug in this clinical context, such as the numerically relevant differences in the percentage of those who responded within the subgroup of Afro-American patients (70% in the group with RTX v. 45% in the control group; $P$=0.02), statistically significant differences in favour of the group with RTX in the reduction of anti-DNA antibody levels, in the increase of C3 and C4 levels, or a smaller percentage of patients who required therapeutic rescue with CPM in this same group (0 v. 11%, $P$=0.006).

In this sense, a recently published SR, including 362 patients, reinforces the idea that RTX is effective in cases of refractory LN.[367] In addition, both in the different open studies and in the RCTs, RTX has presented a good safety profile. SR

There are very few experiences of use in SLE patients, outside technical datasheet, of other biological therapies that are currently on the market and that are indicated in other rheumatic diseases. Therapy with TNF blockers has always led to doubts in SLE due to the effects observed by these agents in patients with AR, consisting in induction of ANA, anti-DNA and induction of lupus symptoms. In a study in which the long-term evolution of 13 patients treated with infliximab was reviewed, good results were observed in nephritis and arthritis but doubts arose about safety in long-term treatments.[368] Case series 3

A recent observational study of the cohort of the Vall d'Hebron Hospital analysed the efficacy of etanercept (added to the regular treatment) on 43 patients with refractory lupus arthritis (of whom 33% also had refractory serositis and 16% had a history of LN). There was articular clinical remission in 90% of the patients after six months and in 100% of the cases of pleurisy, without significant differences (neither improvement nor worsening) in renal parameters. The mean SLEDAI significantly dropped from eight to two. Nineteen patients presented adverse effects, two of whom were considered serious, without any case of severe flare-up of SLE.[369] Cohort s. 2-

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Abatacept has been tested in two RCTs, phases II and II/III in SLE without renal impairment and, more recently, in another RCT on LN, without reaching the primary objectives in either of the two cases.[364,370] However, post-hoc analyses of the first trial have suggested a possible positive effect on arthritis. RCT 1+

In a subsequent analysis, using the response criteria used in other studies (*Aspreva Lupus Management Study* -ALMS, LUNAR and *Abatacept and Cyclophosphamide Combination: Efficacy and Safety Study*–ACCESS), it was observed that the response rates were greater in the treatment groups than in the control groups. The greatest differences were obtained with the use of the LUNAR (complete response rate of 6% in the control group, compared with 22% and 24% in the abatacept groups).[371]

One of the RCTs was carried out to assess treatment with abatacept in SLE patients with no vital risk, and polyarthritis, discoid lesions, pleurisy and/or pericarditis (n=170).[364] The proportion of new BILAG A/B flares over 12 months was 79.7% (95% CI: 72.4-86.9) in the abatacept group and 82.5% (95% CI: 72.6-92.3) in the placebo group (treatment difference -3.5; 95% CI: -15.3-8.3). In the post hoc analyses it was observed that the effect of the treatment was more noticeable in patients whose primary manifestation of SLE was polyarthritis at the start of the study (treatment difference -28.3;95% CI: -46.1-10.5). The frequency of the adverse events was comparable in the abatacept and placebo groups (90.9% versus 91.5%), but severe adverse events were more frequent in the abatacept group (19.8 opposed to 6.8%).

The other RCT was also conducted to compare the efficacy and safety of abatacept in patients with SLE and LN (n=289). There was no difference between the treatment groups in the time that elapsed until confirmed full response or in the proportion of individuals with confirmed full response in the 52 weeks after the treatment.[370] RCT 1++

Finally, with respect to tocilizumab, with the exception of one isolated case reported of clinical response after the use of tocilizumab, there is only one open study in phase I with 10 patients where an improvement in the clinical activity indices was observed.[372] Case series 3

## Summary of evidence

| | |
|---|---|
| 1++ | Belimumab is effective in people with active SLE who do not respond to standard treatment (excluding patients with nephritis or severe CNS impairment).[296,297] |
| 1+ | Belimumab has proven to be effective in the treatment of musculoskeletal and cutaneous manifestations of SLE.[353] |
| 2++ | Those SLE patients not responding to a treatment after at least three months that includes anti-malarial drugs, prednisone and at least one immunosuppressant at adequate dose, are considered candidates to treatment with belimumab, Candidates are also those who need prednisone at a dose of 7.5 mg/day or more to maintain remission, despite anti-malarial drugs and at least one immunosuppressant, or in the event of contraindications for the use of clinically indicated immunosuppressants because of toxicity orbecause the recommended accumulated dose has been exceeded.[356] |

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| | |
|---|---|
| 2+ | RTX is effective in people with active SLE refractory to standard immunosuppressive treatment including severe renal and neurological condition, although in the two RCTs conducted until now (in active SLE without renal impairment or of CNS, and in LN) the primary objectives were not reached.[358-365] |
| 3 | Infliximab has proven to be quite effective in lupus patients with refractory nephritis and arthritis, although with a narrow margin of safety.[368] |
| 2- | Etanercept has been effective in patients with refractory arthritis and serositis, with no severe adverse effects in the short term, and with no worsening of renal activity.[369] |
| 1- | Abatacept could be effective in lupus arthritis.[364] |
| 3 | Tocilizumab has shown certain benefits in the control of the clinical activity of SLE.[372] |

**Recommendations**

| | |
|---|---|
| A | We recommend belimumab treatment for people with active SLE who have not responded to standard treatment and whose activity is not fundamentally due to renal or neurological impairment. |
| B | We suggest considering as candidates to belimumab treatment those people with active SLE not responding to a treatment for at least three monthsthat includes anti-malarial drugs, prednisone and at least one immunosuppressive drug at adequate dose. We also suggest considering as candidates to belimumab treatment those who need prednisone at a dose of 7.5 mg/day or more to maintain the remission despite anti-malarial drugs and at least one immunosuppressive drug, or contraindication for the use of clinically indicated immunosuppressive drugs for toxicity. |
| C | We suggest administering rituximab in patients with severe renal, neurological or haematological impairment who do not respond to first line immunosuppressive treatment. |
| √ | Nowadays, there is no approved indication for the use of other biological agents in SLE. However, in certain situations where normal therapeutic measures (including the use of belimumab and rituximab) have failed or cannot be used, the use of any one of the following agents could be considered. infliximab (in refractory arthritis and nephritis), etanercept (arthritis and serositis), abatacept (especially in arthritis) and tocilizumab (in patients with bad control of their clinical activity). |

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Serious cases of drug-induced liver injury, including acute liver failure, hepatitis and jaundice, in some cases requiring liver transplantation, have been observed in patients treated with tocilizumab. The frequency of serious hepatotoxicity is considered rare.

For additional information, please consult:
https://sinaem.agemed.es/CartasFarmacovigilanciaDoc/2019/DHPC_Tocilizumab_27062019.pdf

## 5.2.2.5. Immunoglobulins

**Questions to be answered:**

- What is the effectiveness and safety of immunoglobulins in treating systemic lupus erythematosus?

The administration of high doses of intravenous human immunoglobulins (Igs) obtained from multiple donors has immunomodulating properties with therapeutic value potential. This is a therapy that is not approved for SLE by the regulating agencies (*Food and Drug Administration*–FDA, *European Medicines Agency*–EMA, Spanish Agency of Medicinal Products and Medical Devices–AEMPS), but it is used quite frequently, above all in situations of severe thrombocytopenia, with favourable results. The rational basis for its use in that situation lies, among other arguments, in the strong pathogenic similarity between ITP, in which the indication for therapy

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with intravenous Igs ha been approved, guaranteed by many RCTs[373] and many of the thrombocytopenia's that appear in SLE. Its mechanism of action is complex and is not well-known, having involved Fc receptor blocking, modulation of the anti-idiotype network, down-regulation of Ig synthesis, expansion of regulatory T lymphocytes, etc.

However, the available evidence on effectiveness and safety of intravenous Igs for the treatment of SLE is very limited.

| | |
|---|---|
| There is only one RCT (n=14) that refers to the treatment of proliferative LN, comparing relative low doses of intravenous Ig (400mg/kg/month) with intravenous pulse of CPM in short-term response maintenance (18 months). No statistically significant differences were found between the two armsof the study.[374] The small number of patients considerably limits the statistical power of this open RCT. Furthermore, the masking method is not specified and there are baseline differences between the two treatment arms (patients treated with CPM were histologically more active), which means a high probability of bias in the design of the study. | RCT 1- |
| Data from observational studies (with maximum of 62 patients and 74 months follow-up), suggest that treatment with intravenous Ig could be effective in patients with some manifestations of refractory active SLE. Complete or partial responses between 63 and 85% cases are described, measured by means of global activity indices (SLAM or SLEDAI) or by organ, as is the case of LN.[375] Treatment with intravenous Ig is associated with a high percentage of relapses after suspending treatment.[376-378] | Observational S. 2- |
| In situations of severe thrombocytopenia, several observational studies with limited number of patients report a rapid platelet response to intravenous Ig, with a large series of 31 treated patients, and with a partial or complete response percentage of 65%, temporary in all cases.[377,379] No comparative studies have been conducted against thrombopoietin receptor agonists, whose use in patients with SLE and severe thrombocytopenia has, to date, been anecdotic. | Observational S. 3 |
| Some authors have found that intravenous Igs are efficient and safe as rescue therapy in a situation of active infection and high activity of SLE, a situation where the intensification of immunosuppressive treatment could entail unacceptable risks.[376,378] | Observational S. 2- |
| The dose or administration schedule has not been established. The usual and most highly recommended dose by international experts is0.4 g/kg/day for five consecutive days.[373,378] However, lower doses (for example, 85 mg/kg/day, three days or 0.5 g/kg one day) may also be efficacious.[376] | |
| Intravenous Igs have an acceptable safety profile when used on patients with active SLE or in haematological complications of SLE. Non-severe infusional reactions are the most common adverse effects, although the available data referring directly to SLE are limited.[375,377,378,380,381] | Observational S. 2- |

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Infusional reactions occur in 0.5 to 3% of the cases, they tend to be mild and may decrease or disappear if an adequate infusion speed is used, and premedication is carried out with anti-histamines and/or paracetamol, although there is no scientific evidence at all about this latter measure. Patients with IgA deficit who possess antibodies with anti-IgA isotypes may suffer anaphylactoid reactions (not mediated by IgE), which are minimised with low IgA preparations. The most frequently reported severe adverse effects are thrombosis, acute kidney failure due to osmotic tubular lesion, but these are rare, however. The kidney failure risk factors identified to date are stage 2-4 chronic kidney disease, the simultaneous use of diuretics or nephrotoxic drugs, diabetes, obesity, hypovolemia or being 65 years old or more. With regards to thrombosis, the presence of added thrombosis risk factors or high concentration of the preparation, as well as a past history of cardiovascular events have been suggested as risk factors. Empirically, thromboprophylaxis tends to be recommended in these situations. In general, the use of 5% preparations is recommended, at least in the first infusion.

Other very occasional complications include aseptic meningitis, respiratory distress of the adult, etc.

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## Summary of evidence

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|---|---|
| 1- | Intravenous Ig could be efficacious as maintenance therapy in lupus nephritis.[374,375] |
| 3 | Intravenous Igs may be efficacious in patients with severe thrombocytopenia associated with SLE, being potentially useful in active bleeding situations, due to their rapid action onset, although their effects are temporary in the majority of the cases.[379] |
| 2- | Intravenous Igs have an acceptable safety profile when used on patients with active SLE or haematological complications of SLE.[378,380] |
| 2- | The use of intravenous Ig is not associated with an increase risk of acute infection.[378,380] |
| 4 | The inherent risks with the use of intravenous Igs may be reduced if the risk factors associated with potential adverse effects are considered and certain preventive measures are applied, such as adequate infusion time.[381] |

## Recommendations

| | |
|---|---|
| D | The use of intravenous immunoglobulins would be justified in severe immune life-threatening thrombocytopenia due to active bleeding or when surgical intervention is required or haemorrhagic risk procedure. |
| D | We suggest taking the necessary measures to reduce the toxicity risk: adequate infusion rate, avoiding products with high saccharose content, ruling out immunoglobulin A deficiency and carefully considering the risk-benefit balance. We suggest considering the use of thromboprophylaxis with heparin if thrombosis risk factors exist, guaranteeing adequate hydration. Likewise, in patients with associated renal failure risk factors, we suggest watching over the renal function during the days following the infusion. |

| | |
|---|---|
| √ | Intravenous immunoglobulins could also be used in patients with high activity whose major organs are compromised in the presence of or suspected severe infection that contraindicates or substantially limits immunosuppressive treatment. |
| √ | We suggest administering the dose of intravenous immunoglobulins of 0.4 g/kg/day for five consecutive days. However, lower doses (for example, 0.5 g/kg one day) may also be effective, except in the case of thrombocytopenia. |
| √ | We do not recommend the use of intravenous immunoglobulins as maintenance treatment in any of the manifestations of LSE, as there are other therapeutic alternatives with more consolidated effectiveness and lower cost. |

## 5.2.3. Adverse effects and monitoring guidelines for immunosuppressive and biological treatments

**Questions to be answered:**

- What are the complications and adverse effects of the most usual biological and immunosuppressive treatments of systemic lupus erythematosus? Which are the most advisable monitoring guidelines?

The description of the adverse effects of the usual treatments of lupus has been grounded in the SR performed by Pego-Reigosa *et al*.[315] Other information sources have been extracted from RCTs that compared several alternatives both in extrarenal and renal lupus. The adverse effects of anti-malarial drugs and glucocorticoids are discussed in section 5.2.2 Treatment Indications.

The monitoring of the adverse effects is mainly based on the recommendations of EULAR[382] and the SR of Schmajuk *et al*.[383]

**Adverse effects**

**Cyclophosphamide**

| | |
|---|---|
| A SR was published about the adverse effects of CPM on people with non-renal SLE, and 19 studies have been reviewed in which CPM was used in patients with extrarenal lupus or LN.[315] Heterogeneously, a relationship was found between treatment with CPM and cervical dysplasia and damage, although the main association was with early ovarian failure.[315] | SR 1+ |
| In comparison with glucocorticoids,[346,384-386] the main adverse effects of CPM in patients with LN were amenorrhoea, infections, neoplasia and hospitalisations, but with no statistically significant differences. | RCT 1+ |
| CPM has more adverse effects at gastrointestinal level and of ovarian failure than tacrolimus in Asian origin patients with LN.[387] | MA 1+ |
| The review of Henderson *et al*.[388] is the most important with respect to the comparison of MMF with CPM in patients with LN. The risk of ovarian failure (RR= 0.15; 95% CI: 0.03-0.80; *P*=0.03) alopecia (RR= 0.22; 95% CI: 0.06-0.86; *P*=0.03) and leucopoenia (RR= 0.49; 95% CI: 0.28-0.88; *P*=0.02) was significantly less than in the CPM group. However, diarrhoea was significantly more frequent in the MMF group (RR= 2.53; 95% CI: 1.54-4.16; *P*=0.0003). | SR 1+ |

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In other studies that compared CPM with MMF in patients with LN, there are no conclusive data about the toxicity of CPM although it seems that it may produce a greater risk of infections.[389-391] RCT 1+

The safety profile of CPM is similar to that of oral cyclosporine.[389,392,393] RCT 1+

Among the studies that compared AZA with CPM in patients with LN, no significant differences were found in terms of adverse effects.[394-396] RCT 1+

**Azathioprine**

Evidence about the use of AZA in extrarenal SLE is limited. Only one RCT has been published with few patients (n=24) that showed a greater risk of hepatic toxicity if the dose of AZA was ≥ 200mg/day.[315] RCT 1+

With respect to LN, the most important reference is the review of Henderson *et al*.[388] which found no differences with respect to the tolerance of AZA compared with CPM, cyclosporine or MMF in patients with LN. SR 1+

The tolerance of AZA seems to be similar to that of tracrolimus.[397] RCT 1+

In a retrospective study of Naughton *et al*.[398] the toxicity of AZA was assessed with respect to the presence of polymorphism related to the reduction of the activity of the methyltransferase thiopurine enzyme, observing a greater risk of serious adverse effects in homocygous patients. The evidence is moderate, as the study was performed in a cohort of 120 patients with SLE, polymorphism was identified on seven patients, and only one of these patients was homocygous; this patient had severe medullar aplasia during treatment with AZA. Cohort S. 2+

**Leflunomide**

There is little evidence about the safety of LEF in the treatment of SLE. In the pilot study of Tam *et al*.[324] (n=12) the efficacy and safety of LEF was compared with placebo for 24 weeks. There was only a temporary rise in transaminases, high blood pressure and leucopoenia. RCT 1+

In the longitudinal study of Chan *el al*.[389] the efficacy and safety of LEF was assessed (1 mg/kg/day) in a cohort of 110 patients with SLE was compared with CPM (0.5 g/m$^2$). Major adverse events, including infection, alopecia and high blood pressure, were similar in both treatment groups.

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### Mycophenolate Mofetil

It may produce non-dose-dependent adverse effects, particularly in the digestive system. Its adverse effect profile is acceptable with few dropouts after 12 months' treatment. RCT 1+

Its use is advised against during pregnancy.[242]

In the study of Zeher *et al*.[342] MMF plus the standard dose of glucocorticoids favoured more infections (57.1 v. 39.1%, *P*=0.056) and herpes zoster 16.7 v. 0%, *P*=0.012) than MMF plus low doses of glucocorticoids. The tolerance of MMF is similar to that of tacrolimus.[399] RCT 1-

### Cyclosporine

There is little evidence about the safety of cyclosporine in the treatment of SLE. The most frequent adverse effects are high blood pressure and impairment of the renal function (in 20% of the cases) and hypertrichosis (approximately in one third of the patients).[315] RCT 1+

### Biological therapies

The two pivotal trials of belimumab[296,297] included safety-related results within their objectives. In the study of Furie *et al*.[297] the adverse effects were considered to be a main objective and after 24 weeks' follow-up, severe adverse events (infections, laboratory anomalies, malignant tumours and deaths) were comparable between the groups. Likewise, in the other pivotal study of Navarra *et al*. the adverse effects were similar between both groups (placebo *vs* belimumab).[296] RCT 1++

Later on, a post hoc analysis of Wallace *et al*.[355] corroborated the data mentioned above.

Two RCTs have been performed on patients with SLE with RTX treatment. One of them focused on SLE without renal impairment (EXPLORER study)[364] and the other on LN (LUNAR study).[365]

In the EXPLORER study the frequency of adverse effects was similar in both groups (36.4 v. 37.9% in placebo and RTX, respectively); there were no differences either with respect to the reactions related to infusion, cardiac effects and infections, although more cases of grade 3 and 4 neutropenia occurred in the RTX group (7.7 vs. 3.4%). RCT 1++

In the LUNAR trial, the serious adverse events rates, including infections, were also similar in both groups. Neutropenia, leucopoenia and low blood pressure occurred more frequently in the RTX group. RCT 1+

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## Monitoring for adverse effects

The review of Schmajuk *et al*.[383] concluded that the following recommendations on monitoring other commonly used drugs in SLE are mainly based on expert consensus: SR 1++

1) Azathioprine: execute a blood and platelet count every four to 12 weeks, or every one or two weeks if there is a change in dose. Every six months, perform a control of creatinine. If renal clearance decreases, the dose of AZA should be reduced. Monitor hepatic enzymes every 12 weeks and, if there are abnormalities, modify the dose. It is recommended to determine the activity of the Thiopurine methyltransferase.
2) Cyclophosphamide: monthly urine analyses during treatment or indefinitely, every three to six months, due to the possibility of haemorrhagic cystitis and urothelial neoplasia, which are more frequent in patients with oral CPM. Annual PAP test for screening cervical cancer.
3) Methotrexate: platelet count, serum creatinine, hepatic enzymes every eight weeks and every two to four weeks during the first three months if there is a change in dose. Albumin every eight or 12 weeks. Biochemical analysis every eight weeks. Alkaline phosphatase every 12 weeks. There is not a clear recommendation about carrying out thorax radiography in the prevention of pneumonitis. Some groups suggest executing hepatitis B and hepatitis C serologies before starting with this therapy.
4) Mycophenolate mofetil: blood and platelet count every 12 weeks or every week for the first month.

## Summary of evidence

| | |
|---|---|
| 1+ | In one SR they conclude that CPM is associated with accumulated damage, development of intraepithelial cervical neoplasia, urothelial neoplasia and with ovarian failure.[315] |
| 1+ | In the treatment of LN, MMF appears as a treatment with a better adverse effect profile than oral or intravenous CPM.[242,387] |
| 1++ | The safety profile of the most usual biological therapies in the treatment of SLE (RTX or belimumab) is favourable and similar to placebo.[296,297,355,364,365] |
| 1++ | There are specific recommendations to monitor the therapies used in SLE, although the majority of them are based on opinions of groups of experts. |

## Recommendations

| | |
|---|---|
| B | To monitor haematological and hepatic toxicity of immunosuppressive drugs, we recommend carrying out complete blood tests and hepatic biochemical analyses at intervals of one to three months. |
| B | In patients treated with cyclophosphamide, we recommend active surveillance of bladder cancer through an urine analyses in order to detect microhaematuria. This surveillance should not cease after stoping the treatment. |
| D | We recommend determining the activity of the thiopurine methyltransferase enzyme or its polymorphisms before start the treatment with AZA. |

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## 5.2.4. Indication for therapeutic aphaeresis

**Questions to be answered:**

- What is the effectiveness and safety of therapeutic aphaeresis in treating systemic lupus erythematosus?

The majority of studies published on the effectiveness and safety of therapeutic aphaeresis in SLE are merely observational; many are not controlled and have a small sample size. In the majority, they assess the efficacy of adding different aphaeresis procedures to normal therapy (glucocorticoids or CPM in the case of patients with a more active disease). Furthermore, the heterogeneity of the procedures and patients makes it very complicated to extrapolate the results to the population of our guideline.

To compare the efficacy of three different treatments (standard treatment, standard treatment with plasmapheresis and standard treatment with MPred) in patients with class IV LN proven through biopsy (n=18), an RCT was performed.[400] No differences were observed in the disease remission rates in the different treatment options. RCT 1+

In another RCT, they compared the efficacy of standard therapy (prednisone plus CPM), with standard therapy plus plasmapheresis in 46 patients over the age of 16 with SLE, with renal biopsy. However, they did not observe any differences in the worsening rates or remission of the disease, either global or renal. The data tendency analysis showed that no additional benefit could be obtained in the group of patients treated with plasmapheresis. Therefore, despite obtaining significant results in laboratory parameters (reduction of 20% in C3 and C4 concentrations after two weeks' therapy with plasmapheresis, $P<0.05$), this benefit did not lead to relevant clinical results.[401] RCT 1++

Eighteen SLE patients with class III or IV renal biopsy were randomly assigned to receive six sessions of CPM alone or combined with three sessions of plasmapheresis (60 ml/kg) per day for each cycle of CPM.[402] It was observed in the results of this study that the levels of serum albumin and C3, and the SLAM scores improved in both groups ($P=0.003$, $P=0.02$, $P=0.01$) respectively), and the level of anti-DNA in patients with plasmapheresis ($P=0.025$). RCT 1++

To assess the effect of the therapeutic plasma exchange compared with sessions of reinfusion without plasma exchange, 20 SLE patients were randomly assigned to each one of the procedures.[403] Sixteen of the 18 patients who completed the study improved or remained stable, with no differences between the plasma exchange group and the reinfusion group. The plasma exchange generated a significant reduction in IgG, IgM, IgA levels and circulating immune complexes ($P<0.01$ for each measurement); these measurements returned to the baseline levels after four weeks' treatment. RCT 1++

One RCT was conducted in order to assess the efficacy of two different immunoadsorption columns (2.500 ml, IMPH-350 v. Ig-Therasorb) in 20 patients with active SLE (>15 SLAM points or an increase > 5 in three months, or moderate to severe impairment of organs).[404] RCT 1+

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The scores in the disease activity (SLAM) decreased in the IMPH-350 group from 14.3 ± 5.6 at baseline, to 9.2 ± 6.2 after one month, and to 9.4 ± 3.9 after six months. In the Ig-Therasorb group they went from 18.3 ± 5.5 to 11.2 ± 7.6 after a month and from 9.2 ± 2.9 after six months. Five of 10 patients in the IMPH-350 group and 8/19 in the Ig-Therasorb group satisfied the treatment response criteria.

The feasibility and safety of the treatment with extracorporeal immunoadsorption was assessed in a small cohort conformed by 10 patients over the age of 18 with SLE, with a disease index (SLEDAI) >3 points and VRT-101 laminin antibody levels of >0.4 (nine women, one man, average age of 36.2 years).[405] Observational S. 2+

After treatment, a statistically significant decrease in the serum level of laminin VRT-101 antibodies was detected (reduction of 38.75%, $P$=0.009). A total of 11 adverse reactions were documented in seven patients, none of whom requested removal from the study.

Some observational studies have obtained improvements in symptomatology of the disease by means of different index (SLEDAI/SLAM) after plasmapheresis.

One study that was conducted in SLE patients (n=21) to assess the therapeutic effect and safety of the treatment with cyclosporine (2.5 mg/kg/day) and plasmapheresis (seven to 15 sessions every two or three days) observed that the clinical symptoms improved in two/four weeks, without the appearance of severe adverse events. 85% of the patients (treated in acute phases of the disease with therapeutic plasma exchange) reported an improvement in their HRQoL. Although the registration method is not specified, this is the only study that includes the patients' viewpoint.[406] Observational S. 2-

Another cohort of 18 patients with SLE and moderate activity (SLEDAI ≥8) (100% women, average age of 47.2 years) was exposed to extracorporeal cytapheresis through a selective adsorbent column for circulating granulocytes and monocytes (once a week for five consecutive weeks).[407] The mean SELEDAI went from 16 at the start of the study to six in week 11 (10 weeks after the first aphaeresis) ($P$<0.001). Significant improvements were observed in the musculoskeletal and dermal systems and no severe adverse events were reported. Observational S. 2+

The possible effect of plasmapheresis on SLE was examined in a study on eight patients.[408] The therapeutic efficacy of plasmapheresis is indicated due to a significant decrease in the SLEDAI scores after treatment ($P$<0.01). The anti-dsDNA concentrations were high before plasmapheresis and they changed in parallel to the disease activity during the plasmapheresis ($P$<0.01). Observational S. 2+

Twenty-eight SLE patients were selected for a cohort with the purpose of discovering the efficacy, safety and clinical usefulness of therapeutic plasma exchange.[409] Combined treatment resulted in a faster clinical improvement (arthralgia, arthritis, pleurisy, cardiac involvement, neuropsychiatric and haematological). Observational S. 2-

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Another study was performed with six patients with SLE and diagnosed with LN, verified with renal biopsy, to assess if treatment with plasmapheresis was efficient with respect to traditional treatments (with glucocorticoids).[410] The anti-DNA titres decreased significantly after plasmapheresis from 79.5 ± 97.7 U/ml in the pre-, to 6.6 ± 5.8 U/ml 12 months after treatment ($P$<0.05). Proteinuria decreased from 2.2 ± 1.7 g/day to 0.4 ± 0.6 g/day after treatment ($P$<0.001). | Observational S. 2-

In another study, a cohort of 14 SLE patients was selected (100% women, average age: 29 years, duration of the disease: four years) to investigate the effect of plasmapheresis.[411] A fast improvement was obtained in the 14 patients. The high baseline mean of the SLAM index dropped from 28.4 to 14.7 after four weeks and to 8.9 after six months. | Observational S. 2+

A controlled clinical trial (CCT) compared the response and the secondary effects of plasmapheresis in patients with proliferative LN treated with intravenous CPM, in a control case study with 28 SLE patients.[412] At the end of the treatment periods, 75% of the patients in the plasmapheresis group presented full remission, opposed to 31% of the patients from the CPM group alone ($P$<0.02); and the percentages were similar in the long term (41 v. 50%). | CCT 1+

Another CCT was performed in order to determine the risks of infection associated with treatment with plasmapheresis. 21 SLE patients were selected for this, who were receiving treatment with intravenous CPM (19 women, two males, average age of 30.2 years) and they were assigned to the plasmapheresis condition (four-six sessions in two weeks) or to the control condition.[413] Seven of the nine patients treated with plasmapheresis had severe bacterial or viral infections, including three cases of infections by cytomegalovirus. Out of the 12 patients treated with CPM, only two had severe infections ($P$<0.01). The efficacy of the treatment, however, was similar for both groups. | CCT 1+

Previous data contrast with the results of the RCT published by Pohl *et al*.[414] which was performed to determine if plasmapheresis increases the risk of infections in immunodepressed patients with LN. 86 patients were assigned to the treatment with prednisone plus CPM for eight weeks (n=46) or to identical therapy plus 12 sessions of plasmapheresis throughout four weeks (n=40). More infections were not found in the plasmapheresis group in this study. | RCT 1++

## Summary of evidence

| | |
|---|---|
| 1++ | Some studies show that the addition of plasmapheresis to traditional therapies does not seem to improve the progress of people with moderate SLE[403] or with LN.[400-402] |
| 1+ | It seems that immunoadsorption is an additional option in the treatment of severe SLE and the choice of the type of treatment with plasmapheresis should be personalised depending on the patient's conditions and on other economic aspects.[404] |
| 2+ | In this line, it seems that synchronised therapy with plasmapheresis could be useful for inducing a remission response in patients with proliferative LN[410,412] and decreasing the clinical activity in SLE;[406,408,409,411] and it appears as an additional option in the treatment of SLE.[407] |

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| | |
|---|---|
| 2+ | Treatment with extracorporeal immunoadsorption is a safe and effective modality to reduce anti-VRT-101[405] anti-dsDNA[402,408,410] antibodies, as well as proteinuria[410], albumin[402] and the levels of C3, C4[401], IgG, IgM, IgA and circulating immune complexes,[403] however, this benefit in biochemical values is not always related to improvements in clinical variables.[401,403,405] |
| 2++ | Some studies point to a greater frequency of potentially mortal infections (bacterial or virus) in SLE patients receiving treatment with plasmapheresis (additional to therapy with prednisone plus CPM).[413] However, these data are not consistent throughout literature.[414] |

**Recommendations**

| | |
|---|---|
| A | We do not recommend plasmapheresis as first or second line treatment in SLE patients, either generally or in patients with nephritis. |
| C | In severe cases that are refractory to other therapies, we suggest considering the use of plasmapheresis in an individualised manner. |

## 5.2.5. Prevention of disease reactivation

**Questions to be answered:**

- Which measures are effective to prevent the reactivation of systemic lupus erythematosus?

SLE is a complex autoimmune, multiorgan and chronic disease frequently characterised by flares and remissions. Lacking curative treatment, the objective of existing therapies is to control the flares, limit organ damage and reduce the requirement of glucocorticoids, and by doing so, the well-known adverse effects of standard therapy.

The effect of anti-malarial drugs on lupus activity has been analysed in a recent SR, which used the MPM assessment system.[327] 11 studies were identified that investigated the relationship of anti-malarial treatment with the SLE activity, obtaining data consistent with a reduction in the lupus activity, both in pregnant and non-pregnant patients, with evidence quality rated as high. The evidence that supports the prevention of severe flares and the adjutant action on the renal activity was rated as low.

SR
1++/2++

To assess the efficacy of CQ phosphate in preventing flares and reducing the maintenance doses of glucocorticoids in SLE patients without life-threatening manifestations (n=24), they were randomly assigned to CQ (a dose of 250 mg/day) or placebo.[46] 18% of CQ patients and 83% of those assigned to placebo presented a flare-up of the disease ($P<0.01$). The risk of suffering a flare was 4.6 times greater in the placebo group than in the group of patients who received CQ.

RCT
1+

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In another double-blinded RCT SLE patients (n=53) were assigned to continue with HCQ or replace it with placebo in order to determine the effectiveness of the anti-malarial drug in preventing flares.[416] The RR of non-severe flares between patients who received placebo was 2.5 times greater (95% CI: 1.08-5.58) than in patients who continued to receive HCQ (*P*=0.02). The use of anti-malarial drugs in SLE is generalised based on this Canadian study.

RCT 1+

A recent study investigated the relationship between the blood levels of HCQ and SLE activity (n=143).[417] A lupus flare was defined as a SLEDAI score ≥6. At the moment the HCQ levels were determined, they were significantly less in the 23 patients with active disease than in the 120 without activity, 694 v. 1079 ng/ml, respectively (*P*=0.001). In the six-month longitudinal follow-up of 120 patients with inactive lupus, 14 suffered a flare, again with significantly lower baseline levels of HCQ, 703 v. 1128 ng/ml, *P*=0.006). In the multivariate analysis of the flare predictors, the HCQ levels were equally significant (*P*=0.01).

Cohort S. 2+

To determine if treatment with prednisone can prevent relapses when there is an increase in anti-dsDNA, 156 patients were studied in another RCT. An increase in anti-dsDNA levels was found in 46 patients, who were randomly assigned to traditional treatment (n=24) or to taking a dose of 30 mg in addition to their normal treatment (n=22) for 18 weeks.[418] In case of flare, patients from the traditional group received prednisone doses of 30 mg/day or 1 mg/kg/day depending on the severity of the flare. The accumulated risk of relapse after a significant increase in anti-dsDNA was greater for the normal treatment group than for the prednisone group (n=20 v. 2; *P*<0.001). However, and despite the high prednisone doses used to treat the flares, the traditional treatment group received a lower prednisone dose (mean 10.0 v. 15.3 mg/day; *P*=0.025).

RCT 1+

Another double-blinded RCT assigned 40 SLE patients to therapy with prednisone (30 mg for two weeks, 20 mg for one week and 10 mg for one week), or placebo, in order to determine if short-term treatment with glucocorticoids can prevent flares associated with a rise in anti-dsDNA and C3.[419] In the analysis of flares (mild/moderate or severe) that occurred in the 90 days following the start of the treatment, they observed that 19% of the patients in the prednisone group and 35% of the patients in the placebo condition experienced at least one flare (RR=2.2; 95% CI: 0.64-7.47). In the placebo group, 30% of the patients experienced a severe flare-up of their symptoms, opposed to none of the patients in the treatment group (*P*=0.0086). It is noteworthy that 60% of the patients from the placebo group did not receive extra prednisone and did not suffer a flare. In fact, the average daily dose of prednisone received by the placebo group was lower, although the authors do not provide specific figures. With respect to the levels of anti-dsDNA, in the subgroup with high levels of the antibody, none of the patients who took prednisone had a severe flare, compared with 38% of the patients who received placebo (*P*=0.07). In the subgroup with low antibody levels, none of the patients who took prednisone had a severe episode, whilst 14% of the patients who received placebo did (*P*=0.16).

RCT 1++

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With respect to the prognostic meaning of the isolated serological activity, Steiman *et al*. analysed the clinical evolution of 165 patients from the *Toronto Lupus Cohort*, 55 with serological activity (high anti-DNS and/or hypocomplementemia) in clinical remission for two years, compared with 110 controls that did not satisfy the previous criteria. In the subsequent follow-up, the accumulated damage (measured by SLICC/ACR DI) was less in clinically quiescent/serologically active patients than in[267] the controls after three, five, seven and 10 years ($P<0.001$ in all the comparisons). The authors concluded that these results do not support the active treatment of patients with serological activity without clinical activity.[313] CCT 1+

The relationship between the 25-HO vitamin D and lupus has been subject to study in a considerable number of publications, included in the recent SR of Sakthiswary *et al*.[420] which compiles a total of 22 studies, 14 of cohorts, and eight cases and controls. 15 of them specifically analysed the relationship between the serum levels of 25-HO vitamin D and SLE activity. 10 of the 15,–all of them were cross–sectional studies–, found a significant association, inversely proportional, between the SLEDAI score and the vitamin D levels. SR 2++

Only two longitudinal follow-up studies have been published in which the levels of 25-HO vitamin D and the SLEDAI score were measured on two separate occasions. In the first of them, after two years' follow-up, there was no relationship between the absolute values of both variables or in those of their variations.[421] Cohort S. 2+

In the second study, although a significant decrease of mean SELENA-SLEDAI was observed, in parallel to the increase in serum vitamin D levels, this variation cannot be considered to have substantial clinical meaning: 0.02 points for every 20 ng/ml, 0.22 points in patients with initial levels <40 ng/ml.[267] No lupus flare prevention studies have been performed via the administration of vitamin D. Cohort S. 2+

In a cross-sectional study on 1002 people with cutaneous lupus from the database of the European Society of Cutaneous Lupus Erythematosus (EUSCLE), they verified the activity and damage of the disease measured by means of the specific CLASI scale (*Cutaneous Lupus Erythematosus Disease Activity and Severity Index*) in patients who had, at some time, been smokers and non-smokers.[422] Likewise, the response to anti-malarial drugs was analysed in both subgroups. Smoker patients had more activity, although the difference was not statistically significant, as well as more cutaneous damage ($P<0.05$). Cohort S. 2+

Another cross-sectional analysis (n=111), this time from the cohort of the University of New Mexico, studied the relationship between the SLEDAI score and smoking *et al*. 2003);[423] which was greater in smokers (15.6) than in exsmokers (9.63) or in non-smokers (9.03) ($P<0.001$). In contrast, a similar study in 223 patients from the University of Helsinki, obtained similar SLEDAI values in smokers, exsmokers or nonsmoker patients ($P=0.20$).[424] Both studies have obvious limitations due to the lack of fit for other variables with potential influence on the activity of the disease and due to its cross-sectional design. Cohort S. 2-

Cohort S. 2-

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| | |
|---|---|
| One of the possible explanations of the negative effect that tobacco has on lupus, at least at cutaneous level, is its interference with the action of anti-malarial drugs. Jewell *et al*. performed a historical study on 61 patients with cutaneous lupus, in which they reviewed response to the treatment with HCQ for eight weeks or CQ for five weeks. The response rate was 90% in nonsmokers opposed to 40% in smokers ($P<0.0002$). The response rate gradually decreased as the number of cigarettes increased.[425] | Cohort S. 2+ |
| In the study of Kuhn *et al*., the response to anti-malarial drugs was also greater in non-smoking patients (93.8 v. 82.1%; $P<0.05$).[422] | Cohort S. 2+ |

## Summary of evidence

| | |
|---|---|
| 1++/1+/2++ | Anti-malarial drugs (CQ and HCQ) reduce the risk of non-severe flares and, possibly, the risk of severe flares in SLE patients, including pregnant women.[327,415,416] |
| 2+ | Low blood levels of HCQ are associated with a greater likelihood of suffering a lupus flare.[417] |
| 1++/1+ | Treatment with prednisone at intermediate doses prevents in the short term the relapse associated with a significant increase of anti-dsDNA antibodies with a significant difference even in severe flares.[418,419] |
| 1++/1+ | Preventive treatment with glucocorticoids results in an increase in the accumulated dose of prednisone.[418,419] |
| 2++ | The clinical evolution of clinically quiescent and serologically active patients is benign, which advises against preventive treatment in situations of isolated serological activity.[313] |
| 2+ | There seems to be a relationship between the levels of 25-HO vitamin D and the activity of lupus.[267,420] |
| 2+ | It has not been proven that supplementation with vitamin D3 in deficient lupus patients results in a clinically relevant reduction of SLE activity.[267,421] |
| 2+ | Smoking is associated with a greater activity and greater severity of lupus cutaneous lesions.[422] |
| 2- | The relationship between smoking and the systemic activity of SLE has not been well-established.[423,424] |
| 2+ | Tobacco interferes with the therapeutic effect of anti-malarial drugs on cutaneous lupus.[422,425] |

## Recommendations

| | |
|---|---|
| A | We recommend prolonged treatment with antimalarial drugs, to prevent reactivations of SLE, even during pregnancy. |

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| | |
|---|---|
| A | Due to the unfavourable balance between the beneficial effect observed and the potential toxicity associated with excess of treatment with glucocorticoids, we do not recommend the preventive administration of prednisone to patients with serological activity without associated clinical administrations. |
| B | We do not recommend that patients with clinically quiescent and serologically active SLE should receive immunosuppressive treatment to prevent flares beyond their basic treatment or the remission maintenance treatment of a lupus nephritis. |
| C | Although we do not recommend vitamin D supplements with the sole objective of preventing activity flares, we do suggest correcting the vitamin D deficiency due to its unfavourable effects on the bone mass and asthenia, not ruling out a beneficial effect in the control of lupus activity. |
| C | In addition to its harmful impact on other aspects of the disease and on health in general, we suggest avoiding smoking due to its possible effect on lupus activity, especially at cutaneous level. |

## 5.2.6. Treatment of associated asthenia

**Questions to be answered:**

- Which therapeutic options are efficient to help people with asthenia associated with systemic lupus erythematosus?

Asthenia is the most frequent symptom in SLE, affecting 67-90% of the patients.[426] Despite the therapeutic advances in the treatment and survival of SLE patients, there are still no therapies of proven effectiveness against asthenia, which limits both the professional support and self-care of patients. These circumstances have been corroborated in the consultation that the authors of this CPG have carried out with SLE patients in Spain.

There is no agreement on the cause of asthenia in SLE.[427,428] Furthermore, the majority of the studies that afford information are limited by their cross-sectional design, by the variable selection of measures used and because no other possible causes of asthenia in SLE (drugs, hypothyroidism or anaemia) were considered.[429,430] The relationship between asthenia and activity of the disease, inflammation, organ damage and duration of the SLE is either controversial or non-existant.[431] Obesity is present in 28-50% of patients, increasing the actual cardiovascular risk of SLE.[432-434] Other secondary variables such as pain, sleep quality, impairment of physical capacity and depression, show consistent associations with asthenia. However, the symptomatological overlapping and causal bidirectionality that seem to exist between these variables and asthenia, hinder the interpretation of the results produced, mainly, by descriptive studies. The complexity and multidimensionality of the causes of asthenia in SLE is also reflected in the different mechanisms used by non-drug therapeutic interventions that have been used and assessed to improve the effects of asthenia in SLE.

There are many asthenia measurement instruments, but it is not possible to confirm that all measure the same problem. In an SR of literature on instruments that measure asthenia and that have been used in SLE, they identified the asthenia severity scale (*Fatigue Severity Scale*, FSS) as the most adequate both for use in clinical trials and observational studies, and in clinical practice.[435] This instrument, designed for SLE, has valid psychometric properties and it is one of the most commonly used. It is also available in different languages.

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Although the majority of studies do not observe any association between the use of drugs in SLE and asthenia, four isolated studies, of limited quality, indicate higher levels of asthenia among patients who use glucocorticoid, anti-depressants and non-steroid antiflammatory drugs (NSAID). One isolated study on the use of alternative medicines in rheumatic diseases informs of greater predisposition for use among patients with more asthenia.[436]

The minimum critically important difference of asthenia has been examined from the dual perspective of patients and health professionals. This parameter corresponds to the smaller differences in the measured level of asthenia that patients perceived as beneficial, and that could require changes in clinical decisions. The consideration and measurement of the minimum critically important difference would permit interpreting the magnitude of the changes observed, in a longitudinal manner, when different therapeutic strategies were tested. Faced with the absence of scientific evidence, experts suggest that the value of the minimum critically important difference should be an increase or decrease of 15% on the FSS scale. In a recent study, patients indicated that a change of 10% was important (95% CI: 4.9-14.6) in several asthenia scales (including FSS).[437]

**Physical exercise**

The response to this question is based on four SRs whose conclusions generally coincide.[438-441]

In order to examine non–pharmacological interventions for asthenia in adults with autoimmune diseases, a SR was performed of the experimental studies indexed in 19 databases between 1987 and 2006. — SR 2++

33 primary studies were recorded (14 RCTs and 19 quasi-experimental designs). Exercise, behavioural, physiological and nutritional interventions were associated with statistically significant reductions in the level of asthenia. Aerobic exercise proved to be efficient, adequate and feasible to reduce asthenia among adults with chronic autoimmune pathologies.[438]

One SR of a CCT was conducted to study the effects of aerobic exercise on the rehabilitation of adults with SLE, indexed in *Medline* before 2006.[441] It seems that intensity, frequency and duration of the exercise programmes should be similar to those recommended in other population groups. In patients with low disease activity, moderate exercise proved to be safe, and different positive effects derived from engaging in it could be expected. These effects included the improvement of aerobic capacity, asthenia, tolerance to exercise, and possibly, of the physical function and depression. — SR 2+

To determine the existing evidence on non-pharmacological strategies, such as physical exercise, which can be used to prevent and treat asthenia in SLE patients, an SR was carried out of articles prior to 2011 indexed in *Pubmed*, *SPORTDiscus*, *Medline*; and of *abstracts* from congresses on the areas of rheumatology, cardiology, physical education and physiotherapy.[439] — SR 2++

18 studies were compiled (6 RCTs and 12 cross-sectional studies). It seems that SLE patients presented less physical aptitude (cardiovascular capacity and muscular strength) and functional capacity in relation to healthy individuals. Likewise, they observed that although, to achieve a significant improvement in physical condition, the importance of supervising the physical exercise programmes is clear, the effects of physical exercise on reducing asthenia in SLE patients have still not been defined.

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Another SR was carried out with the objective of providing a comprehensive examination of literature on asthenia in SLE. 55 relevant articles were obtained in the *Medline*, *Embase*, *Cinahl*, *Amed*, *PsycINFO* and *PubMed* databases (28 cross-sectional, 10 longitudinal and 11 non-pharmacology intervention studies)[440]. With regards to exercise as a non-pharmacological intervention of asthenia in SLE, they observed that a lack of physical activity is often associated with greater levels of asthenia. In general, they observed that SLE patients are less suitable to carry out physical exercise at the start than controls. In some studies, the level of asthenia was reduced through intervention for the improvement of aerobic capacity and vitality. However, these findings are not the same throughout literature.

SR
2++

One single RCT[442] assessed the effectiveness of gradual and clinically supervised training programmes to improve the cardiovascular and muscular state (functional capacity expressed by the significant increase of the maximum oxygen consumption) and to reduce short-term asthenia, in women aged 15 to 65 with stable and non-complicated SLE. This trial informed about the significant improvement of the state of health (0.14 ± 0.21 vs 0.06 ± 0.19; $P<0.01$), of vitality (67.56 ± 17.54 vs. 76.22 ± 14.61; $P=0.002$) and of self-perceived physical capacity (63.32 ± 22.38 vs. 73.17 ± 18.97; $P<0.001$) by the patients. Furthermore, after training, an improvement in the Beck inventory score was observed (8.37 ± 12.79 vs. to 2.90 ± 3.00, $P<0.001$) and in the level of asthenia (3.57 ± 1.47 vs 2.68 ± 1.33 $P<0.001$) in the training group. The comparison between the control group and the intervention group showed a significant difference in the maximum oxygen consumption (24.31 ± 4.61 vs to 21.21 ± 3.88 ml/kg/min, $P<0.01$) and the anaerobic oxygen threshold (17.08 ± 3.35 in contrast to 13.66 ± 2.82 ml/kg/minute, $P<0.0001$).[442]

RCT
1+

## Psycho-educational interventions

The recommendations are supported by two SRs with coinciding results, including a total of six RCTs between the two.[440,443]

One SR was carried out with the objective of providing a comprehensive examination of literature on asthenia in SLE. 55 relevant articles were obtained in the databases of *Medline*, *Embase*, *Cinahl*, *Amed*, *PsycINFO* and *PubMed* (28 cross-sectional, 10 longitudinal cohort studies, and 11 non-pharmacological interventions).[440]

SR
2++

Non-pharmacological interventions developed in the field of asthenia in SLE included: a) self-care and advisory interventions, which proved their efficiency by significantly decreasing the asthenia scores, increasing self-efficiency and coping skills; b) a stress management programme, which informed of the significant reduction in asthenia in comparison with normal care (although this effect was not maintained after nine months' follow-up); c) an expressive writing or emotional disclosure, a technique that consisted in the repeated writing of thoughts and emotions related to negative life events, which showed a capacity to reduce the asthenia levels compared with the control group.

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In order to quantify the effects of the psychological interventions on psychological health, physical health and the disease activity in SLE patients, a systematic search was carried out of all the RCTs indexed in pubMed, *Cochrane Library*, *Web of Science*, *EBSCOhost*, Chinese Biomedical Literature Database and the *Chinese Digital Journals Full-text Database* until June 2011.[443] The articles were independently assessed by means of the Jadad scale. Six studies with a total sample of 537 patients were included. The MA of the data showed, among other results, that psychological interventions could reduce asthenia, the effect direction was as expected, but it was not statistically significant ($P>0.05$). Current data indicate that psychological interventions are promising treatments in the intervention of SLE.

SR and MA
1++

### Acupuncture

Only one pilot RCT informs about the value (applicability and safety) of acupuncture in people with asthenia due to SLE,[444] comparing acupuncture with electric stimulation (n=8) as opposed to minimal needle stimulation (n=8) and with placebo (n=8) in 10 sessions. The intervention was accepted by the patients and did not produce any relevant adverse effects. Asthenia was reduced in two patients with acupuncture. The fact that this study was not designed to assess efficiency in asthenia, its small sample, the limited magnitude of the improvement and the fact that one patient also improved from minimal needle stimulation, mean that these results are considered as exploratory.[444]

RCT
1-

## Pharmacological treatment

### Dehydroepiandrosterone (DHEA):

The efficiency of DHEA to improve asthenia was assessed in two RCTs with regard to placebo with 60 and 381 patients with stable SLE, at a dose of 200 mg/day, for 12 months.[445,446]

381 women with SLE were selected in one RCT to determine if the administration of prasterone produced an improvement or stabilisation of the disease activity and its symptoms (n=189), with respect to a control group (n=192).[446] Asthenia was reduced both in the group treated with DHEA and in the group with placebo.

RCT
1+

Another double-blinded RCT with placebo was conducted to determine the effects of the administration of DHEA on asthenia, well-being and functioning in women with inactive SLE. In all, 60 female patients with SLE received 200 mg of DHEA orally or by placebo.[445] The level of asthenia improved in both treatment groups, in general ($P<0.001$). The change in asthenia level ($P=0.04$) was related to the belief in the use of DHEA; those patients who believed they had used DHEA showed an improvement.

RCT
1+

## Vitamin D:

Three observational studies[421,447,448] afford some information, of limited validity, about the role of vitamin D in asthenia associated with SLE.

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In order to determine the consequences of vitamin D deficiency in SLE patients, a cross–sectional study was performed (n=92)[448] They observed that patients with vitamin D deficiency presented a higher degree of asthenia than patients with levels of 25-hydroxyvitamin D (25(OH) D) > 10 ng/ml mean 5.32 v. 4.03, *P*=0.08).

Cross–sectional S. 3

To analyse the influence whether changes in serum 25–hydroxyvitamin D ((25(OH) D) levels affect activity, irreversible organ damage, and asthenia in SLE, a longitudinal study was performed on 80 SLE patients with follow-up measurements after two years. Of the total number of patients, sixty patients took vitamin $D_3$.[421] Asthenia improved in the entire cohort (4.1 ± 3.0 v. 3.3 ± 2.6; *P*=0.015). However, improvement was only observed in the analogical visual scale of asthenia in those patients who took vitamin $D_3$. A significant reverse association was found in the follow-up between 25(OH) D and the visual analogical scale of asthenia (*P*=0.001).

Observational S. 2+

Another cross-sectional study was performed in order to know the existing relationship between the levels of asthenia, the levels of vitamin D and muscular strength in women with SLE (n=24), compared with healthy controls (n=21)[447] No association was found between the level of asthenia and the level of 25(OH) D (r= -0.12).

Cross-sectional S. 3

**Belimumab:**

One RCT[296] was conducted on the efficiency and safety of belimumab (lymphocyte B stimulator) in 867 SLE patients and another two RCTs that published their data together and performed a post-hoc analysis, by subgroups, a priori not well-defined.[354]

In the first double-blinded pivotal RCT published (BLISS 52), which was carried out to determine the efficiency and safety of belimumab in SLE patients (n=867) with standard of care, doses of 1 mg/kg (n=288) and 10 mg/kg (n=290) were used, compared with placebo with standard of care (n=305); and the effects on asthenia as a secondary objective were assessed.[296]

RCT 1++

The percentage reductions of PGA from the basal value were significantly greater after eight weeks with belimumab 1 mg/kg, and four weeks with belimumab 10 mg/kg than with placebo. These differences were maintained over the 52 weeks (1 mg/kg: *P*=0.0039 in week 52; 10 mg/kg: *P*<0.001 in week 52).

The results on asthenia, measured through the *36-item Short-Form Health Survey* (SF-36) were favourable for patients with belimumab 1 mg/kg and 10 mg/kg in the 52 weeks (1 mg/kg; OR= 1.34; 95% CI: 0.15-2.52; *P*=0.0272/10 mg/kg: OR= 1.35; 95% CI: 0.17-2.54; *P*=0.0247).

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Post-hoc analysis of two RCTs

In the post-hoc analysis, mentioned above, of the two pivotal RCTs on belimumab treatment together with standard therapy (BLISS 52[296] and BLISS 76[297]), the effects on asthenia were assessed as a secondary objective.[354] The results for asthenia were favourable from eight weeks' treatment on, and they reached statistical significance after 52 and 76 weeks' follow-up ($P<0.001$ and $P=0.004$, respectively). These joint results are only applicable to SLE patients with scores of 10 or more on the SELENA-SLEDAI scale, low complement levels, anti-dsDNA positivity, and that require treatment with glucocorticoids.

Belimumab and placebo showed similar rates of adverse effects potentially related to the treatment.

The validity of these results is limited as they originate from post-hoc analyses by subgroups carried out based on the combination of the data from the two independent RCTs executed in different parts of the world. New original longitudinal studies are required to confirm these findings.

**Summary of evidence**

| | |
|---|---|
| 1+ | Supervised aerobic exercise in people with stable SLE does not worsen the course of the disease and seems to help to improve health, vitality and self perceived physical capacity.[442] |
| 2++ | Some degree of professional supervision is required in the design and execution of physical exercise programmes to improve the physical capacity in SLE patients.[439] |
| 2++ | Psycho-education interventions based on cognitive, therapy, either face-to-face or by telephone, manage to reduce asthenia and improve social support among patients who receive family support, also improving self-efficacy in the management of the disease with respect to placebo, after 12 months.<br><br>Interventions to improve the knowledge and understanding of SLE, belief, coping styles and social support, as well as stress management programmes that include *biofeedback* and cognitive treatment; and expressive writing activities produced favourable health results and seem to reduce, in the short to medium term, the levels of asthenia; although not significantly in all the cases.[440] |
| 2++ | Psycho-education interventions based on cognitive therapy contribute to reducing asthenia.[440] |
| | There are no scientific tests available on the effectiveness of acupuncture to improve asthenia in SLE patients. |
| 1++ | DHEA does not add any value to placebo to reduce asthenia.[445,446] |
| 2+/3 | Despite verifying the high frequency of hypovitaminosis D among SLE patients, there is no robust evidence on the efficiency of vitamin D to improve asthenia.[421,447] |
| 1++ | Available evidence on belimumab together with standard therapy at a dose of 1 and 10 mg/kg compared with placebo and standard therapy, indicates that belimumab could contribute to reducing asthenia.[296] |

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**Recommendations**

| | |
|---|---|
| B | We recommend gradual sessions of aerobic physical exercise at home, controlled by a health professional (walking, static cycling, swimming), in people with stable SLE, due to its global improvement effect on a series of self-perceived measures by SLE patients. |
| B | Psycho-educational support should be offered to SLE patients to improve their knowledge and understanding of the disease, restructuring beliefs, improving coping and social support. |
| √ | We do not recommend vitamin D supplements in patients with asthenia and normal levels of 25 (OH) vitamin D. |
| √ | Despite the effectiveness-related data derived from the RCTs, we do not recommend the administration of belimumab with the sole objective of improving asthenia. |

# 5.3. Lifestyle measures

**Questions to be answered:**

- Which lifestyle-related measures should be advised for people with systemic lupus erythematosus?

Impairment of the different organs and systems causes a reduction of HRQoL in SLE patients who suffer different symptoms, such as cutaneous, musculoskeletal, pulmonary, cardiac impairments, peripheral neuropathies, anxiety or depression.[441] Asthenia is one of the most common symptoms, and it is associated with a reduction in capacity to carry out daily activities; in many cases the causes are not clear, but there are several contributing factors such as lupus activity, mood and sleeping disorders, or less physical functioncondition and muscular strength due to less physical activity.[449] The results obtained in several studies that investigate physical condition and functional capacity in SLE reveal that SLE patients have a worse physical condition (defined by cardiovascular capacity and muscular strength) and functional capacity than healthy individuals, as well as higher levels of asthenia.[439]

Identified studies on lifestyle measures that help to improve symptoms and reduce risks in these patients address four research areas: the effect of alcohol, tobacco, physical exercise and diet.

## Tobacco and Alcohol

There is plenty of literature about the relationship between smoking and alcohol, and the development and appearance of the disease, but less about the possible effect that it may have on its course and on the patient's well-being once diagnosed. Four observational studies that address the topic, in this sense, have been identified, but none of them about the effect of alcohol.

Two cohort studies, one retrospective[450] and another prospective[451] and a cross-sectional study[423] performed in Caucasian populations and with a percentage of women between 90 and 100%, assessed the possible association between smoking and the activity and damage produced by SLE.

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| | |
|---|---|
| Two studies observed a significant increase in the global activity of the disease in active smokers compared with those who never smoked. One of them (n=1346) shows an increase in 2.17 points (95% CI: 1.03-3.32)[450] and the other (n=125) with an average score of 15.63 ± 7.78 v. 9.03 ± 5.75, (*P*=0.001), measured in both cases with the SLEDAI scale.[423] | Cohort S/ Cross-sectional S. 2+/3 |
| A greater intensity and duration of tobacco use (packages/day/year) are associated with a greater risk of active *rash* (RR for every 5 packs/year=1.17; 95% CI: 1.06-1.29), with a similar increase of significant discoid *rash*[450] and of the global activity of SLE for each smoking year (*P*=0.003).[423] | |
| The results obtained in two of the studies (n=1346 and n=276) showed that being an active smoker diagnosed with SLE increases the risk of active rash compared with non-smokers (OR=1.63, 95% CI: 1.07-2.48)[450] (OR=6.8 95% CI: 1.63-23.3).[451] One of them also found a greater risk of discoid rash (OR= 1.96; 95% CI: 1.31-2.92)[450], and in the second study higher risk of scars (OR=4.70 95% CI: 1.04-21.2) and of total cutaneous damage (OR=2.73, 95% CI: 1.10-6.81) comparing active smokers with non-smokers. | Cohort s. 2+/2- |
| One study found a significant relationship between smokers and photosensitivity (OR= 1.47; 95% CI: 1.1 1-1.95). No interaction was observed between smoking and anti-malarial drugs (they have not provided data).[450] | Cohort S. 2+ |
| The results of a cross-sectional study (n=181) showed a significant association between being a smoker (n=37) and low levels in the majority of the domains of SF-36, a generic questionnaire of HRQoL.[452] | Cross-sectional S. 3 |
| Two of the studies, which conducted the analysis depending on the patients' smoking habit, distinguished exsmoker, concurrent smoker with the disease and nonsmoker, reported that they did not find a significant association between the disease activity and being an exsmoker.[423,450] | Cohort S/ Cross-sectional S. 2+/3 |

## Exercise

The motivation factors to do exercise in SLE patients seem to be the same as for the general population: pleasure, benefits for health, feeling of achievement, to feel comfortable (better in one's own home) and be individualised. These patients express having difficulties at the beginning due to asthenia and muscular and joint problems but these improve in a short time.[453]

A total of eight identified studies investigated how physical activity affects symptomatology, functional physical capacity and disease activity,[442,454-459] whilst another two studies associated it with cardiovascular risk factors and inflammation markers.[460,461]

Three RCTs,[454-456] with samples exclusively of women (n=23, 45 and 10, respectively) assessed the effect of aerobic physical exercise on the functional capacity and tolerance to exercise, comparing it with the effect of engaging in non-aerobic exercise or with sedentary individuals.

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Robb-Nicholson *et al*.[454] and Miossi *et al*.[455] found significant improvements in the exercise group compared with the control group, and that the aerobic capacity of women with SLE was reduced compared with healthy women of their age. They observed that, compared with inactive patients, aerobic exercise improved heart rate recovery and chronotropic reserve ($P$=0.009 and $P$=0.007, respectively),[455] the duration of the exercise test (with an increase of 12%) and decreased the submaximal exercise heart rate ($P$=0.007 and $P$<0.05, respectively).[454]

RCT
1-/1+

A pilot RCT with a very small number of participants (n=10) carried out by Ramsey-Goldman *et al*. compared an aerobic exercise programme with one of the muscular strength and range of movement, evaluating asthenia, functional capacity and capacity for exercise. No differences were found between groups, although a certain improvement in functional state, capacity for exercise and muscular strength was observed in both groups after the intervention (9 months).[456]

RCT
1-

The beneficial effect of supervised aerobic exercise was also observed in a randomised clinical trial (nRCT) (n=72) which obtained an improvement of the aerobic threshold, maximum O2 consumption, and the functional capacity in the intervention group ($P$=0.0001, $P$=0.007 and $P$=0.03, respectively), compared with the control group, as well as an increase in functional capacity in the intervention group compared with the baseline situation ($P$<0.01).[442]

nRCT
1-

A small, before-after, pilot study (n=6) that assessed aerobic exercise did not obtain relevant clinical results but showed a significant improvement in the vitality subscales ($P$=0.03) and physical function of SF-36 ($P$=0.03) and oxygen consumption ($P$=0.05).[459]

Observational
S.
2-

Five identified studies assessed the effect of aerobic exercise on asthenia.[442,454,456-458]

The RCT with the largest sample size (n=93) found a tendency for asthenia to improve in the intervention group compared with the control group in two of the three tools used to measure asthenia, and it was significant on the Chadler scale ($P$=0.04).[458]

RCT
1+

Two studies showed a significant improvement in this symptom measured with validated scales in the intervention group with respect to the baseline situation but did not find differences between compared groups.[442,456]

RCT
1-

The pilot RCT (n=10) showed a difference in means between the degree of baseline asthenia and at the end of the programme of -0.71 (95% CI: -1.23 a -0.18) in the aerobic exercise group and -0.68 (95% CI: -1.22 to -0.13).[456]

The nRCT (n=72) reported a decrease in score of the scale (indicating less asthenia) after the exercise programme with respect to baseline situation $P$=0.001.[442]

nRCT
1-

Robb-Nicholson *et al*. assessed this symptom with two tools, one validated (the POMS –*Profile of Mood States*– Scale) and the other a visual analogical scale specifically prepared for the study, only finding a significant improvement with the second, when compared with the control group.[454]

RCT
1-

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Finally, one study with before-after design (n=15) whose intervention was a home exercise programme with *Wii Fit*® obtained a significant decrease in this symptom after the intervention (*P*=0.002).[457]

Observational S. 2-

The effect of exercise on the disease activity was assessed in six identified studies, four RCTs, one before-after, and one observational. In all of them, the analysed physical activity included was aerobic exercise, and no changes or worsening was observed in any of them, either in the comparison between groups or in the comparison with the baseline situation.[454-456,458-460]

In the RCT of Ramsey-Goldman *et al*., measurements were carried out with the SLAM index without there being significant changes in the groups at the end of the study respect to the baseline situation: differences in means 2.80 (95% CI: 0.90-4.70) in the aerobic exercise group and 0.40 (95% CI: -2.27-3.07) in the muscular strength and in the range of movement exercise group.[456]

RCT 1-/1+

Tench et al, using the same tool, did not obtain a significant difference in any group (*P*=0.20), nor did any important adverse events arise.[458]

The RCT of Miossi *et al*. (n=45) did not show any difference between the mean of the baseline SLEDAI score and at the end of the study of any group (*P*=0.9 and *P*=0.6).[455]

The RCT of Robb-Nicholson *et al*. (n=23) and the pilot study with before-after design of Clarke-Jenssen *et al*. (n=6), although they show no statistical analyses, report that they did not find any significant difference either after the intervention, in either of the cases assessed with the SLEDAI index.[454,459]

RCT 1-

Observational S. 2-

In a cross-sectional study (n=242) that assessed the association of physical exercise with certain cardiovascular risk markers did not find any correlation between activity or damage of SLE and exercise.[460]

Cross-sectional S. 3

The effect of exercise on the damage of SLE was assessed in the study with before-after design of Yuen *et al*. (n=15) without finding any worsening after the intervention.[457]

Observational S. 2-

Two cross-sectional studies showed results that indicate the existence of relationship between physical activity and certain biological cardiovascular risk markers.

Cross-sectional S. 3

Volkman *et al*. (n=242) obtained a negative correlation between the quantity of metabolic equivalents (METS) invested in the physical activity per week and the thickness of the artery wall (r= -0.4; *P*=0.002), and also the number of atheromatous plaques in carotid artery (r= -0.30; *P*= 0.0001).[460]

In addition, Barnes *et al*. (n=41) compared active patients with sedentary patients and with healthy controls, observing that the arterial stiffness (measured through the Aorta Augmentation Index) was greater in sedentary patients than in active patients and than in the healthy population (*P*<0.05), while carotid stiffness was lower (*P*<0.05). These authors found a reverse correlation between the degree of physical activity and arterial stiffness (r= -0.30) or the tumour necrosis factor α (r= -0.3), but they do not report the *p*-value.[461]

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Both studies showed a relationship between sedentary lifestyle in people with SLE and some inflammatory markers. Volkman el al. found an association between low physical activity and the increase in pro-inflammatory HDL ($P$=0.03).[460] On their part, Barnes *et al*. found greater levels of CRP and of intercellular adhesion molecules in sedentary patients compared with active patients ($P$<0.05).[461]

Of the identified studies that assessed the effect of exercise on HRQoL, anxiety, depression and sleep quality in SLE patients, the RCTs of Robb-Nicholson *et al*. (n=23) and Tench *et al*. (n=93) did not find significant changes in the degree of anxiety due to the intervention.[454,458] RCT 1+

However, the nRCT of Carvalho *et al*. (n=72) obtained significant differences for the intervention group, but not for the control group, in the degree of depression ($P$<0.001) and in the HRQoL in all domains of SF-36 ($P$<0.03), except for pain, when the exercise programme ended.[442] nRCT 1+

A before-after study also obtained significant improvements in anxiety and depression ($P$=0.03) and in the intensity of pain experienced ($P$=0.05c4), using the HADS scale (*Hospital Anxiety and Depression Scale*) and the SM-MPQ questionnaire (*Short-form of the McGill Pain Questionnaire*), respectively.[457] Observational S. 2-

No significant differences were found in terms of sleeping quality in any of the two studies that assessed this.[456,458] RCT 1+

## Diet

Nine studies were identified that analysed the effect of food on different aspects of the disease, two informed RCTs in three publications[462-464] assessed the effect of certain diets on SLE patients, and the other studies assessed the effect of omega-3 polyunsaturated fatty acids on the course and pathophysiology of the disease: three RCTs[465-467] and two observational studies.[468,469]

Davies *et al*. analysed the effectiveness of a hypoglycaemic diet (10-15% energy from carbohydrates, 25% proteins, 60% fats, with no calorie restriction) on patients with corticotherapy (n=23), comparing it with a traditional hypocaloric diet (50% energy from hydrates, 15% proteins, 30% fat and 2000 cal/day), to reduce weight, and secondarily asthenia and cardiovascular markers.[464] A significant reduction in weight ($P$<0.01) and of asthenia ($P$<0.03) was obtained in both groups with respect to the baseline situation, not finding any difference between groups. No variations were obtained in the levels of total cholesterol, HDL, LDL or glycaemia in any group. RCT 1-

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Shah *et al*.[463] analysed the effectiveness of a dietetic programme and of health education (n=17) comparing a group submitted to a low fat diet (1400-1800 calories, ≤30% energy from fats and ≤200g of cholesterol a day), with a group without any type of intervention. The results showed a modest but significant decrease in weight in the diet group compared with the baseline weight (*P*=0.006). Total cholesterol, LDL, HDL and triglycerides were variable in both groups throughout the follow-up, without consistent results except for a decrease in total cholesterol after six (*P*=0.0002) and 12 weeks (*P*=0.01) in patients included in the dietetic programme. An increase in HRQoL was obtained in the experimental group compared with the control group (*P*=0.05) and with the baseline situation (*P*=0.01). RCT 1-

In a subsequent publication of the same study they analysed what happened with the intake of nutrients, energy and haemoglobin in patients submitted to the diet.[462] The results showed that it was effective in reducing the intake of sodium and maintaining the intake of adequate levels of almost all the nutrients except for vitamin B12, which decreased significantly in the intervention group with respect to the control group (*P*=0.02), calcium, folate, iron and fibre that were around 67% the reference value. Anaemia was present in both groups with no significant association with the diet and without any correlation with the intake of iron (r=0.38; *P*=0.2).

Five works assessed the possible relationship between the disease activity and the damage associated with SLE, with polyunsaturated fatty acids.

The RCT of Wright *et al*. (n=60) observed a positive effect of the supplement of 1.8 g eicosapentaenoic acid (EPA) and 1.2 g of docosahexaenoic acid (DHA) per day in the disease activity with the decrease of global scores on both scales, as well as of certain individual symptoms after 12 and 24 weeks with respect to the baseline situation, whilst in the placebo group there was no change (*P*<0.001).[465] RCT 1++

Similar results were obtained by Duffy *et al*. (n=52) who assessed the effect of a supplement of 0.540 g of EPA and 0.360 of DHA per day, above all in the neuromotor, tegumentary and laboratory domains.[467] RCT 1+

The crossed RCT of Walton (n=27) obtained a beneficial effect of the EPA supplement together with a low-fat diet (<20% of energy) compared with the same diet and placebo (*P*=0.01), based on an individualised set of variables according to SLE criteria and analytical parameters that the authors did not report in detail.[466] RCT 1-

A cross-sectional study (n=114) found a negative correlation between the concentration of EPA and DHA in the adipose tissue and the disease activity () (*P*=0.001), as well as a positive correlation between the intake of omega-6 and accumulated damage (r=0.20; *P*=0.045) and lupus activity (r=0.21; *P*=0.028).[468] Cross-sectional S. 3

Davies *et al*.[464] did not observe changes in any of these result measurements (damage and lupus activity) with either of the two diets analysed. RCT 1+

The effect of polyunsaturated fatty acids on the cardiovascular risk markers and on the vascular function was assessed in two RCTs and in one cross-sectional study.[465,467,468]

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The results of one RCT (n=60), which compared supplements of omega-3 with placebo, showed a decrease in arachidonic acid and an increase in EPA and DHA acids in the platelet membrane, compared with the placebo group ($P$=0.001, $P$=0.044, $P$=0.012, respectively), as well as a positive correlation between EPA acids (r= 0.56; $P$=0.002) and platelet DHA (r=0.43; $P$=0.026) and the flow-mediated dilatation. (21) Furthermore, the endothelial function improved in the intervention group compared with baseline ($P$<0.001), whilst there was no change with placebo. At the end of the follow-up (24 weeks), the 8-isoprostane levels had decreased both in the omega-3 group ($P$=0.007) and in the placebo group ($P$=0.027).[465] RCT 1++

Duffy *et al*. also found higher levels of EPA and DHA in the platelet membrane with the supplement at low doses of these acids compared with the baseline levels ($P$<0.05).[467] RCT 1+

Finally, Elkan *et al*. (n=114) observed that the percentage of EPA and HDA acids in the adipose tissue negatively correlated with the presence of arterial plaque ($P\leq$ 0.002) and positively with the apolpoprotein A1 concentration ($P\leq$ 0,004), whilst the percentage of omega-6 and linoleic acid had a positive correlation with the presence of plaque ($P$<0.03). Finally, in addition, it did so negatively with serum apolipoprotein ($P$=0.037).[468] Cross-sectional S. 3

A prospective study (n=216) carried out in Japan, did not obtain significant results that associated diet to the course of the disease and vascular damage. After analysing multiple variables, after a four-year follow-up, only a significant inverse association was observed between vitamin C intake and the disease activity ($P$=0.005), but not with vitamin C supplement intake.[469] Observational S. 2-

**Summary of evidence**

| | |
|---|---|
| 2+/2-/3 | Smokers with SLE have a greater risk of suffering cutaneous manifestations and an increase in the global disease activity than non-smokers. This risk increases as does the intensity and duration of the smoking habit.[420,450,451] |
| 3 | Smoker SLE patients have a lower HRQoL level than non-smokers.[452] |
| 1+/1- | Aerobic physical exercise improves the aerobic and functional capacity, as well as the tolerance to exercise in patients with low or moderate SLE activity.[442,454-446] |
| 1+/1-/ 2- | Several studies have shown an improvement in asthenia and vitality with physical exercise in patients with low or moderate SLE activity.[442,454,456-458] |
| 1+/2-/3 | Aerobic and non-aerobic physical activity does not increase SLE activity or worsen the symptoms.[454-456,458-460] |
| 2-/3 | No increase of the damage associated with SLE has been observed in patients who carry out aerobic exercise.[457,460] |
| 3 | The low physical activity and sedentary lifestyle in SLE patients is associated with an increase in subclinical atherosclerosis and with inflammatory markers and cardiovascular risk.[460,461] |

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| | |
|---|---|
| 1+/1-/2- | Evidence on the effect of exercise on anxiety, depression and pain is contradictory. No harmful effect has been observed in these areas.<br>There is no evidence of an improvement in sleep quality due to physical exercise.[442,454,458,459] |
| 1- | Aerobic exercise may improve HRQoL in patients with stable SLE.[442] |
| 1++/1+/1-/3 | The consumption of omega-3 fatty acids, EPA and DHA have a positive effect on the disease activity in the short run, decreasing both global indices and different individual symptoms.[465-468] |
| 1++/1+ | Supplements with low doses of EPA and DHA cause an increase in their concentration and a decrease in arachidonic acid in the platelet membrane. They improve the endothelial function and reduce the level of 8-isoprostanes.[465,467] |
| 3 | A positive association has been observed between the concentration of omega-3 in adipose tissue with apolipoprotein A1 and a negative association with the presence of arterial plaque.<br>However, omega-6 and linoleic acid are associated with an increase in the activity and damage associated with lupus, and with the presence of arterial plaque.[468] |

**Recommendations**

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| √ | We recommend adopting active measures in order to help give up smoking in all SLE patients. This objective is especially important, not just because of the effect that smoking has on the activity of the disease and quality of life, but also because of its causal association with the increase in risk of cardiovascular disease, infection and cancer. |
| B | We recommend promoting regular physical exercise in people with stable SLE with low to moderate disease activity. |
| C | We suggest avoiding being overweight and a sedentary lifestyle in all SLE patients. |
| C | We suggest recommending a diet that is low in saturated fats and rich in omega-3 fatty acids in SLE patients. |

# 5.4. Photoprotection

The biologically active components of ultraviolet radiation (UV) are UV B (UVB) between 290 and 320 nm, and UV A (UVA) that has a wavelength of between 320 and 400 nm. UVB radiation has a direct impact on DNA and proteins, it causes burns and in the long term favours carcinogenesis. UVA radiation is able to penetrate more than UVB radiation, producing indirect damage by means of genesis of free radicals. It is responsible for immediate pigmentation, for photo-ageing, photo-carcinogenesis and photo-dermatoses. UV radiation at sea level contains 95-98% of UVA radiation and 2-5% of UVB radiation.[470] Infrared radiation (IR) is the main solar spectrum fraction that reaches the earth surface and is responsible for caloric action. Despite its low energy, it is not harmless and it boosts the damage caused by UV radiation.[471]

Photosensitivity is one of the main symptoms of systemic and cutaneous lupus erythematosus (CLE). The role of UV radiation in the induction of skin manifestations of lupus erythematosus is a well-known fact, based on the observation that the lesions are preferably located in

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photo-exposed areas. They also usually flare up in summer and in the weeks following exposure to sun.[472,473]

Protection against UV radiation using sunscreens has improved over time. In 1928, the first sunscreens were designed to avoid sunburn;[474] but today other harmful effects of UV radiation such as sunburns, photosensitivity, photodermatoses, immunosuppression, photoageing and photocarcinogenesis,[475] are well known, so strategies have been designed to prepare photoprotectors that combine several sunscreens to minimise these deleterious effects.

In order to determine the relationship of photosensitivity in lupus erythematosus with the patients' history, the subtype of lupus erythematosus and the presence of autoantibodies, an observational study was conducted in patients with three subtypes of lupus (n=1000), 46 chronic discoid lupus erythematosus (DLE), 30 subacute CLE and 24 SLE.[476] Cohort S. 2-

A test on photosensitivity to UVA, UVB radiation and to visible light was performed on all patients. An abnormal reaction to UV radiation and to visible light was observed in 93% of the patients with lupus erythematosus (87 patients with lupus erythematosus reacted to UVB rays, 83 patients to UVA rays and seven to visible light). No statistically significant differences were observed in the abnormal reaction to radiation (UVA and UVB) between the subtypes of lupus erythematosus.

Sixty-nine patients presented a history that suggested a photo-aggravated or photo-induced form of lupus. Photoprovocation was confirmed in 65 of these patients who also presented a history of photosensitivity. Of the 31 patients without a history of photosensitivity, 28 reacted abnormally to UV radiation. In this case, no statistically significant differences were observed in the abnormal reaction to radiation between the subtypes of lupus erythematosus. No differences were observed in the antibody patterns among patients with photosensitive lupus erythematosus.

Another study was performed on 405 patients with different forms of lupus erythematosus on whom a photoprovocation test was performed.[477] In all, skin lesions caused by UVA radiation were observed in 54% of the patients, 42% reacted only to UVB radiation and 34% only to UVA radiation. Cohort S. 2-

Skin lesions that are characteristic of lupus erythematosus occurred in 175 (54%) of 323 patients; 137 patients (42%) only reacted to UVB irradiation, and 110 (34%) only to UVA irradiation. 60% of the patients were aware of an adverse effect of sunlight on their disease and 62% showed a pathological reaction to the test. This pathological reaction was also generated in 58% of the patients who denied any effect of exposure to sun on their disease.

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A group of 30 patients with photosensitive SLE was identified, and they were compared with another 30 non-photosensitive patients in order to determine the prevalence of toxicity with respect to fluorescent light.478 Thirteen of the 30 photosensitive patients (43%) compared with two non-photosensitive patients (7%) reported a flare-up of the disease after exposure to fluorescent light. The majority of the symptoms were experienced in the first hour after exposure, and they were similar to those experienced after exposure to the sun. Twelve photosensitive patients and two non-photosensitive patients described mild fatigue after prolonged exposure ($P<0.001$). The use of acrylic diffuser screens decreased the emission of UVA radiation by 33% and of UVB radiation by 94%.

Cases/ controls 2+

Herzinger *et al*.[472] performed a historical analysis of 66 patients with CLE submitted to a photoprovocation test, to whom an ample spectrum photoprotector containing parsol 1789, uvinul N539, uvinul T150, Mexoryl XL and titanium dioxide, had been applied. Of the 51 patients who presented lupus lesions in the irradiated area, with the UVA/UVB combination, 96% only presented lesions in the area where the sunscreen had not previously been applied. In the protected areas, almost half the patients showed hyperpigmentation.

Cohort S. 2-

Like other authors, they observed that the UVA/UVB radiation combination was more efficient in reproducing cutaneous lupus lesions in these patients, so they concluded that a sunscreen that protects against both types of UV radiation can be a useful prevention measure.

Specifically, Lehmann *et al*.[479] selected a cohort of 128 patients with different forms of lupus erythematosus on whom a photosensitivity test was conducted.

Cohort S. 2+

The result of 43% of the patients to the photosensitivity test was positive. In 53% of the patients with induced lesion, this was caused by the UVA/UVB radiation combination, in 33% only by UVB and in 14% by UVA.

50% of the patients knew about the effect of sunlight on their disease. A pathological reaction to the test was observed in 66% of the patients, opposed to 46% of the patients who denied any effect of exposure to sun on their disease.

A cross-sectional study was performed in order to explore the relationship between exposure to sunlight and UV light protection measures, and the clinical results in SLE (n=60).[480]

Descriptive S. 3

A questionnaire was used to assess the sunlight exposure behaviours, the use of protective measures and the repercussion of exposure on the disease manifestations.

98.3% of the patients knew about the effect of sunlight on their disease. 81.7% of the patients believed that sunlight aggravated their disease. After a brief exposure to direct sunlight, 71.2% of the patients reported photosensitivity, 81.5% arthralgia, 40% joint swelling, 76.7% anorexia, 71.2% fever, 66.7% tiredness, and 66.7% shivering. In general, 80% of the patients presented at least one symptom associated with exposure to sunlight.

However, only 50% of the patients reported the use of solar protection, with a protection factor of 15 or more, and less than 40% used hats, or long-sleeved clothing to protect against exposure to sunlight.

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Patients who regularly used solar protection had less kidney involvement (13.3 v. 43.3%), thrombocytopenia (13.3 v. 40%), hospitalisations (26.7 v. 75.7%) and demand for treatment with CPM (6.7 v 30%) than patients who did not use it ($P<0.05$).

In a double-blinded RCT, the efficiency of a broad-spectrum sunscreen was compared with respect to its vehicle in 25 patients with CLE subtypes and photosensitivity, who were submitted to photoprovocation with UVA/UVB lamps and photopatch testing for three consecutive days.[481] None of the 25 patients presented characteristic CLE lesions in the irradiated areas where the sunscreen had previously been applied. However, 72% of the patients developed lesions in untreated areas or in areas where the vehicle had not been applied.

RCT 1++

In 2000, Stege *et al*.[482] compared three already marketed sunscreens on 21 patients with cutaneous lupus who were submitted to photoprovocation with UVA and UVB radiation. In this double-blinded and intracontrol study, they observed that the sunscreen that contained the combination of Mexoryl SX and Mexoryl XL, the latter effective against UVA/UVB, was able to prevent skin lesions in 100% of the patients. Furthermore, patients presented a lower expression of intercellular adhesion molecule type 1 in the areas protected with the sunscreen that contained the Mexoryl XL filter, with respect to the mRNA expression of the intercellular adhesion molecule type 1 in irradiation-induced skin lesions. This adhesion molecule participates in the interaction of the keratinocytes with the T lymphocytes that infiltrate the dermis, and this phenomenon can be observed one to two weeks before the appearance of clinical lesions.

RCT 1-

Recently, the EUSCLE assessed the efficacy of the different treatments and prevention measures used by means of a questionnaire with the participation of more than 100 patients diagnosed with CLE.[483]

Cross-sectional S. 3

It was observed that 84% of the patients used broad-spectrum sunscreens, and that these were more effective in patients with lupus erythematosus. The global efficacy of sunscreens in the prevention of skin lesions was 94.7%. The CLASI index was less in those patients who usually applied the sunscreen in contrast to those did not do so.

**Summary of evidence**

| | |
|---|---|
| 2- | The majority of people with lupus present photosensitivity to a certain degree, with no differences depending on lupus subtypes (chronic DLE, subacute CLE, SLE).[476,477,479] |
| 3 | SLE patients who regularly use topical sunscreens seem to have less renal impairment, less thrombocytopenia, less hospitalisation, and they need less treatment with CPM that those who do not use it. Therefore, the use of sunscreens is associated with a better prognosis, reducing the risk of kidney damage and the need for immunosuppressive treatment.[480] |
| 3 | In addition to photosensitivity, following a brief period of exposure to sunlight, other clinical manifestations occur such as tiredness, arthralgias, joint swelling, anorexia, fever and shivering.[480] |

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| 2+ | Exposure to fluorescent light, especially in patients who prove to be photosensitive, causes a flare-up of the SLE symptoms.[478] |
| 1++ | Photoprotection protects against lesions associated with UVA and UVB combination radiation.[472,481] |
| 2- | Photoprotection protects from hyperpigmentation only in half of the cases.[472] |
| 3 | Broad-spectrum photoprotectors prove to be highly efficient in preventing skin lesions in SLE patients.[483] |

**Recommendations**

| | |
|---|---|
| A | We recommend that the regular use of broad spectrum photoprotectors with high solar photoprotection index should be applied in adequate quantity (2 mg/cm$^2$), evenly over all the areas exposed to the sun, between 15 and 30 minutes before exposure and reapplied every two hours and/or after immersion and perspiration. |
| √ | We suggest systematically informing and educating SLE patients, especially those with cutaneous lupus and who have a history of photosensitivity, about the photoprotection measures and the importance of their use to control their disease better and to avoid the appearance of other symptoms. |

# 5.5. Educational programmes for patients

**Questions to be answered:**

- Are structured nursing-based educational programmes addressed to people with systemic lupus erythematosus effective?

There is little evidence available in the literature on the effectiveness of structured nursing education programmes for SLE patients, either individually or in groups. The response is based on eight studies although only one of them tries to answer this question.[484]

In one RCT, SLE patients and their partners were assigned to an experimental group (n=64), who received a theoretic educational intervention designed to improve self-efficacy, communication as a couple on SLE, social support and problem-solving. It consisted of one 1-hour session with a nurse educator, following by monthly advice by telephone for six months. The patients in the control group (n=58) and their partners received control attention, including a 45-minute video presentation on SLE and monthly telephone calls. RCT 1+

After 12 months (6 months after finishing the intervention), significant improvements were obtained in social support ($P$=0.03), self-efficacy ($P$=0.02), communication as a couple ($P$=0.03), and a decrease in asthenia levels ($P$=0.02) in the experimental group compared with the control group. The global mental state of health also significantly improved, as measured by SF-36 questionnaire ($P$=0.04).[485]

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Another RCT, with individual psycho-individual intervention (n=55) based on telephone advice related to six behaviours (self-care in managing asthenia, communication skill, elimination of medical care barriers, self-management with medication, symptom monitoring and stress control methods), improved the short-term health results, related to physical function and social support, in SLE patients.[486] RCT 1+

A final RCT (n=15) suggested that the psychological state of SLE patients improves significantly through counselling interventions, also by telephone calls (30 minutes, every 4-6 weeks for six months), focused on the patient and carried out by counselling experts.[487] RCT 1-

A quasi-experimental study (n=41) examined the effects of an SLE self-management course consisting of six two-hour sessions per week for groups of 10 to 15 literate adults of all ages. The control group did not receive any intervention. A significant improvement was observed in patients from the experimental group in asthenia ($P$=0.049; depression ($P$=0.025), coping skills ($P$=0.007) and self-efficacy ($P$=0.001). There were no significant changes neither in pain nor in the disease the disease activity after the intervention.[488] NRCT 1-

One study (n=17) suggested that psycho-educational interventions in groups of women with SLE aged between 25 and 60 with cognitive impairment, improved self-efficacy in memory, which proportionally correlated to HRQoL of these patients.[489] Observational S. 2-

Another study suggested that a self-help course (*SLE Help Course*) reduced asthenia and depression levels, and increased skills in the use of relaxation techniques and physical exercise. This course was given to 313 SLE patients in 17 different places in the US, in order to promote self-care, using a variety of educational and behavioural modification methods.[490] Observational S. 2-

Another observational study (n=34) whose objective was to assess a specific psychological intervention aimed at improving coping skills in SLE patients, and intervening in levels of depression, anxiety and mental workload, among others, established that a six-month group psycho-educational intervention using psychotherapeutic techniques, improves mental health results in SLE patients, finding significant improvement in the depression and anxiety levels of these patients.[491] Observational S. 2-

Finally, a study was performed recently to assess an educational programme given by nursing, physiotherapy and occupational therapy in SLE patients (n=23). It was observed that the results of this educational programme in SLE were significant in improving HRQoL, perceived disease management, and chronic pain in these patients.[484] Observational S. 2-

**Summary of evidence**

| | |
|---|---|
| 1+/1- | Structured programmes addressed to SLE patients are effective in reducing asthenia, depression and in improving coping skills and self-efficacy in these patients.[485,488] |
| 1- | The psychological state of SLE patients could significantly improve through patient-focused telephone counselling interventions.[487] |

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|---|---|
| 1+ | The health results related to the physical function and social support in SLE patients could improve through an individual telephone counselling-based based on psycho-educational intervention.[486] |
| 2- | Group psycho-educational interventions could improve mental health results in SLE patients.[491] |
| 2- | A multidisciplinary formative educational programme in SLE was effective in improving HRQoL, and in the perceived disease management, and chronic pain in these patients.[484] |

**Recommendations**

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| C | We suggest to perform structured educational programmes address to SLE patients and given by nursing professionals. |

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# 6. Management of specific clinical manifestations

## 6.1. Lupus nephritis

### 6.1.1. Indication for renal biopsy

**Questions to be answered:**

- What are the criteria for recommending a renal biopsy?

SLE patients and renal function disorders present a renal pathology that, in the majority of the cases, can be framed within LN lesions. To better characterise the nature and degree of impairment, having a histological study by means of renal biopsy is necessary. The biopsies should be assessed by expert nephropathologists who, after the study with optical microscope techniques, immunofluorescence, and if necessary, electronic microscopy, characterise the lesions at a glomerular, interstitial and vascular level. Although, due to clinical presentation, the renal biopsy will often show a previously suspected class, the diagnosis confirmation and extension of the lesion degrees, will permit making adjustments in the immunosuppressive treatments, both in terms of intensity and in duration, so the objective of achieving a full remission situation is reasonable. Therefore, renal biopsies are considered today as the *gold standard* for the majority of LN diagnostic procedures. However, there are areas of uncertainty such as when biopsies should be repeated during treatment, which should be assessed in prospective studies designed for these goals.

| | |
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| Renal impairment in SLE in our environment, reaches 40% of the patients at some moment of their disease evolution. Its presence determines, independently, an unfavourable life prognosis. | Cohort S. 2+ |
| At the present time, the histopathological classification, reached by consensus of the *International Society of Nephrology/Renal Pathology Society* (ISN/RPS) in 2003, provides greater precision and less overlapping with respect to previous classifications such as that of the WHO (Annex 6).[493] | Expert opinion 4 |
| This new classification also permits better communication between pathologists and clinicians, and it is also a useful tool for standardising and assessing therapeutic actions, and establishing renal survival prognoses.[494-496] | Expert opinion 4 |
| The analytical abnormalities that should be present to recommend a first renal biopsy (unless this is expressly contraindicated), are related to a rise in serum creatinine and/or presence of proteinuria (over 0.5 g/day). These analytical alterations can appear in isolation or combined with the presence of active sediment.[12,45,496] | Expert opinion 4 |
| Classes I and II prevail in renal biopsies performed on patients with silent lupus, in a study conducted in Spain; the renal survival was 98% after a 46-month follow-up, with no correlation with the class of renal lesion.[497] | Cohort S. 2+ |

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| In a study of 21 patients with analytical alterations of LN, but with 24-hour proteinuria less than 1 g, and on whom a renal biopsy had been carried out due to other disorders, renal pathology appeared in 16 (77%): three with class II; 10 with class III; two with IV class and one with class V. These authors defend performing a renal study with biopsy in the case of mild-moderate analytical alterations as in 13 of their cases, the characterisation of the LN type permitted a modification of the immunosuppressive treatment.[498] | Cohort S. 2- |
| The report on renal biopsy in LN should include, in addition to the class, the activity lesions, chronicity, tubular and vascular lesions (Annex 6).[499,500] A higher score in chronicity lesions inversaly correlates with renal survival.[501,502] | Cohort S. 2+ |
| One study, performed by five nephropathologists, who analysed 126 biopsies (87 first and 39 successive) obtained from 87 patients with proliferative type LN, included in a controlled clinical trial, led to the conclusion that there was a high degree of concordance, which was very high for the activity indices (CCI= 0.716) and lower for the chronicity indices (CCI= 0.494).[503] | Cohort S. 2+ |
| In this vein, another study that re-assessed 99 kidney biopsies of patients with LN, comparing the old classification (WHO) with the new classification (ISN/RPS), showed that, with the new classification, class IV-G had worse renal prognosis than class IV-S. When they analysed global scores of each biopsy, the renal survival was worse in patients with a high score compared with those with a lower score.[504] | Cohort S. 2+ |
| On other occasions, the pathological clinical correlation between classes IV-S and IV-G was poor, a circumstance that reflects the difficulty of one single biopsy being representative of renal parenchyma or the possibility of transformations between classes.[505] | Cohort S. 2- |
| The clinical and morphological differences found in patients with class IV LN, either IV-S or IV-G, could be due to different pathogenesis. This was shown in a pathological study of a series of 65 renal biopsies, which showed that those two class IV lesions expressed degrees of renal impairment that would reflect the different presence of immunocomplexes.[506] | Cohort S. 2- |
| In addition, the renal biopsy may help contraindicate immunosuppressive treatments, when the predominant renal lesions are chronic or also in the case of acute kidney injury (AKI) where the renal biopsy only shows acute tubular necrosis type lesions and/or thrombotic microangiopathy lesions suggestive of APS.[506] | Case series 3 |
| There is controversy regarding the use of repeated renal biopsies as immunosuppression intensity or time markers. In general, repeating a renal biopsy is not recommended if the evolution is good or reasonable. Indications for a second biopsy would therefore be resistant to the treatment or the unexplained increase in serum creatinine or proteinuria,[496,500,508] including possible suspected nephropathies not related to lupus.[509] | Cohort S. 2+/2- |

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In a cohort of 31 patients with LN who were biopsied twice or more times over a period of 10.5 years due to persistence of proteinuria; recurrent nephrotic syndrome or worsening of the renal function, the multivariate analysis of the pathological findings correlated with clinical changes and it was useful for crescent-shaped cells in more than 30% of the glomeruli and a chronicity index of over five (about 12). Thus, indicating a second biopsy due to a rise in serum creatinine or of proteinuria, would permit limiting the immunosuppression, if high chronicity indices were found.[510] Cohort S. 2+

In contrast, repeated biopsies by protocol have limited usefulness as predominant proliferative lesions of classes II and IV are almost always maintained, or exceptionally, are transformed into lupus nephropathy class V.[511] Finally, it is infrequent for patients with proliferative type initial biopsy to show a non-proliferative class in the second biopsy. Only in cases where a first biopsy showed a non-proliferative class, would the re-biopsy be justified, faced with adverse clinical-analytical evolution.[512] Cohort S. 2-

**Summary of evidence**

| | |
|---|---|
| 2+ | Renal biopsy is a useful diagnostic tool in the evaluation of renal lesions of patients with suspected LN as it determines the prognosis of SLE.[497] |
| 2+ | The 2003 ISN/RPS classification of LN defines the main renal lesions of lupus patients with greater precision and less overlapping.[493-495,500-513] |
| 2+ | The renal pathological report should be carried out by expert nephropathologists who can ensure precision in establishing the diagnostic class, and activity and chronicity indices, as well as tubulointerstitial impairment, thus limiting possible interobserver variations.[499,503-505] |
| 2+ | Predominant renal lesions in patients with silent lupus usually correspond to classes I and II with a good renal survival prognosis and with no correlation with histological impairment.[497] |
| 2+ | Chronicity lesions in the first or successive renal biopsies correlate with the prognosis of renal function and condition changes in the immunosuppressive treatment.[501,507,510] |
| 2+ | We do not recommend repeating renal biopsy in lupus patients who achieve remission or good clinical evolution.[496,500,508,509] |

**Recommendations**

| | |
|---|---|
| B | We recommend performing a renal biopsy on all SLE patients who present confirmed proteinuria ≥ 0.5 g/day, especially in the presence of active sediment and/or isolated renal insufficiency, without alternative explanation. |
| C | The renal histopathological study should also inform of the class, degree of activity, chronicity, and presence of vascular and interstitial lesions. |
| C | We do not recommend the routine repetition of renal biopsies, which would be limited to refractory patient or patients with renal relapse when it is considered that the result may determine a therapeutic change. |

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

## 6.1.2. Therapeutic objectives

**Questions to be answered:**

- What are the specific therapeutic objectives?

The specific therapeutic objectives for patients with LN include: a) reaching full clinical-analytical remission or failing this, partial remission; b) reducing the risk of new activity flares; c) stop the progression of their renal disease towards renal insufficiency stages that might require renal replacement treatment with dialysis or transplant; d) reducing mortality.

However, at the present time, there are areas of uncertainty about «ideal» drugs; degree of response to be obtained before going on to maintenance patterns; duration of the maintenance period; optimisation of the treatment in case of relapses, among others.[514]

In agreement with the recent consensus document EULAR/EAR-EDTA[6], the main therapeutic objectives for LN are: — Opinión expertos 4

1.- Preserving the renal function in the long term.

2.- Preventing relapses.

3.- Avoiding secondary damage to the treatment.

4.- Improving survival and HRQoL.

The treatment should aim to obtain full response, or failing this, partial response, which should preferably occur within six months and never later than 12 months. Although there is no consensus in partial response and full response definitions, the last GEAS-SEMI/SEN[45] consensus has proposed the following response criteria:

**Partial response:** In patients with baseline proteinuria ≥ 3.5g/24h. decrease of proteinuria < 3.5g/24 h. In patients with baseline proteinuria < 3.5g/24h. reducction of proteinuria in > 50% compared with initial proteinuria. In both situations, stabilisation (± 25%) and improvement of serum creatinine with respect to initial values.

**Complete response:** Serum creatinine < 1.2mg/dL (or decrease to initial values or ± 15% of baseline value in those with creatinine ≥ 1.2 mg/dL), proteinuria ≤ 0.5 g/24h, inactive sediment (≤ 5 red blood cells, ≤ 5 leukocytes, 0 hematic red cells casts) and serum albumin > 3 g/d.

In any of the LN classes special attention will be paid to controlling blood pressure and to the disappearance of proteinuria, as the high elimination of proteins in urine is considered as an additional risk factor for the progression of renal disease.[515] — Case series 3

For the standardisation of blood pressure and reduction of proteinuria, drugs from the ACE inhibitor group or angiotensin receptor antagonists (ARA) should be used as first choice. The anti-proteinuria action of these drugs is independent from the decrease in blood pressure.[515-519] — Cohort S. 2+

The follow-up of a cohort of 80 patients (21%) of a total of 378 (LUMINA) who received treatment with ACE inhibitors led to the conclusion that 88.1% of those treated, compared with 75.4% of those not treated ($P$=0.02), were renal impairment-free after 10 years (HR= 0.27; 95% CI: 0,09-0,78).[520] — Cohort S. 2+

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

**Summary of evidence**

| | |
|---|---|
| 4 | In agreement with the recent consensus document EULAR/EAR-EDTA[6], the main therapeutic objectives for LN are:<br>1.- Preserving the renal function in the long term.<br>2.- Preventing relapses.<br>3.- Avoiding secondary adverse effects to the treatment.<br>4.- Improving survival and HRQoL. |
| 2+/2-/3 | Controlling blood pressure and adjutant measures to reduce proteinuria are important to achieve remission. To this end, drugs from the ACE inhibitor or ARA group should be used as first choice.[515-520] |

**Recommendations**

| | |
|---|---|
| D | The main therapeutic objective for LN are:<br>1.- Preserving the renal function in the long term.<br>2.- Preventing relapses.<br>3.- Avoiding secondary adverse effects to the treatment.<br>4.- Improving survival and HRQoL. |
| C | To increase the probabilities of remission, we recommend adjutant treatment with angiotensin converting enzyme inhibitors, angiotensin receptor blockers for a good blood pressure control and to reduce proteinuria. |

## 6.1.3. Refractoriness

**Questions to be answered:**

- Which circumstances define a therapeutic guideline as ineffective/refractory to treatment?

There are no standard refractorines definitions. However, considering the adverse prognostic meaning of not achieving a reduction in baseline proteinuria or more than 50% or total proteinuria of below 1g/24h. after six months, the absence of at least partial remission after six months' treatment has been proposed as the main criterion of ineffectiveness.[12,45] CPG

One of the main reasons that should be ruled out before considering that a treatment is ineffective, is therapeutic non-compliance. This risk should be commented with patients during the first visits and if suspected, it may be one of the reasons for establishing levels of drugs or for choosing, in proliferative classes, endovenous CPM pulsed induction patterns.[521] CPG

In agreement with the different, recently published LN treatment guidelines, we recommend the option to change to another drug, of those with proven effectiveness in first line: MMF for CPM or vice versa.[12,45,496] CPG

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| | |
|---|---|
| Fourteen out of twenty-one patients with refractory III-V LN at more than two immunosuppressant regimes, responded satisfactorily after 12 months to the combination of MMF (1 g/day) tacrolimus (4 mg/day) and prednisone (<10 mg/day), with no side effects that entailed discontinuing the treatment.[522] | Cohort S. 2- |
| One five-year observational study on 17 patients treated with tacrolimus for LN refractory to MMF, objectified a response rate of 71%, with 24% relapses.[523] | Cohort S. 2- |
| In 26 patients with LN resistant to CPM, tacrolimus at doses of between 2-3 mg/day induced 88% response after six months.[524] | Cohort S. 2- |
| Rituximab (RTX) has been used in refractory patients as rescue medication. One SR on 26 analysed publications with 300 treated LN and 60-month follow-up, showed that RTX achieved partial or complete remissions in 87% of patient with class III; in 76% of patients with class IV and in 67% of patients with class V, respectively, suggesting that, in selected cases refractory to other immunosuppressants, RTX has proved useful at doses of 0.5-1 g on days one and 15, or 376 mg every week for four consecutive weeks.[367] | SR 2+ |
| The analysis of a group of 164 patients selected from European cohorts due to refractoriness, who were treated with RTX, glucocorticoids (99%) and immunosuppressants (76%, CPM: 58 and MMF: 55) showed complete remission in 30% after 12 months; partial remission in 37% and no response in 33%. Those who did not respond had nephritic syndrome and renal insufficiency to a greater extent.[525] | Cohort S. 2+ |
| The different consensus CPGs of ACR GEAS-SEMI/SEN[45] and EULAR/ERA-EDTA[12] recommend, in cases of refractory LN without satisfactory response to change in first line treatment (CPM and MMF), using RTX, anticalcineurins, Ig, belimumab or drug combinations. | CPG |

**Summary of evidence**

| | |
|---|---|
| 4 | Refractoriness is defined as the absence of at least partial remission after six months' treatment.[12,45] |
| 4 | In patients with refractory LN, we recommend, as a first measure, ensuring correct therapeutic compliance.[45] |
| CPG | The recently published consensus CPGs recommend, in patients with LN refractory to treatment with CPM or MMF, changing to another first line drug (MMF or CPM).[12,45,496] |
| 2- | In patients refractory to standard immunosuppressive patterns, a combination of tacrolimus and MMF in a multitarget approach permits increasing global immunosuppression with lower individual doses.[522] |
| 2+ | Rituximab (RTX) has been successfully used in patients refractory to standard immunosuppressive patterns as rescue medication.[367] |
| CPG | The different consensus CPGs of ACR[496], GEAS-SEMI/SEN[45] and EULAR/ERA-EDTA[6] recommend, in cases of refractory LN without satisfactory response to change in first line treatment (CPM and MMF), using RTX, anticalcineurins, Ig, or drug combinations. |

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**Recommendations**

| | |
|---|---|
| D | We suggest considering as refractory those patients who do not reach at least partial remission after six months' treatment. |
| D | In patients with refractory lupus nephritis we suggest, as a first measure, ensuring correct therapeutic compliance and verifying that the renal lesions are reversible. |
| D | In patients with nephritis who are refractory to treatment with cyclophosphamide or mycophenolate, we suggest changing to another first line drug (mycophenolate or cyclophosphamide). |
| D | In cases of refractory nephritis without satisfactory response to the change in first line treatment (cyclophosphamide and mycophenolate), we suggest using rituximab, anticalcineurinics, Ig, belimumab or drug combinations. |

## 6.1.4. Induction treatment

### 6.1.4.1. Induction treatment of proliferative lupus nephritis

**Questions to be answered:**

- What should be the induction treatment of proliferative lupus nephritis?
- Under what conditions would induction treatment with mycophenolate afford advantages over other drugs?

The immunosuppressive treatment of LN should be organised into two phases: a first induction phase of the response, with higher doses of drugs, and a second longer-lasting maintenance phase of the response but with lower doses of drugs.

The main objective of the induction treatment is to achieve a complete response for the episode as early as possible, and of the maintenance treatment, to prolong the complete response or quiescence state of LN as long as possible.[526,527]

Expert consensus 4+

Maintenance therapy was suggested for the first time by the group of the *National Institute of Health* (NIH),[384] on showing that prolonging immunosuppressive therapy from six to 30 months and adding intravenous CPM glucucorticoids at reduced doses, decreased recurrences (60 v. 13%; $P$=0.006) and increased renal survival ($P$=0.037).

RCT 1+

Although there is some controversy, the times to achieve remission during the induction phase are variable as a clinical-analytical improvement without remission is often noticed, which is not an obstacle for changing to a maintenance phase, after six months' induction treatment, even though only partial objectives have been achieved until then.[528] In a study of 212 Canadian patients, the time to reach complete response may take up to five years, maintaining the same immunosuppressive treatment. Thus, 52% would respond completely after two years, and 74% after five years. Factors that predict late response are baseline proteinuria, male sex and hypocomplementemia.

Cohort S. 2+

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## Induction treatment of proliferative lupus nephritis

To achieve objectives in induction of LN, the combined therapy with immunosuppressants and glucocorticoids has shown better efficacy than corticoid monotherapy.[346,529-537]

The NIH group in Bethesda published several studies comparing corticoid monotherapy with glucocorticoids + CPM several decades ago now.[531,534,535] The first is a cohort of 62 patients rebiopsied after 18 months. Patients treated just with glucocorticoids presented a greater chronicity index ($P$<0.0001) and activity (P=0.01) than patients with combined therapy with any immunosuppressant: AZA or CPM).[531] — CCT 1+

In 1986, the same group notified a CCT of 107 patients with different therapeutic patterns, which included steroid monotherapy, and combined with oral or ev. AZA or CPM.[532] After five years' follow-up, the probability of not doubling serum creatinine was greater in the combined group with any immunosuppressant than in steroid monotherapy, although it was only significant in the group of intravenous CPM versus steroid monotherapy. Five years later, they published similar results in the advanced chronic kidney disease (ACKD),[533] so any immunosuppressant or combination of immunosuppressants (oral AZA + CPM at low doses) was better than steroid monotherapy at the ACKD *endpoint*.[532] — CCT 1+

In 1996, this group published the results of a RCT on 82 patients treated with three patterns: 1) corticoid monotherapy (oral + monthly pulses of MPred for 12 months); 2) combined therapy with intravenous CPM (6 monthly + 8 quarterly pulses) + oral glucocorticoid; 39 2 + 1. Follow-up for 5-8.5 years. The addition of CPM to any of the corticoid patterns obtained better results in response, recurrences and tendency to double serum creatinine. Five years later,[346] they managed to ratify this last endpoint of doubling of serum creatinine in favour of CPM (RR= 0.095; CI 95%: 0.01-0.84).[534] — RCT 1+

Sesso *et al*. did not find any differences between corticoid monotherapy and combined with CPM in doubling serum creatinine in a small Brazilian cohort of 29 patients monitored for 18 months ($P$>0.20).[535] Other authors with the same proposals would find differences later on when the follow-up time was increased.[346] — RCT 1-

Felson *et al*. published a first MA of CCT in which they found less impairment of the renal function and less renal-cause deaths in patients treated with combined therapy (CPM + AZA) + prednisone compared with corticoid monotherapy.[530] — MA 1+

In 1997 Bansal *et al*. published another MA of 19 studies. The analysis of the combined results showed that combined therapy with immunosuppression was superior in terms of: global mortality and development of ACKD. The simultaneous use of oral CPM and AZA together with glucocorticoids was more effective than prednisone alone in reducing the kidney disease rate in terminal stage. There were no differences between different immunosuppressants.[536] — MA 1++

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In 2004 Flanc *et al*. published a new MA with 25 RCTs respect to the efficacy and safety of combined treatment in LN. The combination of CPM with glucocorticoids opposed to prednisone in monotherapy reduced the risks of renal insufficiency. However, there were no differences with respect to global mortality, although there was a greater risk of ovarian insufficiency. None of the therapies were related to a greater incidence of infections.[537] MA 1++

**Doses of glucocorticoids combined with immunosuppressants**

The glucocorticoid dose used in both branches of the *Eurolupus Nephritis Trial* (ELNT) in European SLE patients was groundbreaking as it suggested that higher starting doses than 0.5 mg/kg/day preceded by 750 mg pulse therapy for three days, did not add benefits in terms of efficacy of the treatment, but it did represent less safety.[538] Cohort S. 2+

The observational study of Ruiz-Irastorza *et al*.[345] compared a group of 15 patients with biopsied LN treated with initial average doses of prednisone <30 mg/day (mean 20 mg/day) with 30 historical controls, paired for age, gender and type of LN, who received high doses (mean 50 mg/day). The majority of patients in both groups (86%) were treated with CPM. 100% of the patients of the medium dose group also received HCQ opposed to 33% in the high dose group. The pulse MPred dose was also greater in the medium dose group. Likewise, prednisone was reduced much more quickly in the medium dose group, with a mean until reduction to 5 mg/day of 16 weeks v. 87, ($P$<0.001). The full or partial response rate after six months was 87% v. 63%, respectively ($P$=0.055). In the long term, complete remission was reached in 100% of the patients with medium doses compared with 70% in the high dose group ($P$=0.013). The number of renal re-flares was also less in the group treated with medium doses (13 v. 47%, $P$=0.008). Nine patients in the high dose group suffered long-term renal complications (four kidney transplants, three haemodialysis, two deaths due to active nephritis) as opposed to none in the medium dose group ($P$=0.02). The respective rate of adverse effects attributable to glucocorticoids in the groups treated with medium and high doses of prednisone was 7 v. 67% ($P$<0.0001). It is noteworthy that, in this study, the global toxicity associated with glucocorticoids was related to the dose of prednisone accumulated after six months and that, more specifically, the number of weeks elapsed with doses of prednisone of above 5 mg/g was an independent predictor of the presence of osteoporotic fractures. Cohort S. 2+

Eighty-one patients from an open CCT received three initial pulses of MPred in induction followed by MMF. 42 patients were randomly allocated to prednisone with initial doses of 1 mg/kg/day (varying between 45 and 70 mg/day), insofar as this dose was reduced to half in 39 patients. In both groups, the prednisone was gradually reduced, until a maintenance dose of 5 and 10 mg/day and 5 and 2.5 mg/day, respectively, was reached, with a reduction to 5 mg/day in a maximum interval of 24 weeks). The response after six months was similar in both groups, but infectious complications (above all herpes zoster) were more frequent in the group with higher steroid dose ($P$=0.05).[342] CCT 1-

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The observational study of Fischer-Betz *et al*.[344] analysed the clinical course of 40 patients with first episode of LN treated with 12 intravenous CPM pulses, and who did not receive prednisone on a routine basis but rather depending on the extrarenal manifestations of lupus. 37.5% of the patients received HCQ. After comparing the evolution of patients who received an initial dose of prednisone ≥ 20 mg/day v. < 20 mg/day, the complete response rate was 52.5% and 71.4% respectively ($P$=0.37). The infection frequency was similar in both subgroups. In the long term, the risk of relapses was similar (dose: < 20 v. ≥ 20 mg/day; HR: 0.73; 95% CI: 0.25–2.12, $P$=0.57).[344]

Cohort S. 2+

Pulse therapy with 500 mg intravenous MPred for three days, used in very severe cases of LN seems to have the same efficacy as higher doses and with less side effects, according to a longitudinal study of 20 cases compared with historical control.[539]

Case series 3

**Choice of induction immunosuppressive treatment of proliferative lupus nephritis**

For induction of remission in proliferative LN, intravenous CPM in pulses has shown, over the years, to have proven efficacy.[346,529-537]

However, its high association with amenorrhoea[540-545] among other adverse effects has determined a progressive decrease of dose and the introduction of other immunosuppressants.

The most commonly used CPM patterns in induction are:

- Pulse therapy 0.75-1 mg/m$^2$ month for 6-8 months.[386,538,540,545-547]

- Intravenous pulse therapy 500 mg every 15 days for three months.[386,538,545]

Comparative studies between the two patterns have shown no significant differences in efficacy or in side effects,[542-546] although the higher accumulated dose pattern has been tested in European and American population with possibly more severe NL[384,386,538,545], and the lower dose pattern, above all in Egyptian and European population with 70-85% Caucasians and somewhat less aggressive LN.[386,538,545]

1++ 2+

In the ELNT with 90 Caucasian patients, baseline creatinine 1.15; proteinuria 3.04; activity index: 9.9 and chronicity index: 0.8, fortnightly minibolus of CPM (500 mg) as induction was compared with six monthly + two quarterly pulses (0.75/m$^2$). After 42 months' follow-up (8-62), no significant differences were found between the two groups. Severe infections differed although not significantly (17 v. 7 episodes; $P$=0.20). The incidence of amenorrhoea was low and similar in both groups.[538] The results were maintained after a 10 year follow-up.[548]

RCT 1++

An Egyptian group,[386] following the ELNT protocol, published its experience with 46 patients with one-year follow-up. No differences were found between the two groups in terms of renal survival or flares.

RCT 1+

Combining these two studies, a MA,[549] in terms of efficacy and safety in induction, leans in favour of the fortnightly low dose of CPM (RR= 0.45; 95% CI: 0.20-1.09; $P$=0.053 for treatment failure and RR= 0.68, 95% CI: 0.52-0.90; $P$=0.008 for risk of infection).

MA of RCT 1+

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In a survival analysis, Mitwali *et al*. published their results with 117 patients treated with different patterns of iv CPM. Group I (n=73) received six monthly + six twice-monthly pulses of 10 mg/kg. Group II (n=44) received half the dose by pulse but 18 twice-monthly ones. 6.7 ± 3 year follow-up. With no differences in glomerular filtration parameters, proteinuria was lower, as were amenorrhoea, and neoplasia in group II.[385] RCT 1+

Over the last few years, oral MMF has also proven to be efficient and safe in this field[389,546,549-553] With respect to CPM, it has been seen to be equally efficient in first level studies –RCT–[546,549,552,553] and superior in other first and second level studies[388,554-556] Some studies or MA on the latter have shown a better safety profile of MMF with respect to CPM in infections, [557] leucopoenia,[549,551,555,558] alopecia[552,555,559] and amenorrhoea.[546,549,552,555,558,559] With respect to gastrointestinal disorders, they seem to be similar[546,551,559] or with a better profile for CPM.[551,556]

An open RCT on 64 patients compared 2g MMF for 12 months followed by AZA for 1 m. v. oral CPM for six months followed by AZA 12m, with an average follow-up of 63 months. There were no differences between groups in induction of response, renal survival or relapses. In terms of safety, they observed more severe infections ($P$=0.014) and amenorrhoea (36 v. 3%; $P$=0.004) in the group of CPM + AZA.[389] CCT 1+

Another RCT on 44 patients treated with intravenous CPM every month (0.75-1 g/m$^2$) v. 2g MMF, did not objectify differences, either, after the sixth month, in terms of efficacy (remission $P$=0.070 as main endpoint) or of safety ($P$=0.18). After the analysis of 24 protocol biopsies after six months, a reduction in the activity indices were observed but not in chronicity indices, suggesting greater efficacy for the group treated with MMF.[553] RCT 1-

In a non-inferiority trial on 140 patients whose main objective was also remission after six months, in 2005 Ginzler *et al*. published the superiority of MMF v. CPM in reaching complete remission ($P$=0.005), not so in the partial or in the join one. Significantly, more patients from the CPM group presented infections compared with the group with MMF.[551] RCT 1+

The ALMS study (n=360), which included 66 patients with creatinine clearance under 60 and 32 patients under 30 ml/mn, examined, as primary objective, the induction of remission after six months of MMF (3 g/day) v. CPM (6 monthly pulses of 0.75 g/m$^2$), not finding significant differences, except for cases of the Hispanic/Afro-American ethnic group, in favour of MMF ($P$=0.03). In terms of safety, the total number of patients with adverse effects was similar, the total of patients who discontinued due to adverse events was greater in the MMF group, very close to the statistical significance cut-off point ($P$=0.05), and the total number of events was higher in the CPM group (40.6% more).[546] RCT 1++

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The first MA with all the RCTs published until that time was performed by Kamanamool *et al*.[552] They included five RCTs, four of them already mentioned with a total of 638 patients (317 for MMF at variable dose between 1-3 g/day and 323 for intravenous CPM in four of them at doses of 0.75-1 mg/m$^2$ and oral in another). The baseline levels of proteinuria were similar in four of them (4.10-5.35), and less in one (2.48); the creatinine levels varied between 1.07-1.50 mg/dl statistical heterogeneity presented by the RCTs included ($I^2$= 59%; *P*=0.04) in the outcome measure; complete remission seems due to the study of Ginzler *et al*.[551] in which the percentage of the female gender was higher than in the rest. A bias coefficient/limit error was found (2.03; P=0.049), whose significance dropped (*P*=0.054) when the study of Ginzler *et al*.[551] was eliminated. Thus, the RR for complete remission was 1.60 in favour of MMF but on the limit of statistical significance (95% CI: 0.87-2.93). Neither in complete nor partial remission ($I^2$= 63%; *P*=0.030) were there significant differences (RR= 1.20; 95%CI: 0.97-1.45). MA of RCT 1++

In adverse events, there were no differences in infection (5 RCTs, $I^2$= 63%; *P*=0.03) or in gastrointestinal symptoms (4 RCTs). Ovarian dysfunction was not analysed as there were not sufficient data (2 RCTs) and significant differences were found in terms of leucopoenia in favour of MMF (3 RCTs, $I^2$= 0%, RR= 0.65; 95% CI: 0.44-0.96).

In 2011, Touma *et al*. published another MA with the four RCTs mentioned above, with a total of 618 patients (308 MMF, 310 CPM).[554] In complete or partial remission ($I^2$= 68-75%), they did not find significant differences between the two drugs, but they did find a tendency towards better results with MMF (RR= 0.89: 95% CI: 0.71-1.10). In terms of side effects ($I^2$= 81-87%), they did not find differences in infections, gastrointestinal symptoms or leucopoenia. They did for alopecia (RR= 5.77; 95% CI: 1.56-21) and amenorrhoea (RR= 6.64; 95% CI: 2-22), all in favour of MMF. MA of RCT 1++

Lee *et al*. performed a MA with six studies, finding similar results.[549] In terms of efficacy, MMF does not differ from CPM in reaching any type of remission, either in amenorrhoea or leucopoenia, although the tendency is favourable towards MMF for the latter two. MA of RCT 1++

Seven studies with 725 Asian patients assessed by Liu *et al*. did not find significant differences between CPM (oral and ev) and MMF (2-3 g/day) in induction of remission, with a high heterogeneity index ($I^2$= 53%). When the RCT using oral CPM was eliminated, the heterogeneity ($I^2$= 26%) was reduced and statistically significant differences were found in favour of MMF (RR= 1.72; 95% IC: 1.17-2.55; *P*=0.006 for complete remission and RR= 1.18; 95% CI: 1.04-1.35; *P*=0.01 for partial response).[556] In terms of safety, the total sample was homogeneous, and they observed significant differences in favour of CPM regarding diarrhoea (RR= 2.54, 95% CI: 1.70-3.80, *P*<0.001) and in favour of MMF regarding leucopoenia (RR= 0.47; 95% CI: 0.34-0.64, *P*< 0.001),amenorrhoea (RR= 0.14; 95% CI: 0.04-0.47; *P*=0.001) and alopecia (RR= 0.25; 95% CI: 0.16-0.40, *P*=0.001). Regarding infections, they did find high heterogeneity ($I^2$= 78%) but no differences between groups (*P*=0.02). MA of RCT 1++

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The last MA of six CCTs with 686 patients compared MMF (1.5-3 g/day with intravenous CPM 0.5-1 g/m$^2$/m (10 CCT, n=953). In total terms, it did not find any difference in efficacy (complete remission: OR= 1.39; 95% CI: 0.99-1.95; $I^2$=15%) but it did in terms of safety in favour of MMF (ovarian failure $I^2$= 0%, RR= 0.15; 95% CI: 0.03-0.80), alopecia $I^2$= 33%, RR= 0.22; 95% CI: 0.66-0.86), leucopoenia ($I^2$= 41%, RR= 0.49; 95% CI: 0.28-0.88), except diarrhoea in favour of CPM ($I^2$= 9%, RR= 2.53; 95% CI: 1.54-4.16).[388]

MA of CCT 1++

A study was conducted in Malaga with a cohort of 144 patients treated with four different immunosuppressive patterns at different historical moments: A (intravenous CPM 1 g/month, for 24 months); B (intravenous CPM 1 g/month, six months + 1 g/quarterly, for 18 months); C (intravenous CPM 0.5 g/fortnightly for three months and, later, for 24-36 months, AZA or MMF 1-2 g/day), and D (MMF 2-3 g/day for six months followed by 1-2 g/day for 24-36 months). No significant differences were observed in response/remission to treatment six of 24 months after the start of the therapy.[545]

Cohort S. 2+

There are no comparative studies on doses, although higher doses of up to 3 g/day have been used, above all in American patients and in CCT,[546,551] and lower doses (2 g/day) in Europeans and Asians, and in cohort studies.[342,389,550,553] These studies that use 2g in induction, defend that 2g of MMF could be equally efficient and produce less side effects.

RCT 1+
RCT 1-
Cohort S. 2+

Grootscholten *et al*. tested induction therapy and maintenance with AZA compared with CPM in 87 patients with similar baseline indices to the other studies. There were no differences in response index after 24 months or in the ovarian insufficiency index, but there were differences in infections due to HVZ in contrast to AZA.[558]

nRCT 1+

Cohort studies[559] and one nRCT[392] did not observe differences in efficacy or adverse effects between CsA and CPM in patients with proliferative LN. The majority of all other cases with CsA or tacrolimus were refractory cases.[549]

A study of 40 patients, the majority with proliferative class, with average creatinine of 1.14 ± 0.5 mg/dl, compared tacrolimus 12 months with monthly intravenous CPM 6 m + AZA 6 m.[559] The response/remission was significantly greater in the tacrolimus group. Complete remission was also greater in the tacrolimus group after 12 months (75 v. 40%, *P*=0.025).

Cohort S. 2+

In the Cyclofa-Lune study with 40 patients treated with CPM (non-standard pattern of eight bolus in nine months, progressively every three, four and six weeks, followed by maintenance with 4-5 bolus of oral CPM of 10 mg/day every 6-8 weeks) compared with CsA (4-5 mg/kg/day x nine months as induction and 1.25-3.75 mg/kg/day for another nine months as maintenance), they did not observe differences in complete or partial remission at the end of the induction phase (9 m). Creatinine and creatinine clearance was significantly better in the CPM group.[392]

CCT 1+

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Lee *et al*. published a SR of seven studies (six prospective studies and a nRCT) with 115 patients and 54 controls (placebo, CPM or AZA) treated both in induction and maintenance, for nephritis resistant to glucocorticoids or other immunosuppressants. As the heterogeneity of the studies was very high, they concluded by confirming efficacy and safety of tracrolimus in these nephrites.[549] SR 2+

In one MA, Yang *et al*. summed up four RCTs, one control case and one cohort with 265 patients treated with anticalcineurins + prednisone compared with CPM+prednisone. With a $I^2$ of 0%, they observed better efficacy results in complete remission and total response with anticalcineurins. In terms of adverse effects, those treated with CPM presented more leucopoenia and ovarian failure, and less transient renal insufficiency and hydrocarbonated disorders than those treated with anticalcineurins. On splitting CsA and tracrolimus, it seems that the results with the latter are better in terms of efficacy and safety.[560] SR/MA 1++

RTX added to MMF does not seem to afford benefits in CCT and MA.[365,388] However, observational studies in mono- or biotherapy with glucocorticoids shed positive results in efficacy and safety with RTX mainly in refractory or relapsing nephritis.[561]

In the LUNAR study,[365] RTX was added to the baseline treatment with MMF in 72 patients of the 144 included in the study. Superiority was not noticed with RTX in efficacy (remission) or in safety (RA). nRCT 1+

In Italy, Moroni *et al*. treated 54 patients who presented a renal flare or refractory disease in induction with fortnightly RTX, with monthly intravenous CPM or MMF 2-2.5 g/day for six months. After the fourth month, AZA or CsA were added in the three groups as maintenance therapy. After 3rd and 12th months, the three groups reached a significant response with no difference between them, although it is worthy of note that the characteristics of the RTX group were clearly worse than in the rest of the groups (older age, longer duration of the disease, more previous flares, higher activity and chronicity indices).[562] Cohort S. 3

One MA that analysed the aforementioned studies (LUNAR, RTX+MMF v. MFM)[556] and another similar one (intravenous RXT + CFM v. RTX),[388] confirmed that the addition of RTX to MMF or CPM did not add benefits in terms of efficacy. MA 1+

Before publishing the studies explained above, Ramos-Casals et al observed in a SR of cases with 103 patients with LN treated with RTX alone or combined with CPM, a therapeutic response of 91%. However, the heterogeneity of the patients included entail a high degree of bias.[563] SR of cases 2-

In the RITUXILUP study, RTX was combined with MMF, doing without the daily dose of prednisone. In this observational study, a high percentage of responses was achieved, although 44% of the cases corresponded to nephritis class V, so their results cannot be directly extrapolated to patients with proliferative nephritis (commented in detail in section 6.1.6. Immunosuppressive treatment for lupus nephritis type V).[564] Cohort S. 2+

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**Advantages of treatment with Mycophenolate**

| | |
|---|---|
| In Hispanic and Afro-American patients, MMF offers advantages over CPM.[546] | Subanalysis of RCT 1+/- |
| Asian patients have worse tolerance to the side effects caused by high doses of MMF (3 g/day), and Afro-Americans present more adverse effects due to CPM.[546] In the total group, patients from Asian regions presented less infections than other ethnic groups and in other geographical regions.[391] | |
| One MA published in 2011 of 11 CCT with limited/no heterogeneity between groups studied the induction of response in patients with MMF or ev CPM, revealing that Asian patients responded similarly to both drugs, but those outside Asia seemed to present better results with MMF than with CPM.[565] | MA 1++ |
| In women of childbearing age who have already received high doses of CPM, or women with difficulty to conceive (e.g., age >30 years) who wish to conceive, MMF offers advantages over CPM.[540-542,544,545] | |
| Boumpas *et al*, after seven monthly pulses of intravenous CPM (0.5-1 mg/m$^2$): found amenorrhoea in 0% of under 25s, 12% between 26-30 and 25% in people over 31. After 15 monthly pulses of CPM there was amenorrhoea in 17% of the <24 group, 43% in those aged between 26-30 and 100% in those over 30.[540] | Cohort S. 2+ |
| In the Malaga group, in a historical intention-to-treat analysis, 10 (37%) of patients treated with CPM 0.75 g/m$^2$ a month for 24 months presented amenorrhoea during the first two years' treatment compared with nine (19.6%) treated with CPM at lower cumulative doses.[545] | Cohort S. 2+ |
| In the ELNT there were no differences in amenorrhoea between those treated with eight pulses (6m+2t) of 0.5 g/m$^2$ of CPM (total dose: 8.5±1.9 g) compared with six pulses (fortnightly) of 0.5 g CFM (total dose 3 g).[538] | RCT 1++ |
| Wilson *et al*., in a cost-effectiveness study, compared CPM in monthly pulses of 1.250 g administered in Day Hospital and MMF 2.7 g/day in induction phase. They conclude that, with those premises, MMF is more economical and provides better HRQoL than CPM.[566] | Cohort S. 2+ |

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**Summary of evidence**

| | |
|---|---|
| 1++ | Proliferative LN should be treated with immunosuppressive treatment as well as corticotherapy.[346,529-532,534-537] |
| 1+ | Treatment of proliferative LN should be aimed at achieving induction of response and maintenance of this response.[384,526,527,548] |
| 1++ | The drugs that have proved to have greater efficacy, with more evidence on induction and maintenance treatment, are intravenous CPM and MMF.[385,388,389,536,537,546-554,556] |
| 1+ | CPM is superior to AZA for induction in terms of parameters of efficacy (renal survival) and safety (infection by herpes zoster virus).[558] |
| 1+ | For induction, the most commonly used dose of CPM and MMF in quality studies is pulse therapy with 50 mg/15 days x three months for CPM, and 2 g/day for MMF in Europe, with mild-moderate LN; and 0.75 g-1 g/m$^2$ per month x six months for CPM and 3 g/day for MMF in America with more severe LN.[538,546] For Hispanic people(from Latin America) and Afro-Americans, MMF offers advantages over CPM in terms of efficacy.[391] |
| 2+/2++ | Anticalcineurins for induction have been studied, providing similar or superior efficacy to CPM with different treatment patterns.[392,549,559,560] |
| 1+ | RTX added to CPM or MMF has not shown any benefit according to the RCTs published to date.[365,388] |
| 1-/2+ | In patients with LN, initial doses of prednisone ≤ 30 mg/day, combined with HCQ, immunosuppressants, and/or pulses of MPred, obtain response rates that are at least similar to regimens with higher doses.[342,344,345] |
| 2+ | The accumulated dose of prednisone and the number of weeks with doses >5 mg/day of prednisone are associated with greater toxicity.[308,345] |
| 3 | Pulse therapy with MPred at doses of 0.5-0.75 g/day x three days has a similar efficacy with milder adverse effects than higher doses.[539] |
| 2+ | An accumulated dose of CPM >8g increases the risk of ovarian insufficiency. At older ages, the safe dose is reduced to 5 g in some studies.[540-544] |

**Recommendations**

| | |
|---|---|
| A | We recommend to all patients with proliferative lupus nephritis to be treated with immunosuppressive drugs in addition to corticosteroid therapy. |
| A | The recommended therapeutic strategy should include a response induction phase and a maintenance phase of this response with lower drug doses. |
| A | The immunosuppressive drug of choice recommended for the induction phase of a first flare of LN is cyclophosphamide in pulse therapy or oral mycophenolate. |
| A | We do not recommend azathioprine for induction treatment. |
| C | In Hispanic patients from Latin America or African Americans, we suggest administering mycophenolate instead of cyclophosphamide. |
| A | The recommended dose of intravenous cyclophosphamide for induction is 0.5 g/2 weeks (3 months) or 0.75-1 g/m$^2$/month (6 months). |

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| | |
|---|---|
| B | The recommended dose of mycophenolate mofetil for induction is 2-3 g/day or the equivalent of sodium mycophenolate. |
| C | In women over 30 or with a risk of ovarian insufficiency, we suggest using minimum doses of cyclophosphamide (ELNT standard), or choosing mycophenolate both for induction and maintenance. |
| C | In women of childbearing age who have received cyclophosphamide reaching an accumulated dose greater than 8 g (or 5 g in women over 30), we suggest mycophenolate (or azathioprine) as drug of first choice for maintenance in the current episode, and as induction and maintenance in successive episodes. |
| √ | We suggest pulse therapy with methylprednisolone in the most severe cases (nephrotic syndrome and/or renal insufficiency), with nephritic syndromes and/or renal insufficiency and as oral prednisone saver. |
| C | In general, we suggest starting with oral prednisone doses no greater than 30 mg/day. |
| C | The reduction rate of prednisone should be fast up to doses of ≤5 mg/day, recommending reaching 5 mg/day after about 3 months and never after 6 months. |
| √ | We suggest pulse therapy with cyclophosphamide instead of mycophenolate in cases where therapy non-compliance is suspected. |
| C | We suggest anticalcineurin therapy as alternative induction treatment, supervising the levels of the drug reached to reduce the risk of nephrotoxicity. |

## 6.1.4.2. Induction treatment of lupus nephritis with renal insufficiency

**Questions to be answered:**

- What induction treatment in lupus nephritis with renal insufficiency should be administered?

The incidence of acute deterioration of glomerular filtration or ARI in patients with LN is unknown, probably low, but in any case undetermined, as the majority of large studies exclude this type of patient. Thus only cases, case series and retrospective cohorts remain.

In general, ARI has been considered as an increase in serum creatinine of more than 1.5 times with respect to baseline in less than seven days, or an increase of 0.3 mg/dl in less than 48 hours with or without oliguria.[567]

An increase in creatinine as presentation of LN infers a worse prognosis in long-term renal survival[568,569] and in addition to this alteration of the glomerular filtration, we have the normal causes of the non-lupus general population.

Zu *et al*. described a prevalence of ARI of 20.5% (66/322 biopsies of patients with LN) with average creatinine of 3.82 ± 2.59 mg/dl, and the majority with active sediment, nephrotic syndrome and class IV. In addition to corticotherapy, they received oral CPM (8/66), intravenous CPM 0.6-0.8 g monthly for six months (40/66), MMF (6/66) and LEF (9/66). On comparing the evolution of patients with LN without ARI, differences were found in: Partial response (24 v. 65%, $P<0.001$), treatment failure (53 v. 12%, $P=0.001$), and recurrences (10 v. 33%; $P=0.015$) during a similar follow-up of five years on average. In the multivariate analysis, ARI was a predictor factor to double serum creatinine or reach ACKD (HR= 5.82; 95% CI: 2.41-14.04; $P=0.001$).[568]

Cohort S. 2+

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Another Asian group divided its cohort of 79 patients with proliferative LN according to stage of ARI (according to RIFLE): 23% of the patients presented an increase of 1.5 in baseline creatinine, or reduction of 25% glomerular filtration ("Risk"), 16% presented an increase of twice the baseline creatinine, or reduction of filtration >50% ("Injuria"), and 15% presented an increase of three times the baseline creatinine or reduction of filtration of >75% (*failure*). The area under the curve (ROC) for progression to ACKD was 0.96 (95% CI: 0.91-1.0; $P<0.001$), and is related to the severity of the degree of ARI (OR= 27; 95% CI: 3-249; $P=0.003$). The percentage of crescents was related to the severity of ARI ($P<0.0001$).[570] Cohort S. 2+

Yu *et al*. presented their cohort of 152 patients with LN IV-G, 33 of whom (22%) contained crescents in the biopsy (61% cellular, 29% mixed, 10% fibrous). Presentation in all of them was as rapidly progressive renal insufficiency with average creatinine of 3.75 ± 2.68 mg/dl (range 1.7-11.4). Compared with the rest (119/152), patients with crescents presented more leucopoenia ($P=0.011$), anaemia ($P=0.015$), active sediment ($P=0.0221$), ARI ($P=0.001$) and positivity of antineutrophil cytoplasmic antibodies (ANCA) ($P<0.001$). 30% (10/33) presented positive ANCA (opposed to 2.5% in those without crescents) and 1/33 antiMBG. All of them were treated in induction with corticoid pulses 0.5-1gr/day for three days plus monthly intravenous CPM (30/33) or MMF (3/33), and in maintenance with intravenous CPM (31/33), MMF (1/33), leflunomide (1/33). Eight reached complete remission and 16 partial remission. Patient survival was similar in both groups, but not so renal survival which was only similar in those with crescents (HR= 0.17; 95% CI: 0.08-0.37; $P=0.001$).[571] Cohort S. 2+

Chin *et al*. informed of 37% ANCA positivity in 51 SLE patients. They related ANCA positivity, especially p-ANCA, with the presence of nephritis ($P<0.05$), especially in LN IV ($P<0.05$) with the presence of positive antiDNA ($P<0.05$), and also with the deterioration of the renal function ($P=0.03$).[572] Cohort S. 2+

Hu *et al*. examined 33 patients with LN IV and thrombotic microangiopathy (TMA). 81% debuted with ARI (average creatinine of 3.1±2 mg/dl), almost half of them requiring acute haemodialysis (42%). 52% showed segmentary necrosis, 70% micro-thrombi; 61% crescents, and 60% arteriolar thrombi. They were treated with MPred plus MMF (23), CPM (10) + plasmapheresis (3). After one year, only 55% had responded to the treatment, with 69% patient survival and 47% renal survival after five years.[573] Cohort S. 2+

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Yu *et al*. published a multicentre study with 313 patients with LN II-V and tubulointerstitial lesions. Seventy-eight patients (25%) presented ARI with average creatinine of 1.32 ± 0.97 mg/dl. Separating the sample into four groups according to severity of the tubulointerstitial and glomerular lesions, they only found significant differences in the two extreme histological involvement groups. That is, none of the patients with mild interstitial and glomerular involvement presented ARI (0%) compared with the rest of the patients who presented it in 23-40% ($P<0.05$); and those with severe interstitial and glomerular involvement presented higher figures of baseline creatinine than the rest (1.5 mg/dl v. 0.72-1.38 mg/dl, $P<0.05$). The treatment was corticoids in monotherapy in 13 and with immunosuppressants in the rest (CPM 228, MMF 21, Leflunomide 35, AA 16), with no differences between groups in terms of efficacy measured as chronic kidney disease (CKD)/ACKD. 292/313 patients reached response. After an average follow-up of 62±35 months, 37 patients presented CKD or ACKD. Baseline creatinine, cellular or fibrous crescents, or endocapillary hypercellularity remained in the multivariate as predictor factors of CKD/ACKD.[574]

Cohort S. 2+

A post-hoc analysis of the ALMS study in the subgroup of patients with glomerular filtration <30 ml/min/1.73m$^2$ (n=32, 20 MMF, 12 CPM) revealed a faster recovery of glomerular filtration in the MMF group (RR= 1.51 per week; 95% CI: 0.99-2.02; $P=0.001$), but it did not manage to establish differences in the response primary *end-point* (4/20, 20% responded in the MMF group v. 2/12, 17% in the CPM group; $P=0.9$).[575]

Post-hoc analysis 2+

The Spanish Glomerular Disease Group (GLOSEN) analysed a cohort of 56 patients treated in induction with monthly intravenous CPM for six months, and in maintenance with MMF (1-1.5 g/day). At the start of the maintenance treatment, 18 patients presented glomerular filtration <60 ml/min/1.73m$^2$ (MDRD-4), with baseline differences with respect to the >60 ml/min/1.73 m$^2$ glomerular filtration group in creatinine (1.6± 0.9 v. 0.8±0.1; $P<0.001$), proteinuria (3.3±2.5 vs. 1.2±1.2 g/day, $P=0.002$), age (37±10 v. 29±10, $P=0.01$), anti-DNA (1/169 v. 1/22, $P=0.01$) and haemoglobin (10.4±2 v. 12±2 g/dl, $P=0.01$). 34% of patients (all from the <60 ml/min/1.73m$^2$ glomerular filtration group) had not responded to induction at the start of the maintenance phase. After ensuring similar exposure both to CPM and to MMF in both groups, during the following 12 months, they did not find any differences in global response or in recurrences (25 v. 17% in the group with less glomerular filtration). Greater complete remission was objectified in the group with greater glomerular filtration. There was no relationship in the multivariate analysis between glomerular filtration and the response and recurrence *end-points*.[576]

Cohort S. 2+

Boumpas *et al*. analysed the efficacy of different therapeutic patterns in one nRCT on 65 patients with severe LN who presented deterioration of renal function (glomerular filtration of 25-80 ml/min) or histology of crescents/ necrosis in more than 25% of the glomeruli. Average creatinine was 2.11± 0.23 mg/dl in the group that only received MPred for 6 m. 2.21± 0.22 mg/dl in the group that received CPM for six months, and 1.77 ± 0.20 mg/dl in the group that received CPM for 30 months. After three years' follow-up, 48% of the first group, 35% of the second and only 15% of the third doubled serum creatinine ($P=0.037$ between the first and third group).[384]

nRCT 1+

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| | |
|---|---|
| According to a study of Kong *et al*. of 20 cases of SLE of which nine presented LN with average creatinine of 1.6 ± 1.4 mg/dl, intravenous doses in bolus of 500 mg MPred for three days seemed to have the same efficacy as larger doses, and also, with less side effects.[577] | Case series 3 |
| Pharmacokinetic studies on intravenous CPM in patients with nephropathy in different autoimmune diseases, have shown that clearance is significantly reduced in patients with renal insufficiency, as a result of its reduced urinary excretion, and causing an increase in systemic exposure to the drug measured by area under the curve ($P$<0.001). However, in patients with haemodialysis, the loss of 22% of the drug is observed in a three-hour session.[578] | Diagnostic test S. 2+ |

**Summary of evidence**

| | |
|---|---|
| 2+ | ARI is associated with a worse long-term prognosis of renal survival.[568-570] |
| 2+ | The most common causes of ARI in patients with LN, apart from the traditional causes in the general population (nephrotoxicity, NSAID, etc.) are: Crescents/extracapillary proliferation, ANCA necrotising vasculitis, tubulo-interstitial lesions and TMA.[571-574] |
| 2+ | The presence of positive ANCA in LN associated with crescents or immunonegative necrotising lesions has been described. These cases have been treated with MPred and CPM in induction.[571] |
| 2+ | In a nRCT post-hoc study published in 2009, patients with glomerular filtration <30ml/min responded favourably and without differences to MMF and CPM.[575] |
| 2+ | In patients with mild-moderate ARI (GRF <60 ml/min/1.73m$^2$), MMF has proved to be efficient.[576] |
| 1+ | Treatment with CPM in patients with LN and glomerular filtration between 25-80 ml/min/1.73m$^2$, was useful, although in the mid-term the recovery of the renal function was limited.[384] |
| 3 | Corticoid pulse therapy may be indicated in severe cases of LN with ARI. 500 mg doses for three days could be sufficient.[577] |
| 2+ | In patients with ARI, clearance of CPM is reduced, so the area under the curve increases as well as its systemic exposure.[578] |

**Recommendations**

| | |
|---|---|
| C | Both in cases of mild-moderate acute renal insufficiency (creatinine clearance > 30 ml/min/1.73m$^2$) and severe renal insufficiency (creatinine clearance < 30ml/min/1,73m$^2$), we suggest using cyclophosphamide or MMF as induction immunosuppressive treatment. |
| √ | We suggest adapting the dose of cyclophosphamide in patients with renal insufficiency according to the estimated glomerular filtration and in patients receiving renal replacement treatment with dialysis. |
| √ | We suggest corticoid pulse therapy in all cases of LN with acute renal insufficiency, unless it is contraindicated. |
| D | In LN lesions associated with ANCA+ necrotising glomerulonephritis, we suggest induction treatment with CPM. |

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## 6.1.5. Maintenance treatment

### 6.1.5.1 Maintenance treatment of proliferative lupus nephritis

**Questions to be answered:**

- What is the immunosuppressive maintenance treatment of proliferative lupus nephritis?

The aim of treatments in maintenance phase of LN is to complete and consolidate the response reached during the induction treatment phase and prevent relapses of the disease with an adapted immunosuppression intensity and during the time required to prevent the appearance of adverse effects.[527] The transcendence of presenting relapses or not is closely linked to the evolution of renal survival, among other complications.

The drugs that have usually formed part of the maintenance strategies mainly include: MMF, AZA, CPM pulses, HCQ and glucocorticoids.

To maintain the response of proliferative LN, CPM has proven to be efficient over the years, but accumulated doses of over 8-9 g have been associated with a high risk of gonadal toxicity[543] in women of any age, and doses of over 5 g in women aged 30-32 and over.[540-542,544,545]

MMF has proven to be superior to CPM[547] in efficacy and equal to AZA in some studies[389,549,579,580] and superior in others.[581] In terms of safety, it seems to be superior.[582]

In some studies AZA is equally as efficient as CPM and in others it is superior; this also depends on the result of the variable analysed.[547]

Contreras *et al*. were the first to observe, by means of a RCT of 59 North American patients treated in the same way in induction (intravenous CPM for six months), superiority of MMF and AZA with respect to intravenous CPM on a quarterly basis (0.5-1 g/pulse) in maintenance after 25-30 months.[547] RCT 1+

In one *endpoint* comprised of patient and renal survival, both AZA ($P$=0.009) and MMF ($P$=0.05), were superior to CPM. On dividing this endpoint into its components, only AZA continued to maintain an advantage in patient survival ($P$=0.02), not finding any differences between the three groups in renal survival. In recurrence-free time, MMF was superior to CPM ($P$=0.02). MMF and AZA obtained an advantage with respect to CPM in side effects such as amenorrhoea ($P$=0.03 for both), total infection and major effects ($P$=0.005/$P$=0.002, and $P$=0.02/$P$=0.01), and nausea-vomiting ($P$<0.001 for both); in diarrhoea and leucopoenia, the three drugs were similar.

In the European multicentre study, MANTAIN (*Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy of Lupus Nephritis*) of 105 patients monitored for 48±14 months, and analysed by intention to treat, they did not manage to prove superiority of MMF v. AZA in its main *endpoint* of renal or systemic recurrence-free time. No response in induction was demanded in this study, either, before starting the maintenance phase.[579] No differences were observed, either, in terms of side effects, with the exception of worse results for AZA in cytopenias (HR= 4.54; 95% CI: 1-21; $P$=0.003). nRCT 1+

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The maintenance phase of the ALMS study which compared AZA with MMF in 227 patients, has proven the superiority of MMF in all the main result variables analysed by intention to treat, with significance levels of *P*=0.003 for survival, ACKD and renal insufficiency defined as doubling baseline creatinine; *P*=0.027 for the time that elapses until a renal relapse, and *P*=0.017 in requiring rescue treatment with glucocorticoids.[581] nRCT 1++

The maintenance phase of the Asian group of Chan *et al*., in which they compared MMF (1 g/day) with AZA, did not manage to establish differences between the two groups in the endpoints and renal survival in 63 months follow-up.[389] nRCT 1+

Feng *et al*. analysed the four CCT described herein, with a total of 328 patients. With $I^2$<50%, they did not find significant differences in any efficacy endpoint (death, doubling serum creatinine, ACKD, flare), although for the flare variable, the significance is at the limit, in favour of MMF (RR= 0.70; 95% CI: 0.49-1.00).[583] With $I^2$>50%, they did find differences in leucopenia, but not so in gastrointestinal symptomatology. MA 1++

There are no comparative studies between the different doses of MMF published. The large European-American CCTs used 2 g/day,[579,581] the Asian[389] ones and other European ones, 1 g/day.[545]

The Italian group of Moroni published a CCT with 75 patients, treated with AZA or CsA and monitored for four years, without managing to show any differences between CsA and AZA in the efficacy *endpoints* (renal flare, clearance and proteinuria) or in the safety endpoints after two years.[584] At the end of the follow-up, the percentage of patients in whom proteinuria persisted was significantly greater in the AZA group than in the CsA group (42 v. 15%, *P*=0.045). nRCT 1+

At the end of the maintenance phase of the CYCLOFA-Lune study (*Cyclosporine A or Intravenous Cyclophosphamide for Lupus Nephritis*),[392] there were no differences in the flare variable, but there were in the percentage of patients without proteinuria, in favour of CsA (*P*=0.02). nRCT 1+

After an average follow-up of 7.7 years (range: 5-10.3), both groups of the CYCLOFA-LUNE CCT presented similar figures in terms of renal function, ACKD and adverse effects.[585] Cohort S. 2++

**Summary of evidence**

| | |
|---|---|
| 1+ | AZA obtains similar results to MMF in three RCTs and worse results in another in terms of maintenance of the response.[547,579,581] |
| 1++ | No significant differences were found between the maintenance treatment with AZA or MMF in any of the efficacy endpoints (death, doubling serum creatinine, ACKD or flare).[583] |

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**Recommendations**

| | |
|---|---|
| A | We recommend oral mycophenolate or azathioprine for maintenance therapy of proliferative lupus nephritis. |
| B | As an alternative to these, we suggest intravenous cyclophosphamide in quarterly pulses or cyclosporine A. |

## 6.1.5.2. Suspension of maintenance treatment

**Questions to be answered:**

- When and how should a maintenance treatment be suspended?

The incidence of renal flare in LN, despite immunosuppressive treatment, is high, varying from 12 to 45% during the first 2-5 years in the most recent series of multicentre CCTs and cohorts, in which the minimum duration of the immunosuppressive treatment was 24-36 months. After five years, the appearance of a renal flare became much less frequent, and was exceptional after 10 years quiescence.[225,226,547,579,581,586-588]

Ponticelli *et al*. progressively eliminated immunosuppressants in 14 patients after receiving CG+AZA/CPM for an average of 34 months (8-89); after two years during which the treatment was slowly discontinued, and 38-month follow-up (12-96), only one mild protein flare was seen after 67 months, concluding that in selected and stable population, discontinuing aggressive immunosuppressive therapy is justified.[589] Cohort S. 2+

Later on, the same group, in a cohort treated for 45 ± 25 months and monitored for 16 years, confirmed limited incidence of relapses 0.21 patient/year and 0.06 patient/year, depending on whether the follow-up was less or more than 10 years, respectively.[590] Cohort S. 2+

In the proliferative LN classes, the appearance of a renal flare determines worse renal and patient survival.[227] The nephritic type is associated with a worse prognosis in renal survival than the nephrotic type.[225,227,591-593] However, in the membranous class, renal flare does not appear to affect renal survival as it does in the proliferative classes.[593] Cohort S. 2+

The importance of presenting relapses or not during the follow-up period becomes obvious after assessing the cohort of Moroni, increased to 70 patients monitored for an average of 127 months (5-30). The appearance of renal flare was associated with worse renal survival measured as doubling serum creatinine (RR= 6.8; 95% CI: 0.91-53.5; *P*=0.03), this association being more significant in the case of nephritic flare (RR= 27; 95% CI: 3.8-222; *P*=0.00001). Male sex (RR= 4; 95% CI: 1.3-12.8; *P*=0.015) and the presence of high blood pressure (RR= 3.8; 95% CI: 1.54-9.33; *P*=0.004) were predictor factors for renal relapse in the multivariate analysis.[227]

Eleven years later, they added the absence of complete remission to this group of predictor factors of nephritis flare (*P*=0.0002) in univariate analsyis.[591]

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The same authors[586] published their cohort of 94 patients, eliminating maintenance treatment in 32 of them after six months of clinical-analytical quiescence. Fifteen did not present relapse during an average follow-up of 174 months, and 17 presented flares within 34 months, on average, after complete withdraval. The only differences between these two groups were the time from remission to total discontinuance of the therapy (24 v. 12 months; *P*=0.02) and total duration of the maintenance treatment (57 v. 30 months, *P*=0.009), concluding that the longer the maintenance therapy lasts, the less likelihood of presenting renal flares, and that the immunosuppressive treatment could be safely discontinued in some patients, who remained in remission for years.

Cohort S. 2+

In 2013, Moroni *et al*. published the results of complete withdraval therapy in 161 patients and at least five years' follow-up. Firstly, and in clinically quiescent cases (n=73), they discontinued immunosuppressants and then reduced doses of glucocorticoids very slowly until suspension. During the therapy reduction phase, 21 presented relapses (29%). Of the 52 patients in whom it was possible to completely discontinue the treatment, 32 remained relapse-free throughout the study. The differences between those who presented relapses v. those who did not were: greater baseline proteinuria (4.75 v. 2.77; *P*=0.04); less exposure to cytotoxic drugs during the maintenance treatment (25 v. 62.5%; *P*=-0.019), less exposure to HCQ (10 v. 53%; *P*=0.004), less duration of the total treatment (31 v. 98 months, *P*<0l01), and less time from remission to discontinuance of the therapy (12 v. 53 months, *P*<0.0001).

Cohort S. 2+

In 1992, the NIH group published a nRCT, concluding that prolonging immunosuppressive therapy not only with glucocorticoids but also with intravenous CPM from six to 30 months, reduced the risk of recurrences (60 v. 13%; *P*=0.006) and increased renal survival measured as doubling baseline serum creatinine (*P*=0.037).[384]

nRCT 1+

Illei et al, from the same NIH group, on a cohort of 92 patients who reached (total or partial) remission, described, after an average follow-up of 117 months, 45% of relapses that appear in 18 or 36 months, depending on whether the previous remission attained had been partial or complete.[225] As relapse prognostic factors, they indicated partial response v. complete response (maximum likelihood ratio (LR) = 2.1; 95% CI: 1.08-4.2; *P*=0.022), Afro-American ethnic group (LR= 2.45; 95% CI: 1.00-5.98; *P*=0.049) and levels of C4 < 11 mg/dl at the response time (LR= 14.20; 95% CI: 4.74-42.52; *P*<0.0001). Among the patients with complete response, the chronicity index also appeared as a recurrence predictor (LR = 1.25; 95% CI: 0.90-1.19; *P*=0.017).

Cohort S. 2+

In a cohort study, Mosca *et al*. tried to reduce the total treatment time to nine months (6 induction + 1-3 maintenance), finding that, with an average follow-up of 38 months, young patients (≤ 25 years) and/or with active lesions in the biopsy (activity ratio ≥ 7) were not protected against recurrence with this treatment pattern.[595]

Cohort S. 2++

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Between 1976 and 2000, Mosca, in a series of 91 patients, treated with CPM in induction for nine months, but without any subsequent maintenance treatment, presented 54% recurrences (15.6 recurrences per 100 patients-year after an average of 42 months). The earliest recurrences (26 m) were nephritic and the later ones were nephrotic (54 m) and they were associated with: age <30 years ($P$<0.01), activity index >10 ($P$<0.005) and karyorrhexis ($P$<0.05) in the biopsy.[592] Cohort S. 2+

Moke, with data taken from a selected cohort with 38 type V lupus nephritis treated with oral CPM and later on with AZA, found that 34% relapsed despite the fact that 66% still continued with medication.[593] The patients who continued to be treated with AZA due to persistence of proteinuria or immunological activity recurred even more, up to 56%. They highlight the association of persistence of anti-DNA ($P$=0.025) and hypocomplementemia ($P$=0.018) after treatment with the appearance of renal flare. Cohort S. 2+

A Spanish multidisciplinary group also narrated its experience of almost 30 years, treating 144 patients with LN with different immunosuppressant patterns but treated for the same time interval: A (n=36, intravenous CPM 1 g/month, for 24 months); B (n=66, intravenous CPM 1g/month, six months + 1 g/quarterly, for 18 months); C (n=21, intravenous CPM 0.5g/fortnightly for three months and, later, for 24-36 months, AZA or MMF 1-2 g/day), and D (n=26, MMF 2-3 g/day for six months followed by 1-2 g/day for 24-36 months). 39% recurrences were obtained with pattern C (CPM 3 months + AZA in maintenance) compared with the other patterns, as the only risk factor for renal flare.[596] Cohort S. 2+

Chan *et al*. studied 68 patients treated with oral CPM for six months and then with AZA for at least 24 months. During a 91.7 month follow-up (10 m-11 years), 22/64 patients in remission recurred (34%) in an average interval of 48.8 ± 32.7 months (range: 10-135 months). Five years after moment 0, 71.6% remained recurrence-free.597 Having presented partial remission rather than complete remission had an influence on the occurrence of flares (HR= 06.2; 95% CI: 2.6-14.7; $P$=0.001). Discontinuance of treatment with AZA seemed not to influence the appearance of flare ($P$=0.994), although 37/68 suspended AZA after just an average treatment of 40.3 months.[597] Cohort S. 2+

The same group published a nRCT comparing two groups of treatment on 62 Asian patients (MMF v. CPM-AZA >2 years) monitored for an average of 63 months. They divided the MMF group into two, according to the total duration of the treatment. With a recurrence percentage of 32% in 26±15 months from start of treatment, they did not find any differences between groups or factors associated with them: neither the one-year extension of treatment with MMF nor the response to induction, which other groups did find.[389] nRCT 1+

**How to discontinue with immunosuppression?**

Suddenly discontinuing of immunosuppression has been associated with the appearance of flares, precisely attributed to a "reflare" in the synthesis of antibodies that was previously restrained by immunosuppresion.[598] Cohort S. 2-

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| | |
|---|---|
| A nRCT on discontinuance of AZA in nine non-biopsied SLE patients, 7/9 v. 1/7 of the controls that continued with AZA, presented relapse and exacerbation of the lupus disease 89 days, on average, after discontinuing with the drug.[599] | nRCT 1- |
| Immunosuppression should be discontinued slowly and under close surveillance.[586] | Cohort S. 2+ |

**Summary of evidence**

| | |
|---|---|
| 1++/1+/2+ | The incidence of renal flare in LN, despite immunosuppressive treatment, is high, varying from 12 to 45% during the first 2-5 years in the most recent series of multicentre CCTs and cohorts, in which the minimum duration of the immunosuppressive treatment was 24-36 months. After five years, the appearance of a renal flare becomes much less frequent, and is exceptional after 10 years quiescence.[225,226,547,579,581,586-588] |
| 2+ | In the proliferative LN classes, the appearance of a renal flare determines worse renal and patient survival.[227] The nephritic type is associated with a worse prognosis in renal survival than the nephrotic type.[225,227,591-593] However, in the membranous class, renal flare does not appear to affect renal survival as much as it does in the proliferative classes.[593] |
| 1+ /2+ | Increasing the duration of the maintenance treatment up to 30 m, reduces the early risk of recurrences and increases renal survival and patient survival.[226,384,592,595] However, there are no CCTs that directly compare shorter or longer treatment time using the same therapeutic regimen. |
| 2+ | Before proposing discontinuing the maintenance treatment, a minimum of 12 months' quiescence should be completed.[586,589,594] |
| 2+ | Treatment with HCQ helps maintain the remission of LN and delays the onset of terminal advanced chronic renal failure.[594] |
| 2+ | In patients with prolonged remission and with no risk factors for relapse, considering the discontinuance of the maintenance treatment is justified.[586,589,598] |
| 2+ | Total immunosuppresion therapy withdraval should be done very slowly.[586,594,598] |
| 2+ | Close monitoring over the first five years allowing the detection and early treatment of flares, determines better long-term renal survival.[227,584] |
| 3 | Renal lupus activity is minimal in advanced stages of chronic renal insufficiency of more than 12-24 months.[590] |

**Recommendations**

| | |
|---|---|
| B | We recommend prolonging this maintenance treatment for 2 to 3 years at least. |
| C | We suggest that in cases where the complete discontinuance of the maintenance immunosuppressive treatment is proposed, this should not be done before a clinical-analytical quiescence period of less than 12 months. |
| √ | In patients with frequent relapses without any justifiable cause, or with risk factors for renal relapse, we suggest prolonging the maintenance treatment for at least 5 years. |

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| | |
|---|---|
| C | We suggest that the total suspension of the maintenance immunosuppressive treatment should be slow and progressive. |
| C | We suggest maintaining treatment with hydroxychloroquine for a long period, provided that it has no contraindications or side effects. |

**Renal relapse risk factors described in different studies**

- Male gender[227]
- Age < 25-30 years[224,592]
- Afro-American ethnic group[225]
- HBP[227]
- Persistence of altered levels of C4, C3 and anti-DNA.[225,226,593]
- Karyorrhexis or extracapillary proliferation[592]
- AI >10, high CI[225,226,592,600]
- WHO Class IV[601]
- Having presented flares previously.
- Delay in onset of treatment > 5 months[224]
- Delay in reaching response[584,601]
- Partial response v. complete response[225,389,591]

## 6.1.6. Immunosuppressive treatment for type V lupus nephritis

**Questions to be answered:**

- What should be the immunosuppressive therapeutic strategy of first choice for type V lupus nephritis?

Type V membranous lupus nephritis accounts for 8 to 20% of all biopsied LNs. The main clinical characteristic is proteinuria, which, when it is persistent and severe, leads to a progressive deterioration of glomerular filtration. At times, when it occurs with haematuria or abnormal sediment, its association with proliferative types (III/IV) is not infrequent.

Although the evolution towards advanced stages of chronic renal insufficiency is less than those presented by proliferative forms, this risk after 10 years reaches 12% of the cases treated, either due to progressive glomeruloesclerosis or interstitial damage triggered by massive proteinuria persistence.[602]

The most characteristic pathological features in the renal biopsy in type V glomerulonephritis are the subepithelial deposits, which are characterised as aggregated immunocomplexes in the subepithelial side of the glomerular basement membrane. These deposits correlate with the intensity of the proteinuria. Studies with electronic microscope on 236 patients with LN, of whom 20 were type V, showed that the degree of pedicle lesion resulted in a manifestation of the dysfunction of the epithelial cells, which correlated with the intensity of the deposits.[603]

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A study that evaluated 52 biopsies of LN by means of immunohistochemistry, concluded that, podocyte lesion markers (synaptopodin, Wilms' tumour protein, glomerular epithelial protein 1, and nephrin) in patients with membranous lupus nephritis, reflected different phenotypes in comparison with the pattern observed in proliferative lupus nephritis. Thus, this minor podocytye damage that exists in the "pure" membranous forms could confer a better prognosis to reach partial or complete remissions.[604]

The multivariate analysis of a cohort of 103 patients with membranous LN showed that the concentration of serum creatinine on diagnosis, and the chronicity of the renal biopsy were the variables that defined the highest risk of evolution towards stages of chronic renal insufficiency. In contrast, these factors have a better prognosis when the histological form of membranous lupus nephritis is "pure" and also reaching complete remission at some moment of the evolution.[605]

Patients with membranous lupus nephritis but who, in the biopsy, also presented concomitantly proliferative type lesions (mixed forms), should be treated in agreement with the patterns established for proliferative lupus nephritis (Types III and IV).[606]

A study of 94 renal biopsies performed serially on 44 patients showed the high possibility of transformation, difficult to predict based on clinical-analytical criteria. Of the 16 patients with type V initial biopsy, in 13 (81.3%), the successive biopsies showed mixed type patterns. In cases of relapse or refractoriness to therapeutic patterns, the advisability of a new renal biopsy should be considered in those with initial biopsy of membranous glomerulonephritis, as interclass transitions are not infrequent, and with further information, the immunosuppressive therapy could be better adapted.[607]

The immunosuppressive treatment of patients with membranous lupus nephritis and nephrotic proteinuria is justified, because if it is maintained, progression to advanced stages of renal insufficiency after 10 years is estimated between 8 and 12%,[608] though it is quicker in those cases with high onset serum creatinine.[609]

Cohort S.
2+

In cases with subnephrotic proteinuria there is not sufficient information to justify immunosuppressive treatment. However, given the beneficial effect noticed in other non-diabetic proteinurias, it seems reasonable that they should receive anti-proteinuria and anti-hypertensive drugs.[610,611]

MA
1+

Another MA, more focused on therapeutic trials with membranous lupus nephritis, which includes 24 publications and with low bias by excluding some studies, concluded that therapeutic strategies with immunosuppressants combined with glucocorticoids were more effective in achieving partial and complete remissions of proteinuria. They were not conclusive in other *endpoints* such as relapses, adverse effects or survival.[612]

MA
1+

The following immunosuppressants, either combined with glucocorticoids or not, have been studied for the control of membranous lupus nephritis.

**Prednisone**

The majority of guidelines initially recommend prednisone 0.5 mg/kg/day with progressive reduction.[496] Other authors have recently described the efficacy of patterns with minimisation of prednisone for type V with 15 mg/day in induction phase, and 5 mg/day in maintenance patterns, combined with immunosuppressants and HCQ, in order to reduce adverse effects.[345]

Cohort S.
2-

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In the NIH trial (including 42 patients with membranous glomerulonephritis without proliferation with nephrotic proteinuria and preserved glomerular filtration), the three treatment branches were: Prednisone alone, prednisone plus CPM and prednisone plus CsA. After 12 months of treatment, the remission rate was significantly higher in the groups with CPM and CsA than in those treated with prednisone alone. Unfortunately, the partial or complete remission rate was less in those with proteinuria over 5 g/day.[393]

RCT 1+

**Mycophenolate/Cyclophosphamide**

On grouping together 84 patients with membranous glomerulonephritis originating from the two main RCT, comparing MMF with CPM (42 treated with MMF and 42 with ev CPM), MMF showed no superiority with respect to intravenous CPM in reducing proteinuria, or in the rate of partial remissions (OR 1.19, 95% CI 0.29-4.91) of proteinuria, or greater remission in those who had proteinuria in nephrotic range.[613]

MA 1+

The most common doses are 2-3 g/day for MMF and 720-1440 mg for mycophenolic acid with enteric coating, and in general, with similar efficacy to treatment with CPM pulses, although with less adverse effects, above all gonadal effects.

CPG 4

For intravenous CPM 0.5-1.0 g/m$^2$ in monthly pulses, up to six during the induction phase, and later on every two months up to one year if the pattern defended by NIH is chosen. Mini-bolus of intravenous CPM with 500 mg every 15 days for three months are also efficient.[12,45]

**Hydroxychloroquine**

The association of HCQ with treatment with MMF has been tested on 29 patients with membranous lupus nephritis. Complete remission was reached in 7/11 (64%) after 12 months with combined MMF and HCQ treatment. In contrast, only 4/18 reached complete remission in the group treated exclusively with MMF.[614]

Cohort S. 2+

**Cyclosporine**

In one three-arm CCT (prednisone alone, n=12, combined with CPM, n=15, or with CsA, n=15) a higher rate of remission was observed with combined treatments (27%, 60% and 88%, respectively, $P<0.05$). However, the relapse rates were higher with CsA than with CPM.[393,615]

CCT 1+

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### Tacrolimus

| | |
|---|---|
| An open and multicentre randomised study in the Chinese population, although with only 16 patients, comparing MMF and tacrolimus, showed a similar response after 24 months in both arms. In the tacrolimus group, 4/9 presented severe infections and one, diabetes. In the MMF group, 1/7 presented infection by herpes zoster virus.[399] | RCT<br>1- |

### Azathioprine

| | |
|---|---|
| The study of a cohort with 38 Asian patients with type V LN treated with prednisone and AZA (2 mg/kg/day) in induction pattern, for 12 months, showed partial or complete remission in 89% of the cases.[616] The subsequent follow-up of 12±5.8 years, when they received low doses of prednisone and AZA. showed relapses in 34% of the cases, although the treatment, in general, was very well tolerated.[593] | Cohort S.<br>2+ |

### Rituximab

| | |
|---|---|
| In a study on 50 patients with LN of the RITUXILUP (*Trial of Rituximab and Mycophenolate Mofetil Without Oral Steroids for Lupus Nephritis*) cohort (22 with pure class V), treatment was given with two doses of RTX (1 g days one and 15), MPred 500 mg, days one and 15; and MMF (1-3 g/day) and without oral prednisone, except for the extrarenal activity control. The outcome analysis for patients with class V showed complete remission in 18% after six months, increasing to 36% after 12 months. Furthermore, another additional 24% of patients reached partial remission.[564] | Cohort S.<br>2+ |

### Summary of evidence

| | |
|---|---|
| 1+ | In patients with membranous lupus nephritis, treatment with immunosuppressants is more efficient than if they are treated just with prednisone.[393,612] |
| 2- | The initial dose of prednisone, combined with immunosuppressants and HCQ may be less than 0.5 mg/kg/day.[496] |
| 1+ | MMF and CPM are similar concerning the rate of partial remission and reduction of baseline proteinuria.[613] |
| 2+ | HCQ has an adjutant effect to reach remission in membranous lupus nephritis.[614] |
| 1+ | CsA combined with prednisone obtains higher response rates than prednisone alone, and similar to the prednisone+CPM combination, with higher rate of relapses than the latter combination.[393,615] |
| 1- | Tacrolimus and MMF combined with prednisone obtain similar response rates.[399] |

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| | |
|---|---|
| 2+ | AZA (2 mg/kg) combined with oral glucocorticoids at high doses of 1 mg/kg/day has shown to be efficient in an observational study with similar percentage of relapses as the classical drugs.[593,616] |
| 2+ | Induction treatment with RTX associated with MMF and MPred pulses ("RITUXILUP" pattern) seems efficient and especially useful in saving oral glucocorticoids.[564] |

**Recommendations**

| | |
|---|---|
| A | We recommend immunosuppressive treatment in all patients with membranous lupus nephritis. |
| √ | As in other types of nephritis, we suggest not initially exceeding 30 mg/day of prednisone and then reducing it as soon as possible to 5 mg/day. |
| B | In induction treatment for patients with lupus nephritis type V and nephrotic proteinuria, we recommend MFM and glucocorticoids as the treatment of choice. As an alternative and with the same induction efficacy although with more adverse effects, we recommend cyclophosphamide in intravenous pulses. |
| A/B | For maintenance regimens in patients with membranous lupus nephritis, we recommend treatment with mycophenolate (A) or azathioprine (B). |
| B | We recommend using anticalcineurinics in membranous lupus nephritis when seeking alternative drugs to mycophenolate or cyclophosphamide. |
| √ | We suggest combined therapy with mycophenolate and anticalcineurinics if complete remission is not achieved or if significant proteinuria persists. |
| C | We suggest using rituximab associated with mycophenolate and methyl-prednisolone pulses when avoiding oral glucocorticoids is considered to be especially important. |

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# 6.2. Haematological manifestations

## 6.2.1. Specific therapeutic objectives for each cytopenia

There are no specific studies to establish the therapeutic objectives in the different cytopenias that may appear in SLE. There is no formal consensus in the definitions of partial remission, complete remission or refractoriness. Recommendations are based on accumulated experience.

The objective is not necessarily to recover normal values. What is more interesting is to reach a safe level from the clinical point of view. Depending on the specific cytopenia, different cut-offs are considered.

In thrombocytopenia, the clinically relevant counts are:[617,618]

– $20x10^9$/L: Above this level, there is not usually spontaneous bleeding and it makes possible carrying out not too traumatic daily life activities. It is insufficient for surgery or invasive procedures where there is a possibility of haemorrhage.

– $50x10^9$/L: Above this level, surgical interventions in general (except neurosurgery) are feasible.

– $100x10^9$/L: Above this level, neurosurgery can be performed, and it is considered safe to all intents and purposes.

Regarding neutropenia, the clinically relevant values are:[619,620]

– 500/$mm^3$: Below this level, the infection risk is high, it is considered as severe neutropenia. Above this level, the infection risk is somewhat greater than that of the general population but it is considered moderate neutropenia.

– ≥ 1000/$mm^3$: The infection risk is practically identical to that of the general population.

Insofar as anaemia is concerned, this depends on the haemoglobin level:[621]

– Below 7 g/dL, blood transfusion is usually indicated.

– Above 10 g/dL, transfusion is not usually indicated, and if stable and asymptomatic, no specific treatment is required.

– Between 7 and 10 g/dL, the indication for transfusion will depend on clinical symptoms and individual circumstances.

## 6.2.2. Immunosuppressive treatment

### 6.2.2.1. First-line treatment for severe cytopenias

**Questions to be answered:**

- What is the immunosuppressive first-line treatment for severe cytopenia?

Haematological manifestations are frequent in SLE. The main manifestations are cytopenias (anaemia, leucopoenia, thrombocytopenia) and APS. Furthermore, haematological manifestations may be a form of presentation of SLE as well as activity signs of the disease. Thrombocytopenia deserves a special mention. Although there are several potential causes of thrombocytopenia in

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SLE, the most frequent is related to an underlying immune mechanism, similar to primary immune thrombocytopenia (ITP). In fact, primary ITP may be the first sign of SLE, even years in advance. Treatment of immune thrombocytopenia, in particular, and of autoimmune cytopenias, in general, in SLE patients is very similar to the treatment of patients without SLE.

In general, available studies on the different therapeutic options are not specific of SLE patients, but rather of patients with primary ITP.

Response to the treatment was assessed in a historical cohort of 59 patients with SLE and associated autoimmune thrombocytopenia, with platelet counts < $50\times10^9$/L. Oral prednisone was used in 50 of the 59 patients (initial average dose 1 mg/kg/day). Response was obtained in 80% of the cases: complete response (CR) in 28, partial response (PR) in 12, but only 11 (22%) achieved prolonged response (7 CR; 4 PR). In contrast, the combination of prednisone with danazol (n=18) or HCQ (n=11) resulted in 50% (7 CR, 2 PR) and 64% (4 CR, 3 PR) long-term responses, respectively, allowing discontinuation of prednisone or dose reduction to below 0.2 mg/kg/day.[379] Cohort S. 2-

The effectiveness of high-dose dexamethasone as initial treatment was assessed in a consecutive series of newly diagnosed ITP adult patients with platelet count < $20\times10^9$/L or a count of < $50\times10^9$/L and clinically significant bleeding, between 1997 and 2000. The initial treatment was oral dexamethasone 40 mg/day for four consecutive days. Out of 157 consecutive patients, 125 were eligible. A good initial response was achieved in 106 of the 125 patients (85%), which was sustained at six months in 53 (50%).[622] Cohort S. 2++

Response to treatment was assessed as well as long-term evolution of a group of 26 women with SLE and severe autoimmune haemolytic anaemia. The initial treatment was with glucocorticoids in all cases (average dose: 1 mg/kg/day). Initial response was obtained in 25 patients (96%), with 73% recurrence free after an average of 180 months' follow-up.[623] Cohort S. 2-

A pilot study was performed on 37 patients with severe ITP, aged between 20 and 65 years, treated at one single centre. High-dose dexamethasone was administered (40 mg/day for four days every 28 days, six cycles in all). The response was 89.2%; relapse-free survival of 90% after 15 months; and long-term responses, with average duration of 26 months (range: 6-77 months), were obtained in 25 out of 37 patients (67.6%).[624] Cohort S. 2+

The GIMEMA (*Gruppo Italiano Malattie Ematologiche dell'Adulto*) multicentre study included 95 patients (aged 2-70 years) with severe ITP. High-dose dexamethasone was administered (40 mg/day for four days every 14 days, four cycles in all). The response was 85.6%; relapse-free survival of 81% after 15 months; and long-term responses, with average duration of eight months (range: 4-24 months), were obtained in 67 out of 90 patients (74.4%).[624] Cohort S. 2+

Adults with ITP and platelet count < $20\times10^9$/L or < $30\times10^9$/L with bleeding history were selected in one RCT. One group (n=18) received 10 mg oral or intravenous dexamethasone every six hours for four days, followed by 30 mg/day oral prednisolone. The other group (n=18) received 60 mg/day oral prednisolone. Both regimens were administered for 14 days before reducing the doses. Satisfactory response rates on day 5 were significantly higher in the dexamethasone group (88.8 v. 33.3%, $P$=0.001).[625] RCT 1-

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| Previously non-treated patients, with ITP and platelet count ≤ $20\times10^9$/L (n=101) were randomly assigned to receiving 40 mg/day dexamethasone for four days with or without 375 mg/m$^2$/week RTX for four weeks. Sustained response (≤ $50\times10^9$/L platelet count six months after start of treatment) was greater in patients treated with dexamethasone + RTX (n=49) than in those treated with dexamethasone alone (n=52; 63 v. 36%, *P*=0.004).[626] | RCT<br>1++ |
| A longitudinal assessment of efficacy, safety and duration of response to the combination of low-dose RTX (100 mg/week intravenous for four weeks) and high-dose dexamethasone (40 mg/day intravenous for four consecutive days) as initial therapy was carried out in 21 adult patients with newly diagnosed ITP. The global response on day +28 was 90.5%. Complete response at six months was 76.2% with a 15.8% relapse rate, compared with 30% and 62.5% of the historical control group that had received standard treatment with prednisone (*P*=0.005 and *P*= 0.004, respectively). The incidence of adverse effects was 9.5%.[627] | Case-control study<br>2+ |
| A total of 133 adult patients with newly diagnosed ITP were randomly assigned to treatment with dexamethasone alone (40 mg/day for four days, n=71), or combined with RTX (375 mg/m$^2$ a week for four weeks N=62) Patients with platelet count ≤ $25\times10^9$/L or ≤ $50\times10^9$/L with bleeding symptoms were included. The primary endpoint (sustained response with platelet count ≥ $50\times10^9$/L at six months) was achieved in 58% of the RTX + dexamethasone group versus 37% in the group with dexamethasone alone (*P*=0.02). Time to relapse (*P*=0.03) and time to rescue treatment (*P*=0.007) was greater in the group of RTX + dexamethasone, as well as a greater incidence of grade 3-4 adverse events (*P*=0.04),[628] | RCT<br>1+ |

**Summary of evidence**

| | |
|---|---|
| 2- | First-line immunosuppressive treatment for severe cytopenias of SLE is corticotherapy, as in primary immune cytopenias, but the most appropriate therapeutic strategy has not been established, in terms of initial dose and duration of the treatment, as there are no controlled studies that determine the optimal dose of glucocorticoids.[379,623] |
| 2- | Glucocorticoids are the first treatment modality in thrombocytopenia associated with SLE and around 20% of the patients achieve long-term remission. HCQ or danazol combined initially with glucocorticoids, show an additive effect and allow reducing the dose of glucocorticoids in the treatment of thrombocytopenia.[379] |
| 2- | Glucocorticoids, 1 mg/kg/day or more or prednisone or equivalent, continue to be the baseline treatment for autoimmune haemolytic anaemia, achieving a high response rate (over 80-90%).[623] |
| 2++ | A four-day cycle of high-dose dexamethasone (40 mg/day) is an effective initial therapy in adults with ITP.[358,624,625,627] |
| 1- | In severely ill symptomatic patients, administration of glucocorticoids via intravenous route is initially preferred. Changing to oral route after initial improvement is routine practice.[625] |
| 1+ | RTX + dexamethasone combination induces a higher response rate and a greater duration of response than dexamethasone alone[626,628] or standard treatment with prednisone.[627] |

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**Recommendations**

| | |
|---|---|
| D | We suggest corticosteroid therapy as first-line immunosuppressive treatment for severe cytopenias of SLE. |
| √ | Although oral prednisone is considered first-line treatment for immune cytopenias, there are no data supporting the use of higher doses over lower doses. We suggest using intravenous pulses of methyl-prednisolone and the association of immunosuppressants, which would permit the initial use of lower daily doses of prednisone and quickly reducing to doses of no more than 5 mg/day. |
| √ | We suggest oral treatment with dexamethasone at high doses (40 mg/day for four days), either combined with rituximab or not, as an alternative regimen that achieves a similar remission rate with a probably faster and longer-lasting response in idiopathic cytopenias. |

## 6.2.2.2. Treatment of thrombocytopenia

**Questions to be answered:**

- When should thrombocytopenia be treated?

Thrombocytopenia is a frequent manifestation of SLE related to morbidity and mortality.[629,630]

In most occasions thrombocytopenia is mild or moderate, and does not require specific treatment. In general, close monitoring may suffice in patients with stable thrombocytopenia with platelets over $50x10^9$/L.[618] Discontinuing or adjusting the drugs that might be responsible for haematological alteration should always be considered. However, severe thrombocytopenia usually occurs in the context of disease activity, and requires urgent action.

It is noteworthy that, in the era of evidence-based medicine, treatment of thrombocytopenia in general and in SLE patients in particular, is still essentially based on experience. There are no randomised clinical trials and there are only historical studies, small case series of patients (probably selected) or isolated case reports.

Given the absence of evidence in SLE and the similarity between thrombocytopenia in SLE and primary ITP, the adaptation for Spain of the international consensus guidelines for patients with primary ITP, carried out by the Spanish Society of Haematology and Haemotherapy, and the Spanish Society of Paediatric Haematology and Oncology can be used as reference for therapeutic recommendations.[618]

**Summary of evidence**

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|---|---|
| | There are no studies that determine when thrombocytopenia should be treated in SLE patients. |

**Recommendations**

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| √ | In thrombocytopenia, the decision to start treatment is mainly based on the presence of bleeding manifestations and, on certain occasions, on a platelet count less than $20\text{-}30x10^9$/L. |

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

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|---|---|
| √ | Patients with platelet counts between 20-30 and 50x10$^9$/L and a stable course, without haemorrhagic complications, are not candidates to receive treatment, except for those who present a haemorrhage or are going to undergo surgery or an invasive procedure. |
| √ | We suggest treatment with platelet counts of more than 50x10$^9$/L to be reserved for patients with a high risk of bleeding. |
| √ | Despite the fact that platelet transfusions may be necessary before potentially bleeding procedures in patients with severe thrombocytopenia (platelet counts < 10–30x10$^9$/L), transfusion should be avoided as a general rule if an underlying immune mechanism is suspected. |

## 6.2.3. Treatment with thrombopoietic agents

**Questions to be answered:**

- What are the indications of thrombopoietic agents?

In general, thrombopoietic agents have not been specifically studied in SLE patients, only having reported short series of patients with favourable results.[631-634] Available studies focus on patients with ITP. However, considering that treatments of primary ITP and secondary to SLE are practically identical, the indirect evidence available may give an idea of its profile of efficacy and safety in patients with SLE, too. Currently, there are two thrombopoietic agents available for clinical use: eltrombopag and romiplostim.

Eltrombopag is a thrombopoietin receptor agonist that activates the thrombopoietin receptor on the megakaryocyte surface, which results in an increasing production of platelets. It is approved for treatment of ITP. It has been successfully used in patients with SLE and refractory immune thrombocytopenia and it seems to be effective as fast-acting therapy instead of glucocorticoids. A report on three patients with ITP associated with SLE, refractory to treatment with glucocorticoids and other immunosuppressants who were treated with eltrombopag at a dose of 50 mg/day, showed that they maintained platelet counts of > 50x10$^9$/L for >6 months after suspension of corticotherapy. The drug was well tolerated and there were no adverse events.[635]

Romiplostim is another thrombopoietin receptor agonist approved for treatment of refractory chronic ITP. It is administered via weekly subcutaneous injections and the response is dose-dependent, with a peak at 12-15 days.[636,637] The initial dose is 1 mcg/kg increasing by 1 mcg/kg/week if the platelet count is <50x10$^9$/L, not exceeding the maximum dose of 10 mcg/kg. Maximum response is reached two weeks after the first dose. If the platelet count during two consecutive weeks is > 150x10$^9$/L, the dose should be lowered by 1 mcg/kg. If the platelet count is >250x10$^9$/L, the treatment should be temporarily suspended, starting it up again with a dose of less than 1 mcg/kg when the platelet count is < 150x10$^9$/L.

Review of the literature revealed a case report on the successful treatment of a patient with SLE, 27 weeks pregnant, who presented severe thrombocytopenia with bleeding from multiple sites. The thrombocytopenia was refractory to the majority of therapeutic modalities, including glucocorticoids, intravenous Ig, immunosuppressants and RTX. The addition of romiplostim resulted in an adequate platelet response and control of the haemorrhage.[634]

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| A randomised, double-blinded, placebo-controlled phase III clinical trial in order to study efficacy, safety and tolerability of eltrombopag (50 mg/day) was carried out. Adults with chronic ITP from 23 countries were recruited. Patients received 50 mg/day eltrombopag (n=76) or placebo (n=38) for a maximum of six weeks. At three weeks, patients with platelet count < $50x10^9$/L increased the dose to 75 mg/day. 73 patients in the eltrombopag group and 37 in the placebo group were assessable. 43 patients (59%) responded with eltrombopag and six (16%) in the placebo group ($P$<0.0001). The platelet count returned, in general, to the baseline values within two weeks after the end of treatment.[638] | RCT<br>1+ |
| To study the safety and efficacy of romiplostim, an open cohort study was performed, with long-term follow-up (156 weeks, average= 69 weeks), on 142 patients with ITP. Platelet responses were observed in 87% of the patients.[639] | Cohort S.<br>2+ |
| The French historical study on 80 patients with chronic ITP and compassionate use of romiplostim (after failure of glucocorticoids, Ig, RTX and splenectomy or with no indication for splenectomy) showed a primary platelet response in 74% of the patients, and a long-term response (2 years) was observed in 47 (65%) patients.[640] | Cohort S.<br>2- |
| 234 adult patients with ITP, non splenectomised, were randomly assigned to receive standard medical treatment (n=77) or romiplostim (n=157). The platelet response rate in the romiplostim group was 2.3 times that of the standard treatment group (95% CI: 2.0-2.6; $P$=0.001). Severe adverse events took place in 23% of the patients who received romiplostim (35 of 154) and in 37% of the patients who receive standard care (28 of 75). HRQoL was higher in the romiplostim group than in the standard group by seven scales ($P$<0.05).[641] | RCT<br>1+ |
| In one analysis of two trials in phase III, the use of glucocorticoids decreased from 30% to 26% in patients with ITP treated with romiplostim (n=83) and it was maintained above 30% in patients with placebo (n=42). The use of glucocorticoids continued to decrease significantly, from 35% to 20%, in patients treated with romiplostim up to three years in an extension study (n=101).[642] | Post-hoc analysis<br>2+ |

**Summary of evidence**

| | |
|---|---|
| | There are no studies that support the routine use of these agents in SLE patients. Experience with these agents in SLE is anecdotal. |
| 1+ | Treatment with eltrombopag is effective in thrombocytopenia of chronic ITP.[638] |
| 1+ | Romiplostim increases the platelet count, decreases haemorrhagic events and transfusions, and improves HRQoL in patients with ITP.[641] |
| 2- | The use of romiplostim in clinical practice is effective and safe for severe chronic ITP.[640] |
| 2+ | Romiplostim reduces the use of glucocorticoids in adults with ITP. This reduction of glucocorticoids may be associated with an improvement of patients' HRQoL.[642] |

**Recommendations**

| | |
|---|---|
| √ | We suggest considering the temporary use of thrombopoietic agents only in selected patients with severe symptomatic thrombocytopenia who do not respond to the initial standard treatment. |

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# 6.3. Neuropsychiatric lupus

## 6.3.1. Diagnosis of neuropsychiatric complications

### 6.3.1.1. Usefulness of certain autoantibodies

**Questions to be answered:**

- What is the usefulness of certain types of autoantibodies for diagnosing neuropsychiatric complications?

As of today, there are no tests that can be considered the *gold standard* for diagnosing neuropsychiatric SLE (NP-SLE). However, a series of factors have been determined that are consistently associated with a higher incidence/prevalence of neuropsychiatric symptoms in patients diagnosed with SLE and can therefore be useful in order to guide the diagnosis. These include a series of autoantibodies, especially APL (anticardiolipin IgG and IgM or anti-β2-glycoprotein-I), anti-ribosomal-P antibodies, antiganglioside antibodies and the so-called *brain-reactive-autoantibodies* (BRAA), or antineuronal antibodies, a terms that groups together several autoantibodies directed against different neuronal antigens.[200,244,643]

The available evidence about the association between each one of these four types of autoantibodies and the development of neuropsychiatric symptoms in SLE is described below:

**Antiphospholipid antibodies:** persistent positivity for medium to high titres anticardiolopin antibodies (aCL) or anti beta2-glucoprotein-I (aβ2-GPI) has been associated with the occurence of different neuropsychiatric events in SLE, especially cerebrovascular accidents (ORs= 4.3-22.2 for aCL-IgG and aCL-IgM), epileptic crises (OR= 2.9: 95% CI: 1.0–8.5 for aCL-IgG; OR= 6.2; 95% CI: 1.7–22.5 for aCL-IgM), moderate to severe cognitive impairment (ORs= 1.9–4.9), myelitis (OR= 9.6; 95% CI: 1.8-50.7) and movement disorders (OR= 10.5; 95% CI: 1.1–102 for aCL-IgG).[244]

SR with expert consensus
1+

**Antiribosome antibodies:** different observational studies have found statistically significant correlations between the presence of anti-RibP antibodies in serum or in cerebrospinal fluid and the development of neuropsychiatric symptoms in SLE patients,[194,644-646] although it is true that these results have not been replicated in all the studies.[647] A MA of 14 studies that included a total of 1537 SLE patients, concluded that the detection of these autoantibodies has limited diagnostic usefulness (sensitivity: 26%; 95% CI: 15-42; specificity: 80%; 95% CI: 74–85).[200]

MA of observational S.
2++

In the other cohort study it was observed that anti-RibP antibodies were associated with psychosis.[194]

Observational S.
2-

**Antineuronal antibodies:** although some observational studies have found statistically significant increases in the serum concentration of antibodies against the protein associated with microtubules 2 (MAP-2) in patients with NP-SLE compared to patients with neurological disorders in absence of SLE,[648] one SR found evidence that the reliability of the determination of these antibodies for the diagnosis of NP-SLE was not totally satisfactory, either (77% sensitivity, 96% specificity).[244,649]

SR with expert consensus
1+

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|---|---|
| In a case-control study it was observed that the antibodies against the glutamate receptor (N–methyl–D aspartate) were significantly higher in patients with diffuse NP-SLE compared with the levels in control patients or patients with focal NP–SLE.[650] | Observational S. 2- |
| **Antiganglioside antibodies (aGM1):** Alike previous cases, there are studies showing a statistically significant association between the presence of these antibodies in serum and the appearance of NP-SLE (RR=3.7), however its usefulness for diagnosis has not been sufficiently confirmed.[651] | Observational S. 2- |
| **The anti-NMO antibodies** (neuromyelitis optica or antiaquaporin-4 IgG) are worth a separate mention. It is recommended to determine these antibodies in cases of SLE-associated myelitis when more than three medullary segments are involved (indicative of longitudinal myelopathy), and especially in the case of concurrent optic neuritis.[244] | SR with expert consensus 1+ |

**Summary of evidence**

| | |
|---|---|
| 1+ | Persistent positivity for medium to high titres aCL or anti-beta2-glucoprotein-I (anti-beta2-GPI) is associated with a higher risk of several neuropsychiatric events in SLE.[244] |
| 2++ | Association has been found between the presence of anti-RibP antibodies in serum or in cerebrospinal fluid and the development of neuropsychiatric symptoms in SLE patients. However, these antibodies have limited diagnostic utility.[200] |
| 1+ | Although some studies have found statistically significant increases in the serum concentration of anti-MAP2 antibodies in patients with NP-SLE with respect to patients with neurological disorders in the absence of SLE,[648,649] the usefulness of these antibodies for diagnosing NP-SLE has not been established.[244] |
| 2- | Antibodies against the glutamate receptor (N-methyl-D-aspartate) are present in patients with diffuse NP-SLE.[650] |
| 2- | Anti-RibP antibodies are associated with lupus psychosis.[194] |
| 1+ | Determining anti-NMO antibodies is fundamental in the event of suspected diagnosis of neuromyelitis optica.[244] |

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**Recommendations**

| | |
|---|---|
| B | There is no determination of autoantibodies that enables the execution of a confirmation diagnosis of neuropsychiatric SLE. |
| B | The diagnosis of neuropsychiatric SLE continues to be by exclusion and mainly clinical. However, determining autoantibodies in serum or in cerebrospinal fluid could support the clinical presumption of neuropsychiatric SLE. |
| B | We recommend determining anti-NMO antibodies in the event of suspected neuromyelitis optica associated with SLE. |

## 6.3.1.2. Imaging techniques.

**Questions to be answered:**

- Which are the imaging techniques of choice in the diagnostic process of neuropsychiatric complications of systemic lupus erythematosus?

The results of the imaging tests do not, on their own, uphold the diagnosis of NP-SLE, rather they complement the clinical suspicion and the laboratory results. Their main function, as well as that of other non-invasive diagnostic tests (electroencephalogram, nervous conduction studies, etc.) or invasive diagnostic tests (lumbar puncture, biopsies, etc.) is to rule out other possible causes that might present with similar clinical manifestations to NP-SLE.[652]

The response to this question is based on the recommendations of the EULAR working group,[244] three diagnostic test studies[653-655] and one cohort study.[656]

In 2010, a SR was performed by EULAR in order to issue recommendations about the diagnosis of NP-SLE. RCTs, controlled studies, cohort studies, case and control studies, and other studies published until January 2009 were included.[244]

SR with expert consensus 1+

In the section on diagnostic tests, it was determined, with evidence level I, that the most widely used imaging technique used today is Magnetic Resonance (MRI) in its different modalities (T1 and T2 sequences, diffusion and perfusion images, and using contrast with gadolinium), The sensitivity of MRI to diagnose NP-SLE is, in general, low, however, it can change depending on whether the disease is active (sensitivity 57%) or whether brain injury is focal (76%) or diffuse (51%).

A study performed in 1994 in the US aimed to analyse the correlation of the MRI sequences in T2 with the clinical status of patients with NP-SLE. The study included 54 patients and 45 healthy controls. They observed a correlation between the degree of brain oedema, with higher intensity in T2 sequences and the degree of clinical extension of the disease. The intensity of the signal in T2 was also different between reversible and non-reversible focal injuries. They concluded that the quantification of sequences in T2 increases the utility of MRI when quantifying the degree of brain injury.[654]

Diagnostic test S. III

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The EULAR recommendations establish that the most frequent findings are obtained in sequences in T2. What are normally found are small subcortical hyperintense punctiform lesions, subcortical and in the periventricular white matter, especially in fronto-parietal regions. These lesions can be seen in neuropsychiatric conditions other than SLE and also in elderly people or with cardiovascular risk factors, therefore their specificity is only 60-82%.[244]

Other imaging diagnosis techniques, such as spectroscopic MRI, magnetic susceptibility MRI, diffusion-weighted MRI, *positron emission tomography* (PET), or *single photon emission computed tomography* (SPECT), may show abnormalities in patients with NP-SLE both in white and grey matter, although with limited specificity.[244]

SR with expert consensus 1+

A comparative cross-sectional study of diagnostic tests was conducted in 2001, with the aim of stablishing the relationship between brain perfusion defects detected with SPECT and cognitive impairment. 57 patients diagnosed with SLE were included in the study. Cognitive dysfunction was detected via neuropsychological tests, and MRI was also performed to all patients.655 No significant associations were found between the perfusion deficits seen in SPECT and cognitive impairment, on the other hand,a relationship between the latter and cerebral infarctions identified in the MRI was observed. It was concluded that the SPECT provides little additional information to that obtained with MRI and the neuropsychological tests.

Diagnostic test S. III

MRI is frequently used to study cognitive impairment associated with SLE in patients under the age of 60, with rapid and inexplicable impairment, in those with previous cranioencephalic trauma, in patients receiving treatment with immunosuppressants, antiaggregants or anticoagulants or with new neurological focalty. Brain atrophy, the number and size of white matter lesions and of cerebral infarctions correlate with the severity of cognitive dysfunction.[244]

SR with expert consensus 1+

Several imaging techniques permit visualising the brain metabolism by measuring cerebral flow, such as Magnetic Resonance Angiogram (angio-MRI) or by measuring the levels of N-acetyl aspirate, normally reduced in SLE patients, with spectroscopic MRI.[652]

A study conducted in Germany which included 34 patients who first presented with neuropsychiatric manifestations, assessed the additional utility of diffusion-weighted MRI and RMA over traditional RMI. Abnormalities in MRI were observed in 20 patients, 35% of which were haemorrhagic or ischemic infarctions. In those patients, diffusion-weighted MRI and MRA provided higher precision to identify the cause. It was concluded that, although diffusion-weighted MRI and RMA helped carry out more precise ethiopathogenic diagnoses, their clinical relevance is still limited.[653]

Diagnostic test S. III

In the EULAR recommendations the diagnostic tests of choice in other types of neuropsychiatric manifestations of SLE have been assessed.

SR with expert consensus 1+

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In SLE-associated ictus, MRI is used to rule out haemorrhages, to assess brain injuries or to identify the vessel or lesion responsible for the patient's symptoms. Diffusion-weighted imaging permits identifying acute brain injuries, especially ischemia secondary to ictus.[244,652]

In acute confusional states associated with SLE, MRI is used if there is neurological focalty, history of cranioencephalic trauma or fever. SPECT has 93% sensitivity and helps monitor the treatment.[244]

In convulsive crises associated with SLE, MRI can detect structural lesions such as brain atrophy (40%) and lesions in white matter (50-55%).[244]

In myelopathy associated with SLE, the main utilities of MRI are to exclude spinal cord compression and to detect hyperintense lesions in T2 sequences.[244]

A study conducted in 1995 assessed the applicability of SPECT as biological marker of brain activity during psychiatric manifestations and also measuring the degree of cerebral perfusion in the remission phases was assessed. From a sample of 20 patients, nine presented with florid symptoms at the time the SPECT was carried out, eight presented with psychiatric symptoms in remission, and three had no psychiatric history.[656] It was observed that in all patients who presented acute psychiatric symptoms, there were areas of hypoperfusion. Four of those who were in remission and presented anomalies in the SPECT had flare-ups in the following six months, whilst the four who did not present abnormalities had a better prognosis. Two of the patients without psychiatric history and with anomalous SPECT developed psychiatric manifestations one month after carrying out the test. It was concluded that in severe psychosis associated with SLE, the examination with SPECT may show perfusion deficits appearing in disease remission periods that can predict recurrences.

Observational S.
2-

**Summary of evidence**

| | |
|---|---|
| 1+ | MRI in its different modalities is the most widely-spread imaging technique used today in NP-SLE.[244] |
| 1+ | T2 sequences in MRI increase sensitivity.[244] |
| 1+ | Other types of imaging tests have been studied, such as RMA, PET and SPECT but their role in the diagnosis of NP-SLE is still to be determined.[244] |
| III | A relationship has been found between infarctions, brain atrophy and lesions in the white matter identified by MRI in patients with NP-SLE and cognitive impairment they present.[655] |
| III | Diffusion-weighted MRI and MRA may help obtain a more precise aetiopathogenic diagnosis, but their importance today is still limited.[653] |
| 1+ | In manifestations such as confusional states or lupus psychosis, MRI is indicated in the presence of neurological focalty, in order to rule our complications or other causes. MRI is always indicated in cases with suspected or confirmed myelopathy.[244] |
| 2- | In patients with NP-SLE presenting with severe psychosis, perfusion deficits identified by SPECT during the remission phases may predict recurrences.[656] |

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**Recommendations**

| | |
|---|---|
| A | We recommend performing a MRI to patients with acute NP-SLE involving the central nervous system, mainly as a differential diagnosis tool, especially when neurological focalty appears. |
| A | We recommend MRI using T2 sequences in order to increase sensitivity. |
| C | If no explanation to the patient's symptoms is found after the evaluation with the recommended first line techniques, we suggest using other magnetic resonance modalities or other types of imaging techniques such as the SPECT. |
| C | We suggest using diffusion-weighted magnetic resonance or angio-MR to identify the aetiology of lesions detected in traditional MR, and also in the case of suspected ischemic origin, in order to establish whether they are acute. |

## 6.3.1.3. Indication for neuropsychological tests

**Questions to be answered:**

- Should neuropsychological tests be performed in all patients with suspected neuropsychiatric systemic lupus erythematosus?

Cognitive impairment is one of the most frequent and early neuropsychiatric manifestations of SLE.[244]

There is no doubt that comprehensive neuropsychological batteries of tests are necessary for a correct assessment. However, they require a great degree of time and effort by both patients and health professionals. Thus, an attempt has been made over the last few years to develop batteries of tests maintaining their diagnostic usefulness but requiring less time to be carried out.[657]

The response to this question is based on recommendations of the EULAR working group[244] and on four clinical trials.[657-660]

| | |
|---|---|
| According to 2010 EULAR evidence-based recommendations for managing SLE with neuropsychiatric manifestations, the battery proposed by ACR has 80% sensitivity and 81% specificity and together with the ANAM (*Automated Neuropsychological Assessment Metrics*) is the most commonly used. The ACR battery takes one hour to apple. It is composed of the *Trail Making Test*, *the Auditory Verbal Learning Test*, *the Stroop Colo-Word Interference Test*, *the Rey-Osterrieth Complex Figure Test*, *the Benton Visual Retention Test*, *the WAIS-R Digit Symbol* and *the Block Design* and *Vocabulary*. The ANAM is a computerised cognitive assessment battery that includes 22 individual tests, sensitive to changes in attention, concentration, reaction time, memory, processing speed, decision-making and executive function.[244] | Expert consensus 4 |

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In a clinical trial conducted in the US in 2004, the validity of the complex battery of neuropsychological tests proposed by the ACR was compared with an extensive four-hour battery. The sample consisted of 31 patients with NP-SLE, 22 with SLE with no history of neuropsychiatric manifestations, and a control group of 25 individuals.[657] The degree of agreement observed between both tests in detecting disabilities was 90%. This was higher in the control group and in SLE patients without neuropsychiatric manifestations (95-96%) than in those with NP-SLE (81%). The validity and accuracy of the battery to detect disability, especially cognitive impairment, was confirmed. nRCT 1-

A nRCT was performed in 2011 in order to determine the utility of neuropsychological tests to assess the cognitive impairment present in SLE. SLE patients with and without neuropsychiatric manifestations were compared.[658] After carrying out a neuropsychological examination on 93 patients, it was concluded that the structured interview, by mental health professionals, continues to be the main tool and has the highest validity to assess the neuropsychological state and cognitive impairment of SLE patients, since the biographic data obtained therein are essential to contextualise the information provided by the neuropsychological evaluation. The use of neuropsychological tests provides systematics and reduces variability, when there is no training to carry out an in-depth structured interview. Furthermore, it was concluded that different tests could be useful as tests of first-choice in the early detection of cognitive impairment. nRCT 1-

In 2006, a study was carried out with 60 patients diagnosed with SLE, who had not presented neuropsychiatric symptoms. The objective was to determine the ability of ANAM to predict the probability of suffering NP-SLE. It was also studied whether the mental scale included in ANAM correlated with the validated BDI-II scale (*Beck Depression Inventory-II*). A traditional battery of neuropsychological tests lasting for two hours was administered to all the patients, followed by the ANAM battery.[659] The scores of the cognitive tests of the ANAM significantly correlated with the majority of neuropsychological tests, especially with those measuring the psychomotor processing speed and the executive functions. By stratifying patients according to the premorbid level of cognitive skills and using logistic regression models, it could be predicted which SLE patients were more likely to present with neuropsychiatric symptoms. Global sensitivity and specificity of 76.2% and 82.8%, respectively, were obtained. The ANAM mood scale was also significantly related to BDI-II (r=0.67; $P<0.001$). nRCT 1-

Based on these results, the authors concluded that the ANAM seems to be cost-effective and may be useful as an early diagnosis tool and to monitor the cognitive and emotional functioning in SLE patients, despite its limited specificity.[659]

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| Finally, with respect to the same battery of tests, another trial included SLE patients (n=68), RA (n=33), multiple sclerosis (n=20) and health controls (n=29) in order to compare the cognitive dysfunctions measured with ANAM.[660] The result was that the battery was more efficient in healthy controls. Disturbed functioning was found in 50% of SLE patients in at least one subtest and in 11% in at least four subtests. After comparing these results with those obtained in the other diseases, they concluded that ANAM was sensitive to detect the causes of cognitive failure, however, lacking specificity for the deterioration of specific domains in cognitive skills, and it cannot, therefore, replace a clinical neuropsychological evaluation. It was suggested that it would be useful as an early diagnosis tool. | nRCT<br>1- |

**Summary of evidence**

| | |
|---|---|
| 1- | Structured interviews by mental health professionals are still the main tool with the greatest validity to assess the neuropsychological state and cognitive impairment of SLE patients.[658] |
| 4/1- | The battery of neuropsychological tests proposed by ACR is a sensitive and specific tool for evaluating the neuropsychiatric manifestations of SLE, especially for cognitive impairment.[244,657] |
| 1- | There are different neuropsychological tests that can be useful for the early diagnosis of cognitive impairment.[658] |
| 1- | ANAM is a novel and useful battery with a favourable cost-effectiveness, and as it requires less time to carry it out. It seems useful in order to carry out early diagnosis and monitor the subsequent cognitive functioning thanks to high sensitivity and specificity.[659] |
| 1- | ANAM is not able to identify the specific cognitive domains affected.[660] |
| | No scientific evidence about whether this type of test should be performed on any patient with suspected NP-SLE has been found. |

**Recommendations**

| | |
|---|---|
| B | We recommend using structured interviews for the neuropsychological assessment of SLE patients. |
| C | We suggest using the battery of neuropsychological tests proposed by ACR to assess neuropsychiatric manifestations of SLE , especially in cases of cognitive impairment. |
| C | We suggest using validated neuropsychological tests validated in Spanish to monitor the neuropsychiatric outcomes of the progression of SLE, as well as to assess the effects of the interventions applied. |

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## 6.3.2. Indication for high intensity immunosuppressants

**Questions to be answered:**

- When are high-intensity immunosuppressive drugs indicated in patients with neuropsychiatric lupus?

Therapy with high doses of glucocorticoids or in pulses is still, today, an essential part of the treatment of SLE, and its efficacy has been repeatedly proven in disease activity phases. However, there are cases in which the response achieved by this treatment is not sufficient.[661,662] On the other hand, its long-term use is seriously limited by the excessive adverse effects and potential complications, which makes the concomitant use of immunosuppressants (e.g., CPM, AZA, MMF, etc.) necessary for treating severe cases.[663]

| | |
|---|---|
| Treatment with glucocorticoids and/or immunosuppressants is indicated in NP-SLE, after excluding other possible causes of the neuropsychiatric symptoms, either when it is considered that the neuropsychiatric symptoms are the result of an inflammatory process (i.e., myelitis, aseptic meningitis, cranial or peripheral neuropathy, psychosis, acute confusional syndrome, recurrent epileptic crises, and cerebrovascular accidents secondary to vasculitis) or when there are other systemic manifestations of SLE at the same time as the neuropsychiatric symptoms.[244] | Expert consensus 4 |
| One SR analysed the efficacy and safety of non-biological immunosuppressants in the treatment of extrarenal SLE.[315] 65 articles were selected that satisfied the inclusion criteria. The conclusions reached were: a) several immunosuppressants have proven their safety and efficacy in extrarenal SLE; b) a specific immunosuppressant cannot be recommended for each particular manifestation, although CPM should be taken into account for the more severe cases. | SR of RCT and cohort study, 1++ |
| A RCT that included 32 patients with severe NP-SLE compared intravenous CPM with intravenous MPred as maintenance treatment. Two years later, the response with CPM was significantly better (94.7% [18/19] for intravenous CPM compared with 46.2% [6/13] with ev. MPred). No significant differences were found in terms of adverse effects between the two treatment groups.[317] | RCT 1+ |
| MMF has been used successfully in long-term treatment of nephropathy associated with SLE. However, its efficacy for neuropsychiatric symptoms has not been sufficiently studied. Although the lack of controlled studies does not permit drawing solid conclusions in this regard, a recent SR suggests that the efficacy of MMF in NP-SLE seems modest, recommending the restriction of its use to patients who are refractory or intolerant to treatment with CPM.[664] | SR 2+ |
| For the particular case of lupus psychosis, some series of cases and open clinical trials have obtained responses of between 60-80% by means of induction pattern with glucucorticoids at doses of 1 mg/kg together with CPM followed by AZA in maintenance (although with recurrences in 50% of the cases).[665] | Case series 3 |

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In addition to these classical immunosuppressive drugs, the increasing knowledge about the physiopathology of SLE has permitted developing new therapeutic strategies based on the depletion of B-cells, through the use of anti-CD20 or anti-CD22 monoclonal antibodies. RTX, an anti-CD20 monoclonal antibody, is the biological agent with which there is more experience of use. To analyse the efficacy and safety of this drug in the treatment of non-renal SLE, the literature has recently been reviewed. In the case of NP-SLE, five cohort studies were included, observing 73-100% clinical improvement or improvement of response of the neuropsychiatric manifestations. However, there is little evidence about the use of RTX in the neuropsychiatric impairment of SLE.[357] SR 2+

Although the results have not been conclusive, different reviews of case series have reached very promising results, with response indices to RTX of 85% (29/34) in refractory patients to conventional immunosuppressive treatment.[666] Case series 3

**Summary of evidence**

| | |
|---|---|
| 4 | We suggest treatment with glucocorticoids and/or immunosuppressants in NP-SLE when it is considered that the syndromes occur as a result of an inflammatory process (acute confusional syndrome, aseptic meningitis, myelitis, cranial or peripheral neuropathies, and psychosis) after excluding other causes not related to SLE.[244] |
| 1++ | Treatment with CPM should be taken into account for the more severe cases.[317] |
| 1+ | Intravenous CPM is one of the most frequently used drugs for treating severe NP-SLE, showing greater efficacy than ev. MPred.[317] |
| 2+ | There is no solid evidence about the efficacy of MMF for treating NP-SLE, but the few data available point to modest efficacy.[664] |
| 3 | AZA seems to be efficient as maintenance treatment for secondary psychosis to SLE, although the lack of RCTs on this subject prevents drawing solid conclusions.[665] |
| 2+/3 | RTX as an induction therapy shows reasonable efficacy for treating NP-SLE when conventional immunosuppressants have failed.[357,666] |

**Recommendations**

| | |
|---|---|
| D | We suggest restricting treatment with glucocorticoids and/or immunosuppressants for neuropsychiatric SLE to those syndromes that express an underlying inflammatory process (organic brain syndrome, aseptic meningitis, myelitis, cranial or peripheral neuropathies, and psychosis) after excluding other causes not related to SLE. |
| A | We recommend considering cyclophosphamide as immunosuppressive first-line treatment for severe neuropsychiatric SLE. |
| C | In patients with neuropsychiatric SLE in whom the use of cyclophosphamide is contraindicated, we suggest using mycophenolate as an alternative. |
| C | Rituximab may be used as second-line in patients with neuropsychiatric SLE that are refractory to intravenous cyclophosphamide. |

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# 6.4. Lupus arthritis

## 6.4.1. Evaluation tools

**Questions to be answered:**

- Should a standardised tool be used to assess the state of arthritis? If so, which would be the most advisable?

No joint activity index has been specifically designed to measure arthritis in SLE patients, although the global activity indices of SLE (SLEDAI-2K, SELENA-SLEDAI, BILAG, ECLAM, etc.) include arthritis as one of their parameters.

In today's clinical practice, the DAS-28 activity index is usually used. This is a grouped measure based on joint counts developed specifically to assess the inflammatory activity of patients with RA.[667] However, the DAS-28 is not validated for SLE patients and no studies have been located that study the evolution of arthritis by applying this scale in these patients. Furthermore, bearing in mind the following differences between RA and SLE, whether this tool is useful for SLE patients in a generalises manner is placed in doubt:

1- The arthritis of RA is the main symptom of the disease and on which the prognosis in terms of activity and structural damage depends. In RA, measuring the arthritis means measuring the disease. This is not the case in SLE. The arthritis of SLE is usually a lesser manifestation, and its impact on activity and structural damage is much less than in neurological, renal or cardiopulmonary manifestations.

2- By definition, the arthritis of RA is chronic, multi-joint and often erosive and deforming. In SLE, arthritis may be much less expressive and include:

   a. Inflammatory arthralgia with apparently normal examination and joint ultrasound with positive Doppler signal.

   b. Intermittent migratory acute arthritis.

   c. Arthritis (acute/sub-acute) of less than six weeks' evolution, oligo-multijoint (depending on whether we assess by means of physical examination or by Doppler ultrasound), which in turn can be:

      i. Non-erosive (which is normal)

      ii. Erosive (which is rare):

         1. With RA type erosions

         2. With atypical erosions

   d. Arthritis of more than six weeks' evolution (chronic), which in turn may be:

      i. Non-deforming and non-erosive

      ii. Deforming and non-erosive, or with atypical erosions (Jaccoud arthropathy)

      iii. Type RA deforming and erosive (with or without RA criteria). We should bear in mind that rheumatoid nodules have been described, and rheumatoid factor and citrullinated anti-peptide antibodies may be detected in SLE patients, with or without arthritis (as there is RA without rheumatoid factor of citrullinated anti-peptide antibodies).

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Given that there is no available evidence, the recommendations issued for this question are based on considered judgement and consensus of the guideline development group, and of the group of experts.

**Recommendations**

| | |
|---|---|
| √ | We suggest using the DAS-28 index to assess the state of arthritis in SLE patients only in those cases with arthritis of more than six weeks evolution. |

## 6.4.2. Treatment

**Questions to be answered:**

- Which treatments are efficient and safe for lupus arthritis?

No studies have been located that assess specific treatment for lupus arthritis. The available evidence comes only from results in small subgroups of patients with arthritis in studies with more extensive samples of SLE patients, the majority of which were historical observational studies and in which a large variety of drugs were tested.

The response is based on several primary studies which, in a tangential manner, present the efficacy of different drugs on joint manifestations associated with SLE.[322-324,353,360,362,372,415,668-672]

A double-blinded RCT was performed with placebo group, with 41 SLE patients (39 women, two males, average age: 32.1 yrs, average duration of disease: 85.2 months), to assess the capacity of MTX to control the average activity of SLE. RCT 1++

The global activity of SLE was significantly reduced throughout the treatment of the MTX group (three, four, five and six months ($P$<0.05). At the start of the study, 85% of the patients from the MTX group and 81% of the patients assigned to the placebo, presented arthralgia or arthritis. After six months, 84% of the patients from the placebo group and 5% of MTX presented those symptoms ($P$<0.001). Joint paint was significantly greater in the placebo group than in the MTX group from the first month of the study until the sixth month ($P$<0.05).[322]

In a double-blinded RCT, Fortin *et al*. compared the glucocorticoid saving effect of MTX on 86 patients with moderate-severe SLE (SLEDAI ≥ 8). Forty-one patients were randomly assigned to receive MTX, at initial doses of 7.5 mg/day, which could be increased to 20 mg/day, opposed to 46 patients who received placebo. Glucocorticoids and anti-malarial drugs were administered in both groups, in agreement with the disease activity. Joints in both arms were affected in more than 90% of the patients. After 12 months' follow-up, the number of patients who reduced the dose and did not take prednisone was higher in the MTX group. Patients with MTX reduced their dose of prednisone by 22% compared with the placebo group ($P$=0.01), after adjusting for the initial dose and other potential confusion variables (age, gender, SLICC/ACR DI score and use of anti-malarial drugs). Likewise, a significantly greater decrease in score of the SLAM activity scale was recorded ($P$=0.039).[323] RCT 1++

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A double-blinded RCT, controlled by placebo, assessed the efficacy of CQ in the prevention of flares in SLE patients over a 12 month period; 24 SLE patients without life-threatening manifestations were selected. 18% of the CQ patients and 83% of the placebo patients presented flare-up of the disease ($P<0.01$). Throughout the study, it was observed that the joint implication was more frequent in the placebo group (in 67% of the patients in the placebo group, $P=0.001$).[415] RCT 1+

In another RCT, the efficacy of the two previous treatments (MTX and CQ) on joint and skin manifestations of SLE was compared. To do so, 41 SLE patients were randomly assigned to receive 10 mg a week of MTX (n=15) or 150 mg CQ per day (n=26) for 24 weeks. RCT 1+

The number of swollen joints, the joint swelling index, the number of painful joints, the joint sensitivity index, morning stiffness and pain decreased in a statistically significant manner in the MTX group ($P<0.05$, $P<0.05$, $P<0.01$, $P<0.01$, $P<0.01$, $P<0.01$, respectively) and in the CQ group ($P<0.05$, $P<0.05$, $P<0.001$, $P<0.001$, $P<0.01$, $P<0.001$, respectively) throughout the 24 weeks, but no differences were observed between the two groups.[670]

A double blinded pilot RCT, controlled by placebo, was carried out on a sample of 12 SLE patients with moderate activity to assess the efficacy and safety of treatment with LEF. Six patients were randomly assigned to treatment with a daily dose of 100 mg for three days, followed by a dose of 20 mg until the end of the study, and six patients to the placebo. Arthritis appeared in four patients in the LEF group and two in the placebo group as the main manifestation. The disease activity significantly decreased after six months in the two groups (14.7±6.0 to 3.7±2.3, $P=0.028$ in the LEF group; 9.7±3.4 to 5.2±4.1 in the placebo group, $P=0.027$). However, the reduction in SLEDAI from the baseline to 24 weeks was significantly greater in the LEF group compared with the placebo group (11.0±6.1in the LEF group and 4.5 ±2.4 in the placebo group, respectively, $P=0.026$).[324] RCT 1-

In a post-hoc analysis of the ALMS RCT, which compared MMF with CPM in induction treatment of LN, the joint condition improved considerably and similarly in both treatments arms: 91% of 23 patients with MMF and 96% of 26 patients with CPM.[673] Post-hoc analysis of RCT 1-

Evidence of the usefulness of AZA in lupus arthritis is limited to one RCT which compared this drug with cyclosporine as glucocorticoid-saver in patients with active SLE who were receiving a prednisone dose ≥15 mg/day. Joints were affected in more than 85% of the patients. After 12 months' follow-up, both drugs showed similar efficacy in terms of reducing the doses of prednisone and of global activity of SLE.[321] RCT 1+

A post-hoc analysis of two RCTs[296,297] including 819 and 867 SLE patients was performed in order to determine the efficacy and safety of belimumab (1 and 10 mg/kg) opposed to placebo (more standard treatment). Post-hoc analysis of 2 RCT 1+

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Belimumb, compared with placebo, presented a statistically more significant improvement rate of joint manifestations (of the relative item of SLEDAI), although the difference was not quantitatively very relevant (placebo 49.3%, belimumab 1 mg/kg 58.3%, belimumab 10 mg/kg 56.6%). The similar behaviour of both doses of belimumab is worthy of note.[353]

Abatacept has been tested in two RCTs phases II and II/III in SLE without renal impairment (n=170),364 not reaching the primary objectives. However, post-hoc analysis has suggested a possible positive effect in arthritis.371 In a post-hoc analysis, using the response criteria from other studies (ALMS, LUNAR and ACCESS), the response rates were greater in the treatment groups than in the control group. Furthermore, it was observed that the effect of the treatment was more noticeable for patients whose primary manifestation of SLE was polyarthritis at the start of the study (treatment difference -28.3; 95% CI: -46.1, -10.5).

Post-hoc analysis of RCT
1+

To study if rapamycin is beneficial in SLE patients, 16 SLE patients were studied (100% women). Nine patients received treatment with rapamycin (2 mg/day) and the other seven were included as disease controls. During the last follow-up on the patients treated with rapamycin, an average reduction in the BILAG scale was obtained of 1.93±0.9 ($P$<0.0218) compared with the baseline measurements. The SLEDAI was reduced by an average of 5.3±0.8 ($P$<0.00002). In one patient assigned to the rapamycin group, the arthritis and fatigue disappeared after seven months' treatment.[669]

nRCT
2-

A cohort of 52 SLE patients, treated with RTX was selected, in order to study the efficacy and safety of the treatment, and determine if the baseline parameters predict the flare-up of the disease. Of the 52 patients, 25 presented severe musculoskeletal conditions (three presented erosive symmetric polyarthritis and 22 non-erosive polyarthritis). In nineteen patients, the numbness and joint pain remitted completely after an average of 10 weeks from the start of the treatment. The use of RTX was associated with a significant reduction in the average disease activity ($P$=0.004) and its efficacy was greater in patients with erosive polyarthritis ($P$=0.004). No baseline parameter was an independent predictor of flare.[362]

Cohort S.
2-

A multi-centre study was carried out in 2012 with 131 SLE patients who had not responded to standard therapy and were treated with RTX. Of the 116 patients who completed the follow-up, 73 (62.9%, 95% CI: 49.3-79.1) responded after the first course of RTX; 22 patients (19.6%; 95% CI: 12.3-29.7) responded completely and 51 patients (45.5%; 95% CI: 36.1-55.2) responded partially. One of the best responses to the drug was observed in patients with arthritis (81.5%).[360]

Cohort S.
2-

A recent observational study of the Hospital Vall d'Hebron cohort has analysed the efficacy of etanercept (added to the regular treatment) on 43 patients with refractory lupus arthritis. There was a remission of joint symptoms in 90% of the patients after six months, with no significant differences (improvement or worsening) in renal parameters. The mean SLEDAI significantly dropped from eight to two. 19 patients presented adverse effects, two of which were considered severe.[369] (For more information, see section 5.2.2. Treatment Indications).

Cohort S.
2-

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| | |
|---|---|
| To assess the safety, and clinical and immunological efficacy of tocilizumab in SLE patients, 16 patients with moderate activity were selected. They were treated every two weeks for 12 weeks with three doses of tocilizumab (2 mg/kg, n=4; 4 mg/kg, n=6; 8 mg/kg, n=6). The SELENA-SLEDAI scores dropped from 9.5 to 5.5 ($P$=0.0001), mainly due to the improvement in arthritis and skin rash. Seven patients presented arthritis at the start of the treatment, four in the group of 4 mg/kg and three in the group of 8 mg/kg. The average of swollen joints improved from 7.7 to 5.4 after six weeks, and to 1.1 after 20 weeks, with complete resolution of arthritis in four patients. Six patients presented a rash that was resolved in three cases between weeks two and six.[372] | Cohort S. 2- |
| To determine the safety/tolerability and efficacy of anakinra in SLE patients with joint impairment, four SLE patients and non-erosive polyarthritis were selected (two males and two women, with average age of 38 years). A reduction of swollen and painful joints was found in the four cases.[672] | Case series 3 |
| In a final study, three patients with active SLE and polyarthritis, in whom traditional treatments had failed, were treated. In two of the three patients there was a temporary effect on muscle pain and/or polyarthritis. In one patient with lupus with myositis there was no effect. The therapy was well-tolerated and the only significant side effect was a temporary drop in complement levels (C3 and C4), with no clinical or laboratory signs of increase of the SLE activity.[671] | Case series 3 |

**Summary of evidence**

| | |
|---|---|
| 1++ | MTX reduces SLE activity, arthralgia and arthritis.[322] |
| 1++ | The addition of MTX allows a reduction of glucocorticoids and of global lupus activity in patients with active mainly joint-affected SLE.[322,323] |
| 1+ | CQ prevents flares in SLE patients with joint impairment.[415] |
| 1+ | Both MTX and CQ reduce the number of swollen joints, the index of joint swelling, the number of painful joints, the joint sensitivity index, the morning stiffness and the pain.[670] |
| 1- | LEF decreases the disease activity, even in patients whose main manifestation is arthritis.[324] |
| 1- | AZA and CsA are similarly effective in reducing the dose of glucocorticoids and the activity of lupus with joint participation.[673] |
| 1- | MMF and CPM may improve the accompanying joint condition in patients with active LN.[673] |
| 1+ | Belimumab, both at doses of 1 mg/kg and 10 mg/kg, produces an improvement in joint symptoms.[353] |
| 1+ | Abatacept could have a beneficial effect in patients whose main manifestation of SLE is polyarthritis.[371] |
| 2- | The use of RTX is associated with a reduction in the disease activity, especially in patients with arthritis.[362] |
| 2- | Etanercept may improve refractory lupus arthritis with no severe adverse effects.[369] |

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| | |
|---|---|
| 3 | Tocilizumab decreases the activity of lupus, mainly due to the improvement in arthritis and skin rash.[372] |
| 3 | Anakinra could improve lupus arthritis.[671,672] |

**Recommendations**

| | |
|---|---|
| A | Methotrexate and anti-malarial drugs are the medications of choice in the case of joint manifestations of SLE. |
| C | There is little evidence about the use of other drugs for the specific treatment of lupus arthritis. The concrete indication for each one of them will depend therefore on the accompanying symptoms, the potential toxicity (including the possibility of pregnancy) and economic considerations. |
| √ | We recommend hydroxychloroquine with or without low doses of glucocorticoids (or pulses of 125 to 250 mg of methylprednisolone) in patients with inflammatory arthralgias, intermittent arthritis or arthritis of less than six weeks evolution. |
| √ | Patients who do not respond to the treatment, require > 5mg of prednisone (or equivalent) for its control, with symptoms that last for more than six weeks or in cases where erosions or deformities appear, should be treated as chronic patients. The following regimens are recommended to treat chronic arthritis:<br>– Methotrexate as drug of choice<br>– If a satisfactory response is not obtained at full and subcutaneous doses within three months, add (or change) to another synthetic disease-modifying drug (leflunomide, azathioprine, cyclosporine A or mycophenolate), bearing in mind the other manifestations of SLE and the toxicity of each synthetic disease-modifying drug.<br>– If there is no response in three months, we recommend adding biological therapy, more specifically, starting with belimumab. If remission is not achieved within six months, rituximab, abatacept, etanercept, tocilizumab or other biological disease-modifying drugs could be used, although, unlike belimumab, none of them have authorised indication in SLE. |

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Serious cases of drug-induced liver injury, including acute liver failure, hepatitis and jaundice, in some cases requiring liver transplantation, have been observed in patients treated with tocilizumab. The frequency of serious hepatotoxicity is considered rare.

For additional information, please consult:
https://sinaem.agemed.es/CartasFarmacovigilanciaDoc/2019/DHPC_Tocilizumab_27062019.pdf

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# 6.5. Mucocutaneous manifestations

## 6.5.1. Cutaneous lupus evaluation tools

**Questions to be answered:**

- Should a standardised tool be used to evaluate the stage of the disease? If so, which would be the most appropiate?

The course of skin lesions in SLE or the time required for patients to present a response to the treatment is unpredictable.

The SLEDAI, BILAG and SLAM activity indixes are sensitive in the detection of the presence of mucocutaneous manifestations in SLE, but they do not enable the adequate determination of the impact of the treatment on their activity.

In a retrospective study of 176 patients with CLE the evolution of the disease in time and after treatment was determined in 50 of them. It was concluded that SLAM may be useful to monitor the activity of skin lesions in patients with lupus. However, this index includes skin manifestations that are not equivalent in the same group (for example, scarring alopecia and non-scarring alopecia). Observational S. 3

In 2005, Albrecht *et al*.[674] designed the CLASI, a tool to assess the activity and the sequelae of skin manifestations of lupus erythematosus. They based this on a review of literature of the tools used in dermatology to assess skin lesions in lupus erythematosus. CLASI has two different scales: one measures the activity of the disease by assessing the rash, descaling/hyperkeratosis, mucous impairment, acute hair loss, and non-scarring alopecia; the other measures the sequelae of the disease (hypopigmentation, scars, scarring alopecia). If the hypopigmentation has lasted for more than 12 months, it is considered as permanent and scores double. The anatomic location involved is established for each one of the signs, so that extension of the disease is also assessed. Expert opinion 4

To determine the usefulness of this tool, these researchers assessed nine patients with histological diagnosis of CLE (five with discoid lupus, and four with subacute lupus erythematosus; two of the patients satisfied SLE criteria). Interobserver concordance was established among 11 experts. The intraclass correlation coefficient was r= 0.86 (95% CI: 0.73-0.99) for the activity scale, and r= 0.92 (95% CI: 0.85-1.00) for the damage scale. The Spearman Þ (SÞ) of intraobserver concordance for the activity evaluation was 0.96 (95% CI: 0.89-1.00), and for damage evaluation 0.99 (95% CI: 0.97-1.00).[674]

Another longitudinal study performed in 2008 included eight patients with CLE who would start a new treatment after being included, four patients had generalized DLE; two localized DLE, and two had subacute lupus erythematosus; one patient with generalized DLE and one with localized DLE, satisfied SLE criteria. The improvement was defined as a change of at least two points in the global assessment carried out by the doctor, and of at least three points in the assessment carried out by the patient.[675] Observational S. 2-

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A correlation between improvement of the CLASI activity and improvement of pain was obtained (r= 0.98; *P*=0.0004; n=5), whilst the correlation with the improvement of pruritus was not statistically significant (r= 0.67; *P*=0.10; n=7). An excellent correlation with the global assessment of skin health was also verified, both from the doctor's viewpoint (r= 9.97; *P*=0.003; n=7), and from the patient's (r= 0.85; *P*=0.007; n=8), and it permitted to document the severity and extension of the disease. The change in the CLASI activity was significantly different in patients who had a significant difference in the global assessment of skin health compared with those who did not, both by the doctor (*P*=0.008) and by the patients (Range test with Wilcoxon sign: 0.00; *P*<0.008). The correlation between the change in the CLASI scale of damage with the change in global assessment of skin health by the doctor was moderate (r= 0.52; *P*=0.23; n=7). There was a poor correlation between the change in the CLASI scale of the damage with the change in scale of itchiness (r=0.45; *P*=0.32; n=7), of pain (r=0.64; *P*=0.24; n=5) and with the global assessment of the state of health by the patient (r= 0.32; *P*=0.45; n=8). The study highlights the importance of assessing the activity and damage separately. This damage or sequelae could alter the patient's perception of the activity improvement.

In 2008, the validity of CLASI was assessed for use by rheumatologists. To this end, dermatologists and rheumatologists classified 14 individuals with CLE, one patient with a skin lesion similar to cutaneous lupus and two patients with both lesions. The intraclass dermatology correlation coefficient was 0.92 for activity and 0.82 for damage; and the rheumatology coefficient was 0.83 for activity and 0.86 for damage.[676]

Observational S. 2-

A longitudinal study performed in India (n=96) assessed activity and damage CLASI on 75 SLE patients. They concluded that CLASI is a useful tool to assess the activity and damage produced from specific LE cutaneous lesions and that it also permitted assessing response to treatment. The correlation between the duration of the disease and damage CLASI was statistically significant. (rs =0.477; *P*<0.001).[677]

Observational S. 2+

A more recent study (n=75) showed that CLASI can be useful to classify the skin impairment of SLE as mild, moderate or severe, depending on whether the activity scores are between 0-9, 10-20 and 21-70, respectively, enabling patients with response to treatment to be identified.[678]

Cohort S. 2-

Finally, Jolly *et al*. recently tried to validate CLASI bearing in mind SELENA-SLEDAI, the SLICC/ACR ID damage index (SLLICC/ACR DI), the HRQoL (LupusPRO) and body image (BIALI), on 31 patients with CLE, finding that the score obtained in the CLASI correlates with the activity and severity assessed by the specialist. The increased CLASI activity in visible anatomical locations significantly correlated with a worse HRQoL and perception of body image. For example, having lesions on the face correlated with the difficulty to establish relationships with people of the same sex (r= -0.52; *P*=0.001).[679]

Observational S. 2-

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In 2010, a revised version of the CLASI was proposed, bearing in mind different clinical characteristics of the different subtypes of cutaneous lupus. For this purpose, 12 patients with different cutaneous lupus subtypes were selected and assessed by nine dermatologists. The inter-evaluator reliability studies resulted in an intraclass correlation coefficient of 0.89 for the activity score (95% CI: 0.79-0.96) and of 0.79 for the damage score (95% CI: 0.62-0.92). The test-retest reliability was 0.92 for the activity score (95% CI: 0.89-0.95) and 0.95 for the damage score (95% CI: 0.92-0.98). Cohort S. 2-

**Summary of evidence**

| | |
|---|---|
| | The indixes used to assess SLE activity (SLEDAI, BILAG, SLAM) do not permit the identification of cutaneous sequelae or the impact of the treatment. |
| 4 | The CLE activity and severity index (CLASI) is a useful tool to assess the activity and sequelae of cutaneous manifestations of lupus erythematosus.[674] |
| 2- | The CLASI activity is correlated with the global assessment performed by specialist and patient.[675] |
| 3 | CLASI permits performing comparative studies and its standardisation may be useful in clinical research.[676] |
| 2+ | The damage CLASI is correlated with the duration of the disease.[677] |
| 2- | CLASI permits classifying the cutaneous manifestations of SLE into mild, moderate and severe.[678] |
| 2- | CLASI permits identifying patients whose skin lesions are going to respond to the treatment.[678] |
| 2- | CLASI seems to be a reliable instrument for use by rheumatologists.[676] |
| 3 | CLASI is correlated with the global activity and damage measurement scales of SLE (SELENA-SLEDAI, SLICC/ACR DI).[679] |
| 2- | Revised CLASI is a valuable instrument for the clinical assessment of the activity and damage in different disease subtypes.[680] |

**Recommendations**

| | |
|---|---|
| √ | In patients in whom there is a prevalence of skin impairment, we suggest using a standardised cutaneous activity index. |
| D | We suggest using CLASI to assess the activity, damage and evolution of skin lesions in SLE patients. |

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## 6.5.2. Topical treatment

**Questions to be answered:**

- What is the effectiveness, safety and cost-effectiveness of topical therapies in treating systemic lupus erythematosus with cutaneous manifestations? In which situations would they be indicated?

Although clinical practice suggests that topical glucocorticoids are efficient in treating cutaneous manifestations of lupus erythematosus, mainly reducing rash and descaling, there is not sufficient scientific evidence to use topical treatment in cutaneous manifestations of SLE. There is only one RCT, published in 1980, which compared fluocinonide 0.05% (high potency) with hydrocortisone 1% (low potency) (n=115), observing an excellent response after six weeks with fluocinonide, suggesting that high/medium potency topical glucocorticoids are more efficient that the low potency ones (17% benefit in favour of fluocinonide; 95% CI: 0.9-0.34; number of patients needed to be treated: 6).[681] RCT 1+

Given the adverse effects of the use of topical glucocorticoids in the long term, mainly skin atrophy, the topical use of calcineurin antagonists has been tested. In 2008, Tzellos *et al*. published a review of literature to determine the efficacy of topical tacrolimus/pimecrolimus on skin lesions of SLE. A search was made in *Medline, Embase and Cochrane Database* for RCTs, nRCTs and SRs indexed before August 2007. Of the 32 articles recovered, five studies were included, only one of which was a RCT.[682] SR 1-

The RCT included was a double-blinded study which compared the efficacy and safety of tacrolimus 0.1% with clobetasol propionate 0.05% in 18 patients with facial lesions due to lupus erythematosus (13 with SLE malar rash, four with DLE, and another with subacute cutaneous lupus) (11 women and seven males, average age: 33 years).[683] The patients were instructed to apply tacrolimus 0.1% twice a day on the affected areas of one side of the face, and clobetasol propionate 0.5% on the other side, randomly assigned for each patient. Both the tacrolimus and the clobetasol reduced the rash, the descaling and the induration ($P<0.05$, compared with the baseline score), with no differences between both groups. In this study, the tracrolimus ointment produced less local side effects (telangiectasias), which were observed in up to 61% of patients on the half-face treated with clobetasol propionate.

In another study, an open test in phase II, the aim was to determine the safety and efficacy of pimecrolimus in DLE lesions. 10 patients were treated with pimecrolimus 1% in cream, twice a day for eight weeks. An improvement of skin damage was observed in all patients after the therapy, as well as a reduction of 52% in the global clinical severity score (from 6.1±1.4 before treatment to 2.9±1.5 after treatment; $P=0.005$). Treatment was well-tolerated, adverse reactions consisted in minimum rash and pruritus, which were resolved without any additional measure.[684]

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Uncontrolled studies include a case series of 11 SLE patients with different types of cutaneous manifestations, who were treated with pimecrolimus 1% in cream twice a day for three weeks. In this case, a considerable improvement of skin lesions was observed in all patients, with a reduction of 57% in a non-standardised clinical score ($P<0.001$).[685] Case S. 2-

Another case serie of 12 SLE patients whose skin lesions did not respond to standard treatments, received local treatment with tacrolimus 1% for at least six weeks in order to determine its efficacy. Eleven of the 12 patients completed the therapy: one patient discontinued due to descaling and burning feeling, six clearly improved, one had a slight remission and four remained the same.[686]

Finally, in another case series included in the SR, 11 patients with cutaneous lupus and dermatomyositis were treated with tacrolimus. Six of the 11 patients (three with SLE, one with DLE and two with dermatomyositis) showed a marked regression of the skin lesions after treatment with tacrolimus, but four patients (three with DLE and one with dermatomyositis) were resistant to the therapy. A good response was observed for facial erythematosus lesions with edematous or telangiectatic changes in SLE and dermatomyositis. There was no improvement in typical DLE lesions with tacrolimus.[687]

The authors of the aforementioned SR conclude that there does not seem to be significant differences between the efficacy of tacrolimus and clobetasol; however, tacrolimus is tolerated better and both, tacrolimus/pimecrolimus, may be useful in initial skin lesions of SLE. However, we should take into account that the main limitation of this SR was that the majority of available studies that could be included, probably due to economic reasons, assessed tacrolimus and pimecrolimus (which have proven to be comparable with medium-potency glucocorticoids in many other diseases but more expensive). In one single study that uses topical glucocorticoids as a comparison, [683] despite being the only RCT included, the sample was heterogeneous (mixing different forms of cutaneous lupus with very different degrees of response to treatments), so the results were difficult to interpret.

A multicentre, double-blinded and controlled RCT with placebo performed later than the review of Tzellos *et al*., selected 30 adult patients with cutaneous lupus (14 patients with DLE, 11 tumid lupus, four with subacute cutaneous lupus, and one patient with acute cutaneous lupus) (18 women, 12 males, average age: 45.2 years) to assess the efficacy of the topical application of tacrolimus 0.1%, mainly on rash and facial edema in recent lesions.[682] RCT 1+

An improvement was observed in the cutaneous lesions of patients treated with tacrolimus 0.1% after 28 and 56 days ($P<0.05$), but not after 84 days. The edema responded more quickly to tacrolimus 0.1% ($P<0.001$) after 28 days. Changes were also observed in the clinical score in rash, where patients assigned to tacrolimus 0.1% showed a considerable improvement ($P<0.05$) after 28 days, but not after 56 and 84 days. Patients with chronic hyperkeratosic lesions did not respond well to treatment with tacrolimus.[688]

**Summary of evidence**

| | |
|---|---|
| 1+ | High/medium-potency topical glucocorticoids are efficient in reducing rash and descaling of lesions of acute, subacute and chronic cutaneous lupus.[681] |

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

| | |
|---|---|
| 1+ | There is certain evidence that topical tacrolimus may be efficient in reducing rash and edema of cutaneous lupus lesions localized on the face.[688] |
| 2- | Cream with pimecrolimus for DLE seems to be a safe and clinically efficient option.[683-685] |
| 2- | Tacrolimus 0.1% may be an efficient alternative in patients with resistant cutaneous manifestations in lupus[686,688] and in skin lesions caused by other collagen diseases.[683,687] |
| 1- | Topical tacrolimus produces fewer local side effects (telangiectasia) than clobetasol propionate.[682,683] |
| | There are no cost-effectiveness analyses of topical therapies for cutaneous manifestations of SLE. |

**Recommendations**

| | |
|---|---|
| √ | In cutaneous lupus, we suggest the initial use of high-potency topical glucocorticoids. |
| √ | In refractory cases, we suggest using topical treatments with calcineurin inhibitors (tacrolimus or pimecrolimus). |

# 6.6. Antiphospholipid syndrome

## 6.6.1. Antiphospholipid antibodies

**Questions to be answered:**

- What types and combinations of antiphospholipid antibodies increase the risk of thrombosis in people with systemic lupus erythematosus?

APLs are considered a risk factor of thrombosis, both in the presence and in the absence of a concomitant autoimmune disease such as SLE.[689] However, the real frequency of thromboembolism may vary depending on the type, serum level and persistence over time of each of the individual APLs.

The MA of Wahl et al, which includes 26 studies published between 1983 and 1996 and which only includes SLE patients, found an association between lupus anticoagulant (LA) and thrombosis. This risk varies depending on the result variable. For venous thrombosis it presents an OR 5.612 (95% CI: 3.80-8.27), for deep vein thrombosis and pulmonary embolism, OR 6.32 (95% CI: 3.71-10.78) and for recurrent venous thrombosis, OR 11.6 (95% CI: 3.65-36.91). The association between aCL and thrombosis is positive although less strong than for LA. For venous thrombosis OR 2.17 (95% CI: 1.51-3.11), deep vein thrombosis and pulmonary embolism, OR 2.5 (95% CI: 1.51-4.14) and recurrent venous thrombosis OR 3.1 (95% CI: 1.14-13.38).[690] SR 2+

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

Two observational studies have analysed the relationship of the combinations and persistence of APL with thrombosis in SLE patients. The study of Martinez-Berriotxoa *et al*. included 237 patients[205] and the study of Tektonidou *et al*. 144 SLE patients APL-positive and 144 SLE controls APL-negative.[329] In both studies, the patients with APL were classified into three groups: those with positive LA; those with aCL at positive medium-high titres in at least 2/3 of the determinations carried out; and those with aCL at positive medium-high titres less than 2/3 of the determinations carried out. The results of both studies were identical, showing that, compared with APL-negative patients, the risk of thrombosis increased in patients with persistently positive LA and in those with persistently positive aCL, but not in patients with intermittently positive aCL. In the study of Tektonidou *et al*.,[329] the triple positivity, AL-aCL- anti-β2-GPI increased the risk of thrombosis six-fold.

Cohort S. 2+

Pengo *et al*. also analysed the combinations of antibodies in a prospective study that included 618 individuals, 27 of them with SLE, finding the triple positivity for LA, aCL and anti-β2-GPI being an independent risk factor for thrombotic events, OR 33.3 (95% CI: 7.0-157.6), although this result did not consider patients with SLE or primary APS separately.[231]

Cohort S. 2+

Scascia et al, in a study that included 230 SLE patients, analysed the combination of LA antibodies, anti-phosphatidylserine/prothrombin (aPS/PT) and anti-β2-GPI, finding the greatest risk of thrombosis when the three antibodies are combined, OR 23.2 (95% CI: 2.57-46.17), followed by the combination of LA and anti-β2-GPI+ with OR 13.78 (95% CI: 2.04-16.33) and of LA with aPS/PT with OR 10.47 (95% CI: 2.21-26.97).[211]

Cohort S. 2+

**Summary of evidence**

| | |
|---|---|
| 2+ | LA increase the risk of thrombosis in SLE patients.[205,690] |
| 2+ | aCLs increase the risk of thrombosis in SLE patients only if combined with LA, or, if isolated, being persistently positive at medium-high titres (more positive than negative determinations).[205] |
| 2+ | Combinations of APL generally increase the risk of thrombosis, the combined positivity for LA, aCL and anti-β2-GPI being associated with the greatest likelihood of thromboembolic events.[231,329] |
| 2+ | In the future, aPS/PT antibodies may become thrombotic risk markers in SLE patients, especially if combined with other APL.[211] |

**Recommendations**

| | |
|---|---|
| C | We recommend determining antiphospholipid antibodies (lupus anticoagulant, aCL and anti-β2-GPI) on a regular basis as thrombotic risk markers in SLE patients. |

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## 6.6.2. Prevention and treatment of thrombotic complications

**Questions to be answered:**

- What preventive and treatment measures should be taken for thrombotic complications in people with systemic lupus erythematosus and antiphospholipid antibodies?

SLE patients have a greater risk of thrombosis. It has been estimated that one quarter of the patients with lupus eventually die due to thrombotic complications.[22] SLE patients suffer thrombosis at a younger age than the general population. Although classical cardiovascular risk factors play an important role in the development of CVD, other variables also come into play to explain the high incidence of thrombosis in SLE patients.[691] The most important of these is the presence of APL, particularly aCL and LA.

Most studies focusing on the prevention and treatment of thrombosis in patients with APL include patients with and without lupus, so that it is not easy to discriminate specific measures for patients with SLE and APL. In general, recommendations for patients with APS are applied, considering that the concomitant diagnosis of SLE entails, per se, an increase in the risk of thrombosis.[692]

**Primary prevention of thrombosis**

| | |
|---|---|
| The effect of anti-malarial drugs on thrombosis has been analysed within a SR on the efficacy and toxicity of anti-malarial drugs in SLE patients.[693] The conclusion in this topic, based on eight observational studies, is that anti-malarial drugs prevent thrombosis in patients with lupus with a moderate degree of evidence according to the MPM classification. | SR 2+ |
| After the publication of the SR, two observational studies confirmed the role of anti-malarial drugs in preventing thrombosis. Tektonidou *et al*. examined the thrombotic risk factors and primary antithrombotic prophylaxis in SLE (n=144) with and without APL. The rate of thrombosis was 20.1% in patients APL-positive vs. 7.6.% in patients APL-negative ($P$=0.003). The duration of treatment with low-dose aspirin had an independent antithrombotic effect in patients with APL (HR= 0.98; $P$=0.05), as well as the duration of treatment with HCQ, both in APL-positive (HR= 0.99; $P$=0.05) and APL-negative patients (HR= 0.98, $P$=0.04).[329] | SR 2+ |
| A nested case-control study within the inception cohort of the University of Toronto matched 54 patients with thrombosis with 104 without thrombosis.[330] In the multivariate study, only the age (OR=1.04; 95% CI: 1.01-1.07) and the use of anti-malarial drugs (OR= 0.32; 95% CI: 0.14-0.74) were significantly associated with the risk of thrombosis. In the univariate analysis, the protective effect of anti-malarial drugs was similar for both venous and arterial thromboses. | Case-control study 2+ |

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In 2011, the recommendations of the *Task Force* at the *13th International Congress on Antiphospholipid Antibodies* were published, the latest consensus document available to date. The methodology chosen was the SR of literature and the agreement on recommendations by the panel of authors.[692] The assessment of evidence was carried out with a modification of the MPM methodology (1-2 and A-B-C). In patients with SLE and the presence of LA (alone or combined with aCL), or isolated, persistently positive aCL at medium-high titres, they recommended treatment with HCQ (1B recommendation, although some authors lowered this recommendation to 2B) and aspirin (recommendation 2B). SR 2+

After the publication of this document, a MA was carried out to determine if aspirin has a protective effect on the risk of first thrombosis in patients with APL. 11 primary studies were included (10 observational and one CCT) with a total of 1208 patients and 139 thrombotic events. Prophylaxis with low-dose aspirin significantly reduced the risk of first thrombotic events in asymptomatic individuals with APL, patients with SLE or obstetric APS (OR in SLE patients= 0.55; 95% CI: 0.31-0.98). However, significant reductions in the risk were not found when only prospective studies or studies with a higher methodological quality were considered, although in this analysis it was not possible to analyse SLE patients separately.[694] MA 1+

**Secondary prevention of thrombosis**

After a thrombosis occurs in patients with APL, two basic questions arise: should long-term treatment be more intense than in patients without APL with a similar clinical picture? Does the presence of APL imply a difference in the duration of treatment? The evidence to answer both questions comes from series of observational studies and clinical trials, compiled and analysed in a recent SR by the *Task Force* at the *13th International Congress on Antiphospholipid Antibodies*. However, many of the conclusions are considerably limited by facts like the over representation of patients with venous thromboses, and above all, the difficulty in the few clinical trials published to effectively maintain high-intensity anticoagulation. There are no specific studies in SLE patients, so the conclusions are based on studies that combined patients with primary and secondary APS.

As mentioned in the primary thromboprophylaxis sections, the recommendations of the Task Force at the 13th International Congress on Antiphospholipid Antibodies are based on a SR of the literature assessed with MPM methodology. Separate recommendations are offered for venous and for arterial thrombosis.[692] SR 2+

For venous thrombosis in patients who suffer a first episode and satisfy APS classification criteria, anticoagulant treatment with a target INR (*International Normalised Ratio*) of 2.0-3.0 is recommended (1B recommendation). This recommendation is based on two clinical trials with important limitations with regard to the degree of compliance of the arms treated with high-intensity anticoagulation.

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For arterial thromboses, anticoagulation with a target INR > 3.0 or the combination of anticoagulants with INR 2.0-3.0 + low-dose aspirin is recommended. Due to the low quality of the data, most of them coming from subanalyses of published studies, some of the authors disagreed about these conclusions, so it was not possible to reach an agreement on the degree of recommendation.

In general, both for arterial and venous thromboses indefinite anticoagulation was recommended (1C recommendation).

To date, there are no studies that assess the impact of the control of vascular risk factors on the risk of initial or recurrent thrombosis in patients with SLE and APL.

* INFORMATIVE NOTE Spanish Agency of Medicines and Medical Devices (20th May 2019)

New recommendations have been stablished on the use of direct oral anticoagulants (DOACs) in patients with antiphospholipid syndrome (APS) and a history of thrombosis.

For additional information, please consult:
https://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2019/NI_MUH_FV-8-2019-anticoagulantes-orales.htm

Commentary from the guideline coordinators:
"According to the new available evidence, the use of direct oral anticoagulants (DOACs) is not recommended, as a general rule, in patients with antiphospholipid syndrome (APS) in association with systemic lupus erythematosus (SLE), since DOACs could be ineffective for the prevention of recurrent thrombosis, especially in arterial thrombosis. DOACs could be considered in certain clinical scenarios such as in patients with allergy to vitamin K antagonists, they could be also an alternative in patients with a history of exclusively venous thrombosis and without a high risk antiphospholipid antibody profile (presence of lupus anticoagulant, aCL antibodies and antibeta2 glycoprotein I antibodies)"

For additional information, please consult: Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N, Cuadrado MJ, Dörner T, Ferrer-Oliveras R, Hambly K, Khamashta MA, King J, Marchiori F, Meroni PL, Mosca M, Pengo V, Raio L, Ruiz-Irastorza G, Shoenfeld Y, Stojanovich L, Svenungsson E, Wahl D, Tincani A, Ward MM. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis. 2019 May 15.

**Summary of evidence**

| | |
|---|---|
| 2+ | Anti-malarial drugs reduce the risk of thrombosis in SLE patients, with and without APL.[329,692,693] |
| 2+ | Low-dose aspirin reduces the risk of thrombosis in patients with APL, with a risk reduction to one half in patients with SLE and APL.[692,694] |
| 1+ | Anticoagulation with a target INR 2.0-3.0 is sufficient in APS with only venous thrombotic events.[692] |
| 2+ | Patients with APS and arterial thrombosis could benefit from anticoagulation with a target INR > 3.0 or the combination of anticoagulants with INR 2.0-3.0 + low-dose aspirin.[692] |
| 2+ | Patients with APS and thrombosis benefit from indefinite anticoagulation.[692] |
| | To date, there are no studies assessing the impact of control of vascular risk factors on the risk of initial or recurrent thrombosis in patients with SLE and APL. |

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**Recommendations**

| | |
|---|---|
| C | We suggest the use of hydroxychloroquine to reduce the risk of thrombosis in SLE patients, especially in those with antiphospholipid antibodies |
| C | In SLE patients and high-risk antiphospholipid antibodies (presence of lupus anticoagulant, alone or combined with aCL or persistently positive aCL at medium-high titres or triple positivity), we suggest treatment with low-dose aspirin to reduce the risk of thrombosis. |
| B | In patients with SLE and antiphospholipid syndrome with venous thrombosis, we recommend anticoagulation with a target INR 2.0-3.0. |
| C | In patients with SLE and antiphospholipid syndrome with arterial thrombosis, we suggest anticoagulation with a target INR > 3.0, or combining anticoagulants with INR 2.0-3.0 + low-dose aspirin. |
| C | In patients with SLE, antiphospholipid syndrome and thrombotic episodes, we suggest indefinite anticoagulation. |
| √ | We suggest early identification and strict control of vascular risk factors in patients with SLE and antiphospholipid syndrome. |

* INFORMATIVE NOTE Spanish Agency of Medicines and Medical Devices (20th May 2019)

New recommendations have been stablished on the use of direct oral anticoagulants (DOACs) in patients with antiphospholipid syndrome (APS) and a history of thrombosis.

For additional information, please consult:
https://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2019/NI_MUH_FV-8-2019-anticoagulantes-orales.htm

Commentary from the guideline coordinators:
"According to the new available evidence, the use of direct oral anticoagulants (DOACs) is not recommended, as a general rule, in patients with antiphospholipid syndrome (APS) in association with systemic lupus erythematosus (SLE), since DOACs could be ineffective for the prevention of recurrent thrombosis, especially in arterial thrombosis. DOACs could be considered in certain clinical scenarios such as in patients with allergy to vitamin K antagonists, they could be also an alternative in patients with a history of exclusively venous thrombosis and without a high risk antiphospholipid antibody profile (presence of lupus anticoagulant, aCL antibodies and antibeta2 glycoprotein I antibodies)"

For additional information, please consult: Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N, Cuadrado MJ, Dörner T, Ferrer-Oliveras R, Hambly K, Khamashta MA, King J, Marchiori F, Meroni PL, Mosca M, Pengo V, Raio L, Ruiz-Irastorza G, Shoenfeld Y, Stojanovich L, Svenungsson E, Wahl D, Tincani A, Ward MM. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis. 2019 May 15.

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# 7. Sexual and reproductive health

## 7.1. Pregnancy

### 7.1.1. Planning pregnancy

**Questions to be answered:**

- How would pregnancy be planned in women with systemic lupus erythematosus in order to maximise success possibilities?

SLE is an autoimmune multisystem disease that mainly affects women of childbearing age, so pregnancy is a potentially frequent situation in this group of patients. There is a large number of medical and obstetric complications that may complicate gestation in women with SLE. However, adequate planning and management of the pregnancy in specialised multidisciplinary units quite significantly increases the probabilities of success.[695-697]

In the SR of Smyth *et al*.[698] of the results of pregnancy in women with SLE (37 studies, n=1842 women affected with SLE, 2751 pregnancies), a MA was also carried out on the association between LN and the adverse results of pregnancy.

SR+MA
1+

Active LN was associated with maternal high blood pressure (*P*0.001) and with prematurity (*P*=0.02). The history of nephritis was related to maternal high blood pressure (*P*0.001) and with preeclampsia (*P*=0.017). The presence of APL was also associated with high blood pressure (*P*=0.029), with prematurity (*P*=0.004) and with foetal loss (*P*=0.016).

The same results were found when the subgroup of patients with lupus nephropathy, proven by biopsy, was specifically analysed (n=272).

In the multicentre prospective study of Le Thi Huong *et al*.[699] the results of 103 pregnancies in 84 women affected with SLE were evaluated (follow-up period: 1987-1992).

Observational
S.
2+

As predictors of foetal loss they found the history of proteinuria >5 g/day and the absence of anti-Ro antibodies (*P*0.05). A history of previous foetal loss, history of seizures or psychosis, history of lupus in childhood, activity of lupus at start of the pregnancy, proteinuria during pregnancy (≥ 0.5 mg/day), high blood pressure, hyperuricemia, (≥ 300 $\mu$mol/l), low levels of C4 or C3, anti-DNA antibodies, presence of lupus anticoagulant, use of prednisone (≥ 20 mg/day) or use of aspirin, were not prediction parameters of foetal loss.

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A history of foetal loss, activity of SLE at start of pregnancy, high blood pressure and treatment with prednisone (≥ 20 mg/day) during pregnancy (*P*0.05) were predictors of prematurity. No relationship was found between prematurity and SLE in childhood, history of proteinuria (< 0.5 g/day), hyperuricemia (≥ 300 μmol/l), thrombocytopenia, low levels of C3 or C4, anti-DNA antibodies, APL and the use of aspirin.

With respect to the delay in intrauterine growth, the following predictors were found: lupus activity at start of pregnancy (*P*0.05), low levels of C3 or C4 (*P*0.05), high blood pressure (*P*0.06) and absence of anti-Ro antibodies (*P*0.01). No relationship was observed between the delay in intrauterine growth and proteinuria (>0.5 g/day), hyperuricemia (≥ 300 μmol/l), anti-DNA antibodies, APL, treatment with aspirin or treatment with prednisone (≥ 20 mg/day).

In 2005, Clowse *et al*.[700] assessed the impact of the disease activity during pregnancy on the miscarriage rates, the gestational age at time of birth, and the rate of small babies for the gestational age in a prospective cohort (n=267 pregnancies). — Observational S. 2+

There were less live births with women with high activity (73 v. 88% in those with low activity, *P*=0.063), less pregnancies to term (26 v. 61% in those with low activity, *P*<0.001) and more foetal losses (42 v. 11% in those with low activity, *P*<0.0001).

An Italian observational study with 100 anti-Ro antibody carrier patients found a 2% prevalence of congenital heart block. The two cases of block were detected in weeks 20 and 22 of gestation.[701] — Observational S. 2+

Several documents contain expert recommendations with relation to planning pregnancies in women with SLE.[697,702,703] In these recommendations, a series of contraindications for gestation are established, such as pulmonary hypertension or severe organ damage (kidney, heart or lung). Furthermore, they recommend that lupus should be in remission for at least six months before aiming at pregnancy and that a pre-gestational consultation should be carried out, when information about pregnancies and previous complications will be updated, determining the degree of organ impairment and the profile of autoantibodies (APL and anti-RO are particularly important), and adapting the treatment to include safe drugs during pregnancy. Unfortunately, a considerable proportion of patients are already pregnant on arrival. A complete assessment should be carried out on them as soon as the pregnancy is recognised. — Experts' opinion. 4

**Summary of evidence**

| | |
|---|---|
| 1+ | The presence of APL is associated with foetal losses, prematurity and hypertensive disorders of pregnancy.[698] |
| 1+ | Active nephritis is associated with prematurity and the history of nephritis is related to preeclampsia. Both are associated with gestational high blood pressure.[698] |
| 1+/2+ | The activity of SLE during gestation, maternal high blood pressure and treatment with prednisone with a dose of more than 20 mg/day during pregnancy, are associated with prematurity.[698-700] |

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| | |
|---|---|
| 2+ | The activity of SLE and history of proteinuria > 0.5 g/day are associated with foetal losses.[699,700] |
| 2+ | The delay in intrauterine growth is associated with low levels of C3 or C4, with maternal high blood pressure and with the absence of anti-Ro antibodies.[699] |
| 2+ | Mothers with anti-Ro antibodies have a risk of around 2% of their children suffering congenital heart block.[701] |
| 4 | Experts recommend planning the pregnancy at a preconception consultation to determine the risk profile and adapt the treatment towards the gestation.[697,702,703] |

**Recommendations**

| | |
|---|---|
| D | We suggest planning the pregnancy, including a preconception consultation, so that the gestation takes place in a clinical situation that minimises the risks for the foetus and for the mother. If it has not been planned, we suggest assessing the patient as soon as the pregnancy has been acknowledged. |
| B | In the pre-gestation consultation we recommend estimating the maternal risk profile based on the lupus activity, the extent to which the organs are affected, the autoantibody profile and the treatment received. |
| √ | In the preconception consultation, we suggest adjusting the treatment, substituting the medications that are contraindicated during pregnancy with others that are safe. |
| C | In planned pregnancies, the positivity or negativity of antiphospholipid and anti-Ro antibodies should be known in order to plan the monitoring of specific complications (heart block, placental insufficiency, preeclampsia). |
| √ | We suggest postponing pregnancy after a lupus flare until at least six months after remission, especially if the flare has affected vital organs. |
| B | We recommend advising against pregnancy in women with SLE with pulmonary hypertension or with severe organ damage (kidney, heart or lung) due to severe risk for the lives of mother and foetus. |

## 7.1.2. Monitoring pregnancy

**Questions to be answered:**

- What specific monitoring should be carried out and how often in pregnant patients with systemic lupus erythematosus?

SLE is a disease that mainly affects women of childbearing age, and it is well-known that both the disease and some of the drugs used to manage it are risk factors for certain complications during gestation and repetition miscarriages, growth delay, prematurity or preeclampsia. On the other hand, gestation per se represents a risk of flare-up of the disease.[697,702-704]

Quality care for this type of patient during gestation depends, first of all, on controlled management by a multidisciplinary group during its course. SLE's patients need to be controlled within the context of a high risk pregnancy unit, with the participation of expert personnel in

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autoimmune diseases. Secondly, it requires the establishment of a personalised and well-defined monitoring protocol. Finally, the existence of a Neonatology Unit is very important. However, although all the authors coincide in this concept, the number of publications that describe specific monitoring protocols is very limited, and none of the cases carry out a comparative analysis on which of these monitoring patterns is the best. The majority of the works are narrative reviews, clinical observations or case series.[697,702-704]

Carmona *et al*.[705] analysed the evolution of the pregnancy in 46 SLE patients from the clinical and analytical viewpoint, and with serial ultrasounds as well as foetal echocardiography(it takes into account everything described in the previous chart).

Observational S. 2+

The management protocol included: 1) planning conception for when the disease is inactive; 2) frequent monitoring visits by a team comprised of an expert in autoimmune diseases and an obstetrician; 3) execution of sequential ultrasounds, Doppler study and foetal echocardiogram; 4) serial assessments of the mother's immunological situation; 5) administer low doses of aspirin from the first month of gestation until birth in the case of women with positive APL.

The authors concluded that gestation in SLE patients should not be considered as an unacceptable risk condition for mother and/or foetus providing that it is planned and that patients are managed by a multidisciplinary team.

The study of Mintz *et al*.[706] sought to define the reciprocal pregnancy-SLE relationship to reduce maternal mortality and morbidity and foetal losses. They compiled data from 102 gestations in 75 patients prospectively from 1974 to 1983. A baseline visit was carried out by the rheumatologist, and then monthly until six month and then every two weeks until birth. Monthly visits were made after birth. The obstetrician made one visit every two weeks during the first and second trimesters, and then weekly until birth.

Case-control study 2+

They concluded that in SLE patients, planned care during the pregnancy by rheumatologists, obstetricians and neonatology may reduce the high mortality and morbidity in mothers and foeti.

A study of 116 pregnancies analyses the usefulness of placenta Doppler ultrasound during the second trimester in women with SLE and/or APS. Sixteen pregnancies ended up in miscarriage before the first Doppler was carried out, so the final analysis was restricted to 100 patients. The 72 patients with two normal Doppler studies gave birth to healthy babies, 88% of them without obstetric complications (low weight, preeclampsia or prematurity). In contrast, only 27% of the 18 women with abnormal Doppler gave birth at term without complications. In the multivariate analysis, the abnormal Doppler of uterine arteries during the second trimester was the only predictive factor of adverse foetal prognosis (OR= 13.84; 95% CI: 3.41-56.16; *P*=0.001)[707]

Observational S. 2++

**Summary of evidence**

| | |
|---|---|
| | There are no available studies that assess the effects of specific monitoring protocols on pregnant women with SLE. |

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| | |
|---|---|
| 2+ | Gestation in SLE patients should not be considered as an unacceptable risk condition for mother and/or foetus providing that it is planned and that the patients are managed by a multidisciplinary team. The monitoring protocol should include a series of clinical and laboratory parameters, maternal and foetus ultrasounds, and foetal echocardiograms to be carried out during each trimester of the pregnancy. This planned care during pregnancy may reduce the mortality and morbidity of mothers and foeti.[705,706] |
| 2++ | The results of the placenta Doppler ultrasound during the second trimester are the best predictors of the long-term evolution of pregnancy.[707] |

**Recommendations**

| | |
|---|---|
| C | We suggest multidisciplinary management of pregnant woman with SLE by the obstetrician and the specialist in autoimmune diseases, with the participation of other specialists if considered necessary. |
| √ | From the medical viewpoint, we suggest making one visit during the first trimester, every 4-6 weeks until week 26 of gestation, and every two weeks from week 27 until birth. This is subject to modifications according to obstetric and medical criteria. |
| √ | During each visit, we suggest monitoring the weight, blood pressure and the presence of proteinuria, especially in women with risk of lupus nephritis and/or preeclampsia. |
| √ | We suggest determining C3 and C4 to monitor lupus activity, even though their levels are altered by the actual pregnancy. |
| √ | We do not recommend repeatedly determining antinuclear antibodies, anti-ENA and antiphospholipid antibodies. |
| √ | We suggest requesting anti-DNA in agreement with the clinically suspected flare. |
| √ | We recommend performing a series of ultrasound examinations similar to the following, always subject to the obstetrician's criterion:<br>– Week 8-9: Pregnancy confirmation ultrasound.<br>– Week 12: Ultrasound for triple screening of chromosomopathies. During this week, a first Doppler study of uterine arteries may be carried out in order to estimate the probability of preeclampsia in women at risk (those who test positive to antiphospholipid antibodies, have a history of nephritis, preeclampsia and/or high blood pressure).<br>– Week 20: Malformation ultrasound. If the uterine artery Doppler has not been carried out during week 12 or it was abnormal, we recommend carrying it out this week.<br>– Week 24: The uterine artery Doppler can be repeated for the last time if it was abnormal, to see if has become normalised. If not, the pathology is considered as definite.<br>– Starting in week 24, growth ultrasounds and umbilical Doppler according to the obstetrician's criterion. |
| √ | When the pregnant woman has positive anti-Ro and/or anti-La antibodies, we suggest regular monitoring the foetal heart calculating the ultrasound PR interval between week 16 and 34, always in agreement with the criteria of the obstetrician and of the specialist in foetus cardiology. |

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## 7.1.3. Treatment with antimalarial drugs

**Questions to be answered:**

- Should anti-malarial drugs be maintained if a pregnancy occurs? Which would be the drug of choice?

Flare-ups during pregnancy in women with SLE have been associated with irreversible damage both for the mother, especially if it affects internal organs such as the CNS or the kidney,[327] and for the embryo-foetus, firstly because they could be exposed to a large number of potentially hazardous medications and, secondly, because it has been demonstrated that the activity itself is a predictor of adverse obstetric results.[697]

Anti-malarial drugs, HCQ and CQ have proven to be efficient in reducing the risk of flares of the disease, and improving the long-term survival of SLE patients. However, for years there has been speculation about its potentially harmful effect on the developing foetus.

In the SR of RCT and observational studies carried out by Ruiz-Irastorza *et al*., whose objective was to analyse all the evidence published about the beneficial and adverse effects of anti-malarial drugs in SLE, data are included about the efficacy and toxicity of HCQ and CQ in pregnant women.[327] SR 2++

A RCT and two cohort studies evaluated the activity of SLE during pregnancy. The SR considered that the quality of the evidence that supported a reduction of SLE activity in patients who take anti-malarial drugs as high, even during pregnancy.

With respect to safety (10 studies, 275 pregnant women took HCQ and 36 CQ), no cases of ocular or auditory toxicity were reported, and a greater frequency of congenital malformations among those exposed compared with those not exposed was not observed.

In the prospective observational study of Clowse *et al*.,[708] contained in the SR of Ruiz-Irastorza *et al*.,[693] the effect of suspending HCQ on SLE activity during pregnancy was specifically analysed. The flare-up rates observed among those who did not take HCQ during the previous three months and during pregnancy (group 1, n=163 pregnancies), those who took HCQ during pregnancy (group 2, n=56 pregnancies), and those who suspended HCQ during the three previous months or during the first trimester of pregnancy (group 3 n=38 pregnancies) were 36% v. 30% v. 55%, respectively ($P$=0.053). Observational S.

In one SR, synthesising the evidence published about the safety of anti-malarial drugs during pregnancy, and focusing on ocular toxicity in descendants (588 children exposed to CQ or HCQ of 337 mothers with rheumatic disease, above all SLE, and 251 with malaria), of a total of 12 studies included, in five (n=251 children exposed), a clinical assessment of the visual function was performed, not finding any visual anomalies as reported by the mother, by the general practitioner or by the paediatrician.[709] SR 2++

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In four studies (n=59) an ophthalmologic examination was carried out in detail during the first year or later, reporting normal results in all cases. The electroretinography studies carried out on three small cohorts of children exposed before birth to anti-malarial drugs (n=31) showed normal results except in the three infants aged 3-7 months, who were submitted to a study of the back of the eye when they were four years old. No anomalies were noticed at that time.

In another SR identified, recent literature was reviewed and assessed on the safety of disease modifying anti-rheumatic drugs (DMARD) used during pregnancy. Monitoring studies were compiled on pregnant women receiving treatment with HCQ or CQ opposed to placebo (one RCT and seven observational studies).[710] SR 2++

No sight nor hearing disorders were observed in the entire cohort of live newborns (n=224) with monitoring periods that varied between nine months and 19 years. No study of those included found a relationship between taking HCQ or CQ, and hearing or sight abnormalities, nor a greater risk of congenital malformations among those exposed to these drugs compared with those not exposed.

The women who contacted the Israeli Information Service on Teratology, due to gestational exposure to HCQ between the years 1998 and 2006 (69% SLE), were included in the prospective observational study of Diav-Citrin *et al*.[711] to assess the rate of congenital anomalies after intrauterine exposure to HCQ compared with a group without exposure to teratogenic drugs. This control group was randomly selected from women who contacted this information service during pregnancy and exposed to agents that are known not to be teratogenic, within a similar time frame. With respect to major anomalies evaluated during the monitoring of the pregnancy and during the first year of life, 7/97 were observed in the exposed group and 15/440 in the non-exposed group, a difference close to statistical significance ($P$=0.094). Regarding anomalies without genetic, chromosomic entity, or congenital infections, 5/95 appeared in the exposed group compared with 15/440 in the control group($P$=0.355). Cohort S. 2+

There is no information about the safety of mepacrine during pregnancy.

**Summary of evidence**

| | |
|---|---|
| 2++ | Treatment of pregnant SLE patients with HCQ reduces the disease activity. [327] |
| 2+ | Suspending HCQ during the first trimester of pregnancy increases disease flares.[708] |
| 2++/2+ | Treatment with HCQ of CQ during pregnancy in SLE patients is not associated with hearing or sight anomalies or with a greater risk of developing anomalies/congenital malformations in newborns. However, there is less available evidence for CQ (less number of patients studied) than for HCQ.[693,709-711] |
| | There is no information about the safety of mepacrine during pregnancy. |

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**Recommendations**

| | |
|---|---|
| B | We recommend maintaining hydroxychloroquine during pregnancy. |
| √ | As hydroxychloroquine is safer during the pregnancy and more studies have been performed than with chloroquine, we suggest using it as the antimalarial drug of choice in this situation. |

## 7.1.4. Prevention of obstetric complications in patients with antiphospholipid antibodies

**Questions to be answered:**

- What preventive measures should be taken for obstetric complications in patients with antiphospholipid antibodies?

APLs are associated with arterial and/or venous thrombosis and obstetric morbidity. These antibodies are present in one third of SLE patients and their presence is associated with a worse pregnancy outcome in SLE patients.[712,713]

The evidence identified to prevent obstetric complications in patients with APL originates from very heterogeneous observational studies.

A recent study has compared the obstetric complications of 513 patients with obstetric APS criteria, without previous thrombosis, treated with unfractionated or low molecular weight heparin (LMWH) + acetylsalicylic acid (ASA) with those of the control group, conformed by 791 patients, with prior history of repetition abortions or foetal deaths, without APS and without treatment.[714] The rate of live births in the pregnancy studied were 69% and 68%, respectively, with 84% and 85%, respectively, of those that exceeded the 10th week of pregnancy. However, the frequency of placenta complications (preeclampsia, placenta detachment, intrauterine growth delay) was greater in treated patients with APS than in the control group (25% v. 17%, *P*=0.0032).

Observational
S.
2++

In 2002, a SR analysed the effect of different agents on the prevention of obstetric losses in women with miscarriages and/or foetal deaths and APL.[715] 10 CCT were finally included, comparing ASA with placebo or regular treatment (n=3), ASA compared with ASA + unfractionated heparin (n=2), ASA + heparin at low doses compared with ASA + heparin at high doses (n=1), prednisone + ASA compared with ASA or placebo (n=2), prednisone + ASA compared with ASA + heparin (n=1) and immunoglobulins + heparin + ASA compared with placebo + heparin + ASA (n=1). The authors concluded that only the comparison of ASA + heparin v. ASA showed a statistically significant difference (RR= 0.46; 95% CI: 0.29-0.71).

SR
1-

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A MA with metaregression analysed five RCT or with consecutive assignment of treatment comparing the effect of adding LMWH to ASA in women with recurrent obstetric losses and APL. The authors concluded that patients treated with combined therapy showed a greater frequency of live births (RR= 1.3; 95% CI: 1.04-1.63). They also observed a non-significant tendency for preeclampsia to be reduced insofar as they did not observe differences in the rate of prematurity or in the weight at birth.[716] MA 1-

In 2010 Ziakas *et al*. published a third MA that analysed the studies that compared ASA alone with unfractionated heparin (n=3) and with LMWH (n=2) separately. A significant reduction was only observed in the rate of early miscarriages with the ASA – unfractionated heparin combination (RR=0.26; 95% CI: 0.14-0.48). No significant differences were found between ASA and ASA + LMWH in early miscarriages or between any of the combined therapies and ASA in terms of the number of foetal deaths.[717] MA 1-

Despite the surprising uniformity of the results of the three SRs, there are a series of factors that considerably limit the conclusion that combined treatment with ASA and heparin should be administered to all women with obstetric APS. On the one hand, the CCTs, on which the difference in favour of combined therapy is based, are the same in the three SRs. Two CCTs were carried out in the decade of the 90s, with considerable limitations in terms of the obstetric and immunological profile of the patients, as a significant number of patients did not meet the strict criteria of APS. Furthermore, in one of them, the treatment was not assigned randomly, but consecutively.[718] In fact, the main discrepancy between the different CCTs lies in the group treated with ASA, which, in the aforementioned CCTs, obtained much lower results than those observed in practically all randomly assigned and observational studies. On the other hand, the absence of differences between the treatment with ASA or combined as from the first trimester is surprising. All of this leads to questioning the universal combined treatment in women with obstetric APS with history of miscarriages in the first trimester. The recommendations in patients with a history of foetal death or severe preeclampsia are not grounded in evidence either, given the limited representation of patients with this profile in the published studies. Experts' opinion. 4

Therefore, the most wide-spread recommendations for preventing obstetric complications in women with obstetric APS (without history of thrombosis) are as follows:[718]

a) Early repetition miscarriages. Aspirin at low doses, alone or associated with LMWH at normal propylactic doses (e.g., enoxaparin 40 mg/day or dalteparin 5000 U/day - subcutaneous).

b) Foetal death (>10 weeks' gestation) or premature birth (<34 weeks' gestation) secondary to severe preeclampsia or placental insufficiency: Aspirin at low doses associated with LMWH at normal prophylactic doses (e.g., enoxaparin 40 mg/day or dalteparin 5000 U/day - subcutaneous).

In an observational study of 77 pregnancies in 56 women with APS, Carmona *et al*. analysed the factors associated with an adverse prognosis of the pregnancy. In the final multivariate model, the preconceptional treatment with ASA was associated with a greater probability of a live birth.[719] Observational S. 2+

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| | |
|---|---|
| A SR that analyses three RCTs concluded that intravenous Ig is not useful as treatment for obstetric manifestations of APS.[720] | SR 1+ |
| In an observational study, 18 women (23 pregnancies) with obstetric APS, refractory to aspirin and heparin were treated with prednisolone 10 mg/day, in addition to combined anti-thrombotic treatment, from the diagnosis of pregnancy until week 14. 61% of the pregnancies ended successfully, 60% of them without complications.[721] | Case series 3 |

**Summary of evidence**

| | |
|---|---|
| 2++ | The treatment of women with obstetric APS with LMWH and ASA during a new pregnancy reduces the frequency of miscarriages and foetal deaths to similar figures to those of patients with bad obstetric history without APS. However, they continue to present a higher rate than the controls of complications such as preeclampsia, placenta detachment and intrauterine growth delay.[714] |
| 1- | The combination of ASA plus heparin is more efficient than ASA in monotherapy in reducing the number of miscarriages and foetal deaths in women with APL and adverse obstetric history; however, this greater efficacy is limited to the first trimester.[715-717] |
| 4 | Given the limitations of the clinical trials and the lack of studies that focus on foetal deaths, the treatment recommendations in women with obstetric APS are still marked to a great extent by recommendations from experts.[718] |
| 2+ | Treatment with preconceptional ASA is an independent factor of good foetal prognosis in women with APS.[719] |
| 1++ | Intravenous Ig are not a useful treatment for obstetric manifestations of APS.[720] |
| 3 | Prednisone at doses of 10 mg/day until week 14 of pregnancy may increase the success rates in women with obstetric APS refractory to treatment with ASA and heparin.[721] |
| | Treatment with obstetric APS and of asymptomatic APL carrier women during pregnancy is based on ASA and heparin; however, there is not sufficient evidence to establish specific patterns. |

**Recommendations**

| | |
|---|---|
| √ | We suggest that patients with obstetric antiphospholipid syndrome and a history of repeated early miscarriages (≤10 weeks) should be treated with aspirin, with or without associated heparin. |
| √ | We suggest that patients with obstetric antiphospholipid syndrome and a history of foetal death (>10 weeks) or severe preeclampsia with placental insufficiency should be treated with aspirin and heparin at prophylactic doses. |
| √ | We suggest that asymptomatic carriers of antiphospholipid antibodies should be treated with aspirin. |
| C | We suggest starting with aspirin prior to conception. |
| √ | Due to its availability in Spain and its convenience, we suggest using low molecular weight heparin rather than unfractionated heparin. |

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| | |
|---|---|
| A | We do not recommend using intravenous immunoglobulin for treating obstetric manifestations of the antiphospholipid syndrome. |
| √ | Prednisone at a dose of ≤10 mg/day until the 14th week can be used in refractory cases, although this measure is not risk-free. |

# 7.2. Fertility and contraception

## 7.2.1. Assisted reproduction techniques

**Questions to be answered:**

- Are assisted reproduction procedures safe and efficient in systemic lupus erythematosus? Is ovarian stimulation safe in women with systemic lupus erythematosus?

The recommendations that are made on the safety and efficacy of assisted reproduction procedures, including ovarian stimulation, in SLE patients, have only been obtained from two observational studies and responding to the questions asked was not the main objective of either of them. All of them include not only SLE patients but also patients with APS.

Two historical small-sample studies (n=19 and 21, respectively) analysed the safety and efficacy of assisted reproduction procedures, including ovarian stimulation.[722,723]

In the first, the efficacy and safety of ovarian stimulation and *in vitro* fertilisation techniques were analysed during 68 cycles in patients who were stable in terms of disease activity, and received treatment with HCQ and/or glucocorticoids and/or immunosuppressants. Their authors concluded that these procedures were efficient in patients with SLE and APS but they entailed a high rate of maternal and foetal complications during the procedures themselves and during pregnancy: mild flares of SLE in 25% of the cycles, ovarian hyperstimulation syndrome in two patients (13%), eclampsia (one patient) and LN (one patient). There were no cases of thrombosis. There were multiple gestations and prematurity (50%) with secondary complication to this in 38% of the births.[722]

Observational
S.
2-

The second study focused on the importance of planning the ovarian stimulation to avoid complications. It included 13 patients with autoimmune disease (nine with SLE, one with discoid lupus and three with APS), and eight patients without any diagnosed disease but with some symptoms that, retrospectively, suggested autoimmune disease. 114 ovarian stimulation cycles were carried out. The incidence of flares of SLE was three times greater in patients in whom ovarian stimulation was not planned (the disease was active or they did not receive treatment because it had still not been diagnosed). The disease activity also increased three times more in patients treated with gonadotropins than in those treated with clomifene. There were no cases of ovarian hyperstimulation syndrome. The authors concluded that ovarian stimulation was safer when planned and carried out on patients with controlled disease.[723]

Observational
S.
2-

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**Summary of evidence**

| | |
|---|---|
| | The available evidence on the efficacy and safety of assisted reproduction procedures in SLE is very limited and of very low methodological quality. |
| 2- | Severe flares of SLE and ovarian hyperstimulation syndrome do not seem to be frequent in women submitted to ovarian stimulation treatments.[722,723] |
| 2- | Reactivation of the disease is less if patients are in remission.[723] |
| 2- | Multi-gestation is common. Prematurity may reach 50% of the births, and more than one third of them may present complications associated with this prematurity.[722] |

**Recommendations**

| | |
|---|---|
| √ | We suggest carrying out a comprehensive assessment of the cardiovascular risk and of the activity of the disease before starting assisted reproduction procedures, including ovarian stimulation, programming them under controlled disease situation. |
| √ | We suggest administering prophylactic treatment with low molecular weight heparin in patients with positive antiphospholipid antibodies. |

## 7.2.2. Contraception methods

**Questions to be answered:**

- What contraception methods are safe in women with systemic lupus erythematosus?

The side effects of these drugs should be taken into account when choosing a contraception method for SLE patients. Oestrogens may potentially increase the risk of thrombosis and of reactivating SLE.

According to an observational study published in 2011, 78% of the SLE patients under the age of 45 with a risk of undesired pregnancy, had used contraception in the last three months; however, just only 41% had received advice about contraception during the previous year.[724]

A high methodological quality SR analysed the available evidence on the safety of the different contraception methods in women with SLE (13 studies, n=4117 women).[725] The methods assessed were combined oral hormone contraceptives (two RCTs and two cohort studies), those that only contained progesterone (three cohorts, one RCT and one nRCT) and intrauterine device (IUD) (one RCT and one cohort study). Results provided were mainly about the disease activity, incidence of flares and vascular complications.

SR
1++/2++

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One double-blinded randomised study[277] that included 183 women with SLE, inactive (76%) or with moderate but stable activity (24%), who randomly received an oral three-phase contraceptive or placebo, did not find significant differences in terms of activity of SLE, incidence, severity and moment the flares appeared. Another RCT (n=162) randomly assigned combined oral contraceptives, a progestin only pill, or an IUD to patients. No differences were found in the activity among the results obtained.[726] Women were excluded from both tests if they presented contraindications to any of the medications of the study, past history of thromboembolic events, CVD or of the liver, or they were smokers and aged over 35.

The evidence about the hormone contraceptives and cardiovascular events assessed in this review was more limited due to the variability of the studies in terms of quality and outcome measurements. The two studies that specifically assessed the risk of thrombosis only included patients with positive APL and they observed a positive association tendency between the use of hormone contraceptives and thromboembolism, above all them arterial.

The use of the IUDs was studied in two of the studies included in this SR, one RCT (n=54) and a historical observational study (n=28). No differences were found in the lupus activity with respect to other methods. There were no cases of infection in the genital tract or pelvis, or any important haemorrhagic complication. The observational study reported 43% permanence of the device after three years.

A subsequent study of multicentre cohorts (n=187) assessed the gynaecological tolerability of two oral hormone contraceptives that only contained progesterone (cyproterone acetate 50 mg/day and chlormadinone acetate 10 mg/day), and secondary, the vascular safety and activity of SLE measured by the incidence of flares.[727] Cohort S. 2-

The gynaecological tolerability was the main outcome measurement and the following results were obtained: amenorrhoea was more frequent in the cyproterone group than in the chlormadinone group (17.7 v. 12.6%, $P$=0.015); however, the need to discontinue the treatment for this reason was no different between the groups (0.8 and 4.6%, respectively, $P$=0.142). Hypoestrogenic symptoms were more frequent in the cyproterone group ($P$=0.01) and treatment was suspended in two patients from this group. Four and three people in each group discontinued the treatment due to depression, weight gain and headaches. Contraceptive effectiveness was 100% in the entire cohort.

In terms of SLE activity, a reduction in the number of flares was observed, compared with the previous period without progesterone. Vascular events included one venous thrombosis, one myocardial infarction and one thrombosis of the posterior tibial artery. This represented a similar incidence of thromboembolism and arterial thrombosis to that observed in another cohort without hormone treatment.

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**Summary of evidence**

| | |
|---|---|
| 1++ | The use of combined hormone contraceptives does not lead to an increase in flares or of disease activity in patients with stable or inactive SLE, with no past history of thrombembolic events, without APS, without CVD, or of the liver, non-smokers and aged under 35.[725] |
| 2++/2- | Complexes with progesterone are effective, well-tolerated and do not increase the incidence of flare-ups.[725,727] |
| 2++ | Women with SLE have a greater risk of thromboembolism, especially those who are APL positive. There is a tendency to associate a history of use of hormone contraceptives with thromboembolisms.[725] |
| 2++ | IUDs do not cause the appearance of flares nor do they seem to increase genital tract infections. However, there is very little available evidence.[725] |

**Recommendations**

| | |
|---|---|
| √ | Although the benefits of hormone contraception may be greater than the risks in many women with SLE, we suggest carrying out a comprehensive assessment of the cardiovascular risk and of the activity of the disease before starting treatment with combined hormone contraceptives. |
| B | In women with positive antiphospholipid antibodies, we recommend avoiding combined hormone contraceptives due to having a greater risk of suffering arterial and venous thrombotic phenomena. |
| B | For their safety, we recommend bearing in mind the use of the IUD (including devices with progestogens) or barrier methods, within the possible contraceptive methods for women with SLE, especially for women for whom the use of oestrogen contraceptives is contraindicated. |

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# 8. Comorbidity

## 8.1. Cardiovascular risk

### 8.1.1. Cardiovascular risk level and cardiovascular risk assessment

**Questions to be answered:**

- Have people with systemic lupus erythematosus got a greater cardiovascular risk? Is this risk similar in different ethnic groups?
- Should the cardiovascular risk be evaluated in people with systemic lupus erythematosus? How should this be done and how often?

CVD is a common and important cause of morbidity and mortality among SLE patients.[728] Traditional cardiovascular risk factors appear early on in the course of the disease, and in younger patients, in comparison with the general population. In addition, SLE patients present other risk factors in the development of CVD, important among which are the use of glucocorticoids, the activity and damage associated with SLE.[729]

28 studies were identified through a SR, which analysed the epidemiological association between SLE and atherosclerotic CVD. Among the studies found, seven compared the risk of clinical atherosclerotic disease in SLE patients with the risk of the general population; 20 analysed the risk factors for the clinical atherosclerotic disease in SLE patients and one examined the risk of cardiovascular death in SLE patients.[730]

SR
2++

In connection with coronary diseases (four cohort studies and two case-control studies, n=15822, 1232 events), the results indicated an increase in the risk of acute myocardial infarction (AMI) of between two and 10 times greater in SLE patients. This figure increases in patients aged between 35 and 44 years old. Furthermore, SLE patients had one or three times more probabilities of being admitted with congestive cardiac insufficiency according to a case and control study. The RR of suffering a CVA also increases in young SLE patients, and the absolute risk increases with age (n=9657, 177 events). With respect to peripheral vascular disease, no differences were observed with the general population; however, it was observed that peripheral vascular disease predicts a greater degree of clinical activity in SLE.

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The review concluded that the risks factors associated with CVD include:

- Hypercholesterolaemia (5 cohort studies): an increase of one to two times the risk of CVD in SLE patients.
- Nicotine addiction: this is presented as an independent risk factor of CVD in SLE.
- High blood pressure: an increase of one to two times the risk of CVD in SLE.
- Gender: Greater risk of CVD in males with SLE.
- Age: Advanced age is an independent predictor of CVD in SLE.
- Disease activity: Its prediction of CVD is variable.
- APL: They increase the risk of CVA, but it is not clear if there is an increase in atherosclerotic origin CVD.

It also concluded that the effect of different drugs on the risk of CVD is variable. In different studies, glucocorticoids appear as a risk factor of atherosclerosis in SLE patients, but the results are not homogeneous. Although glucocorticoids decrease systemic inflammation, and may reduce the atherogenic load, their use is associated with flare-up of multiple traditional risk factors, including total cholesterol, glycaemia, BMI and blood pressure, so they could have opposite effects on the development of CVD, although not well defined. On the other hand, HCQ improves the lipid and glycaemic profile.

One of the first studies that examined cardiovascular risk in SLE patients through non-traditional cardiovascular risk factors, retrospectively analysed the risk of developing CVD, non-fatal AMI, general coronary disease and death by coronary disease, compared with the general population, in a sample of 296 SLE patients.[731] The RR of suffering a non-fatal AMI (after adjusting for classical cardiovascular risk factors) was 10.1 (95% CI: 5.8-15.6), of general coronary disease 7.5 (95% CI: 5.1-10.4), of fatal coronary disease 17 (95% CI: 8.1-29.7) and of CVA 7.9 (95% CI: 4.0-13.6).

Cohort S. 2+

To determine the association between the diagnosis of RA or SLE and the risk of developing an AMI for the first time, a study was performed on 8688 patients with AMI and 33,329 controls. The risk of AMI in SLE patients was 2.67 (95% CI: 1.34-5.34) compared with the controls. The association between AMI risk and SLE was greater than for RA. The risk of AMI associated with SLE was greater in men than in women.[732]

Case-control study 2-

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In one study in which a seven-year follow-up was carried out on 277 SLE patients (85% women, average age: 51.2 years) to determine the incidence of vascular events and their predictor factors, a standardised incidence ratio (SIR) of AMI or CVA was obtained of 1.27 (95% CI: 0.82-1.87), eight times greater for women in the 40-49 year-old age group (95% CI: 1.65-23.38). The SIR of AMI was 2.31 (95% CI: 1.34-08), 1.75 in women (95% CI: 0.84-3.22), 2.9 in men (95% CI: 16-5.98). The average age of patents was 69.6 years when AMI was suffered, and 64.8 years for CVA. The disease activity (HR= 1.16; 95% CI: 1.06-1.26) and the presence of IgG aCL antibodies (HR= 3.08; 95% CI: 1.32-7.17) were identified as risk factors for the development of cardiac events.[733]

Cohort S.
2+

Another population-based study prospectively researched the association between SLE and the incidence of CVD in women (n=119184).[734] 8169 cardiovascular events occurred and 148 women developed SLE. The RR of CVD was 2.26 (95% CI: 1.45-3.52), 2.25 (95% CI: 1.37-3.69) for coronary disease, 2.29 (95% CI: 0.85-6.15) for CVA, 1.81 (95% CI: 0.75-4.37) for AMI.

Cohort S.
2-

A cohort of Asian SLE patients (n=11673) and a control cohort (n=58185) matched by age, gender and comorbidity, were selected to determine the incidence of ischemic CVA on SLE patients.735 During a seven-year follow-up, ischemic CVD appears in 258 SLE patients (2.22%) and in 873 people without SLE (1.5%). SLE patients presented a RR of ischemic CVA of 1.67 (95% CI: 1.45-1.91; *P*<0.001).

Case-control study
2+

One sample of SLE patients (n=241) and another of controls (n=237) were selected, carrying out a seven to nine-year follow-up, in order to determine the development of coronary disease in SLE and the associated risk factors.736 Coronary disease was more frequent among SLE patients than among the controls (7.1 v. 2.1%, *P*=0.01). The mutivariate analysis showed that age (HR= 1.08; *P*=0.002), the actual disease (HR= 4.23; *P*=0.007), and a triglyceride level ≥2,8 mmol/l were significantly associated with coronary disease.

Case-control study
2+

A study with 53 patients with SLE and coronary disease (infarction or chest angina) and 96 patients with no past history, was conducted, in order to examine the risk factors for developing atherosclerosis and premature coronary disease in SLE patients.[737] SLE patients with coronary disease were older (53 v. 42 years; *P*<0.001), they were more likely to be male (20 v. 7%; *P*<0.001) and with greater exposure to traditional risk factors. They were also more likely to be treated with glucocorticoids (OR= 2.46; 95% CI: 1.03-5.88) and AZA (OR= 2.33; 95% CI: 1.16-4.67) and of having evidence of accumulated damage (OR= 2.20; 95% CI: 1.09-4.44).

Case-control study
2-

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In one study that analysed the incidence of cardiovascular events and risk factors in SLE (n=1874), 134 cardiovascular events were observed (65 CVA, 27 AMI, 29 anginas and 13 peripheral vascular disease) in a follow-up of 9.486 patients-year. The risks of cardiac events was 2.66 times greater in SLE patients than in the rest of the population. Among the demographic factors, a higher relative rate of cardiovascular events was observed in men than in women (RR= 2.15; 95% CI: 1.33-3.46; *P*=0.0017). Patients treated with ≥ 20 mg/day of glucocorticoids at the time of the study presented a substantial increase in risk, even after adjustment for the disease activity (RR= 5.4: IC 95%: 2.4-12.3; *P*<0.0001).[738] Cohort S. 2-

In another study, whose objective was to determine the risk factors associated with cardiovascular events in SLE (n=498), it was observed that the risk of suffering a cardiovascular event increased with hypercholesterolaemia (RR=3.35; 95% CI: 1.34-8.36; *P*=0.003) and the advanced age at the time of diagnosing SLE (RR= 1.21; 95% CI: 1.09-1.35; *P*=0.02).[739] It was observed in this study that, in women with SLE aged between 35 and 44, the probability of AMI was up to 52 times greater than for healthy women of the same age (RR= 52.43; 95% CI: 21.6-98.5). Cohort S. 2-

In a study whose objective was to determine the incidence and risk factors of thrombotic events in SLE patients of different ethnic groups (n=625)[740], it was observed that the incidence of arterial thrombotic events (65% CVA and 19% AMI) and venous thrombotic events (80% peripheral venous thrombosis and/or pulmonary embolism) was 1.6 patients/year and 1.3 patients/year, respectively. The accumulated risk of arterial thrombotic events 60 months after the diagnosis of SLE was 8.5% for Chinese patients, 8.1% for Afro-Americans and 5.1% for Caucasians. The accumulated risk of venous thrombotic events was 3.7%, 6.6% and 10.3%, respectively. Despite these inter-ethnic numerical differences, statistical significance was not reached in any case. The risk factors for arterial thrombotic events were advanced age (*P*=0.03), disease duration (*P*=0.04) and HDL level ≤ 1mmoles/l (*P*=0.001). The risk factors for venous thrombotic events were male gender (*P*=0.02), HDL level ≤ 1mmoles/l (*P*=0.005), BMI ≥ 27 kg/m$^2$ (*P*=0.001), persistent nephrotic syndrome (> six months) and any APL (*P*<0.001). Cohort S. 2+

The LUMINA cohort (n=637) aimed to determine the factors that predicted cardiovascular origin damage (defined as the SLICC/ACR DI damage index) in SLE patients.[741] 43 cardiovascular damage events were recorded. The damage risk was seen to increase with age (OR= 1.06; 95% CI: 1.03-1.09) and male gender (OR= 3.57; 95% CI: 1.35-9.09), the presence of C reactive protein (OR= 2.63; 95% CI: 1.17-5.91) and accumulated disease damage (OR= 1.28; 95% CI: 1.09-1.5). The probability of suffering cardiovascular damage depending on the ethnic group was 6.8% for Texan Hispanics, 1% for Puerto Rico Hispanics, 7.6% for Afro-Americans and 8.8% for Caucasians (*P*=0.047). Cohort S. 2+

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In another study, they compared the frequency and risk factors of subclinical CVD measured through mode B ultrasound of the carotid artery and electron beam computerised tomography of coronary arteries among Afro-American and Caucasian women with SLE, recruited from the *Chicago Lupus Database* and *the Pittsburgh Lupus Registry*, without prior cardiovascular events (n=309).[742] It was observed that, among the traditional risk factors, Afro-American women presented a higher BMI (29.5 v. 27.1 kg/m$^2$) and diastolic blood pressure (77.8 v. 74.7 mmHg) than white women. The systolic blood pressure was also higher in Afro-Americans, after adjusting for age and for place of study. Lipoprotein A and C reactive protein also differed between the two groups, with higher levels in Afro-Americans compared with Caucasians. Afro-American women showed a greater disease activity (SLEDAI: 4.4 v. 2.6), greater accumulated damage (SLICC/ACR DI mean: 2.4 v. 1.2), more use of glucocorticoids (61.9 v. 36.3%), longer average duration of the treatment with them (10.9 v. 9.2 years) and greater frequency of positive anti-dsDNA compared with Caucasians. Afro-American women also presented suggestive analytical parameters of a greater degree of inflammation, and a higher level of fibrinogen, higher figures of ESR or a higher degree of hypoalbuminemia. Compared with Caucasian women, more Afro-American women had plaque on the carotid artery (43.5 v. 29.6%, OR = 1.94; 95% CI: 1.03-3.65).

Cross-sectional S. 3

Another study selected 160 SLE patients and 245 controls to compare frequency, phenotype and characteristics of the metabolic syndrome in these patients and their possible associations with cardiovascular diseases.[331]

Cross-sectional S. 3

A numerically greater frequency of metabolic syndrome was observed in the group of SLE patients than in the control group (20 v. 13%, *P*=0.083). The frequency of CVD was 28 times greater in the group of SLE patients than in the control group (11.3 v. 0.4%, *P*=0.001).

In order to determine if there is racial/ethnic disparity insofar as age is concerned with respect to SLE patients experiencing cardiovascular diseases, and specifically those associated with death, a cohort of 3625 SLE patients with 124,668 hospitalisations, and people without SLE with 31,927,484 hospitalisations was selected.[743] The age differences between the women with SLE (n=3625) and women without SLE admitted for CFD were significant (60.8±13.7 v. 71.3±13.4; *P*<0.0001). In white SLE patients, the age was higher than the other racial/ethnic groups, with the exception of Asian groups. Both in women with and without SLE, black women with fatal CVD were significantly younger (*P*<0.0001).

Case-control study 2+

Toloza *et al*. assessed the risk factors associated with the appearance of vascular events in the LUMINA cohort (n=546), initially and every six months (73.8 months average follow-up).[744] Thirty-four patients developed vascular events (18 cerebrovascular, 13 cardiovascular and five peripheral vascular events). The number of traditional risk factors for vascular events was higher in patients who finally developed it than in those that did not (7.2 ± 2.2 v. 5.2 ± 2.2; *P*<0.001). The independent predictors of vascular events were advanced age (*P*<0.001), active nicotine addiction (*P*=0.009), the follow-up time (*P*<0.001), high serum levels of C-reactive protein (*P*=0.015), and the presence of any APL (*P*=0.003).

Cohort S. 2+

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|---|---|
| In another work, a sample of SLE patients (n=1072) was selected to determine the frequency and risk factors of CVD in Chinese patients. A global frequency of 6.6% was observed. Stratifying by ages, among patients ≤19 years old, the frequency was 3.4%, between 20 and 39 years, 9.2%, between 40 and 69, 5.5%, and for the over-60s, 20.4% ($P$<0.001). The probability of suffering CVD increased in patients who had LN (7.6 v. 3.8%; $P$=0.026); who were 60 or over (RR= 5.09; 95% CI: 1.33-19.49), had high diastolic pressure (RR= 1.05; 95% CI: 1.02-1.08); high creatinine (RR= 1.002; 95% CI: 1.00-1.003), and the prolonged use of glucocorticoids (RR= 1.005; 95% CI: 1.00-1.01) were associated with CVD. HDL cholesterol levels (OR= 0.121; 95% IC: 0.04-0.36) were negatively associated with CVD.[745] | Cross-sectional S. 3 |
| A study with 111 Chinese SLE patients and 40 healthy controls analysed the frequency and risk factors of premature atherosclerosis, assessed through ultrasound (mode B Doppler).[746] Greater prevalence of carotid plaques was observed in SLE patients than in controls (14 v. 0%; $P$=0.007) and greater thickening of the intima-medial wall ($P$=0.001). It was also found that SLE patients had greater prevalence of high blood pressure ($P$=0.001), hypercholesterolemia ($P$=0.022) and hypertriglyceridemia ($P$<0.001). In SLE patients, the prevalence of atheroma plaques increased with age, from 2% in women under 35 to 32.4% in women over 39. In SLE patients, predictors of the presence of carotid plaques were age, longer disease duration, higher BMI, increase in blood pressure, less prothrombin time, higher C reactive protein level, greater accumulated damage, a higher dose of accumulated prednisone, less use of HCQ and greater thickening of the intima-medial wall. | Case-control study 2- |
| Another case study (n=179) and controls (n=197) assessed the prevalence of atherosclerosis, examined through ultrasound, and its relationship with CVD risk factors. Subclinical atherosclerosis was more frequent among SLE patients than among the controls, 3.71 v. 15.2%, (RR= 2.4; 95% CI: 1.7-3.6; $P$<0.001). In the multivariate analysis only advanced age (OR= 2.4 per 10 years, 95% CI: 1.8-3.1), suffering SLE (OR= 4.8; 95% CI: 2.6-8.7) and a higher serum cholesterol level (OR= 1.1 per 10 mg per decilitre [0,26 mmol/l]; 95% CI: 1.0-1.5) were independently associated with the presence of atherosclerosis.[747] | Case-control study 2- |
| Another study was performed to examine if the prevalence and degree of calcification of the coronary arteries was greater in SLE patients (N=65); compared with a control group of the same age, race and gender (n=69).[748] Coronary calcification was more frequent in SLE patients (20/65, 30.8%) than in the controls (6/69, 8.7%, or= 4.7; 95% CI: 1.7-12.6; $P$<0.002). Furthermore, the average score of calcification was greater among SLE patients (68.9 ± 244.2 v. 8.8 ± 41.8; $P$<0.001). | Case-control study 2- |
| To assess the changes in the carotid intima-medial thickness and its association with risk factors, a Spanish cohort was recruited with 101 SLE patients, obtaining measurements of the carotid intima-medial thickness by ultrasound, in a two-year interval. Moreover, the cardiovascular risk factors, disease activity, accumulated damage and biochemical parameters were assessed. It was observed that the baseline carotid intima-medial thickness ($P$<0.001), the diagnosis age ($P$<0.001), disease duration ($P$<0.044), homocystein ($P$<0.041), C3 ($P$<0.003), and C5 ($P$<0.033) appeared as risk factors of the progression of the carotid intima-medial thickness.[749] | Cohort S. 2+ |

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To determine the prevalence and clinical correlates of atherosclerosis by means of multiplane transesophagial echocardiography in SLE patients, a group of patients (n=47) was compared with a group of healthy people of the same age and gender (n=21).[750] The prevalence of atherosclerotic plaques, increased aorta intima-medial thickness, or the presence of both findings had greater incidence among the patients than among the controls (37 v. 14%, 23 v. 0%, and 43 v. 14%, *P*=0.02 in all the cases). Among the SLE patients, the age at the time of diagnosis was the only independent predictor of aorta atherosclerosis (OR= 1.12 per year as from the diagnosis of SLE; 95% CI: 1.4-1.19; *P*=0.001) while therapy with CPM was a protection factor (OR= 0.186; 95% CI: 0.15-0.95; *P*=0.04).

Case-control study
2-

In order to determine the prevalence of subclinical atherosclerosis (presence of carotid plaque or increase in carotid intima-medial thickness) and endothelial dysfunction (measured by flow-mediated dilation), as well as its association with traditional cardiovascular risk factors, a cohort of 60 SLE patients was selected and compared with 38 healthy controls. SLE patients had a higher proportion of subclinical atherosclerosis (26/60, 43.3%) compared with the controls (1/43, 2.3%; *P*<0.01). In addition, flow-mediated dilation was more frequently altered in SLE patients than in the controls (18.97 v. 9.97%, *P*<0.0001). In the multivariate analyses, both SLE per se, and accumulated damage were independent predictors of subclinical atherosclerosis and suffering SLE of the endothelial dysfunction. Both in patients and in controls, age (R2= 0.028; *P*=0.036) and D reactive protein (R2= 0.105; *P*=0.005) showed a significant association with endothelial dysfunction (*P*<0.05). And, in SLE patients, the diastolic blood pressure (R2= 0.065; *P*=0.05), the accumulated use of HCQ (R2= 0.087; *P*=0.02), very low density lipoproteins (R2= 0.117; *P*=0.05) and HDL (R2= 0.087; *P*=0.025) had a significant association with endothelial dysfunction.[751]

Case-control study
2+

Kiani et al studied the prevalence and association of the calcification of the aorta valve with SLE, measured with tomography, observing calcification of the aorta valve in 1.5% of the sample (n=199), while coronary calcification was observed in 43% and calcification of the carotid in 17%. Calcification of the aorta valve was associated with hypercoagulability (*P*=0.0287), but not coronary calcification or carotid plaque calcification. Risk factors for the calcification of the aorta valve were found to be C reactive protein (*P*=0.0592), fibrogen (*P*=0.0507) and lipoprotein A (*P*=0.025), the use of prednisone (*P*=0.04) and also of MTX.[752]

Cohort S.
2-

In order to assess the impact of traditional risk factors, and certain biomarkers in premature subclinical atherosclerosis, 182 patients with CVD-free SLE were included in a cohort study with eight-year follow-up. 13% of the patients presented CVD for the first time (n=24). Among the traditional risk factors, only age (*P*<0.0001) and nicotine addiction (*P*=0.03) were significant predictors. APLs (*P*=0.002), the elevation of the endothelial activation markers (P≤ 0.005), and fibrinogen (*P*=0.02) predicted CVD.[753]

Cohort S.
2+

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McMahon *et al*.[754] examined if pro-inflammatory HDL and leptine increased the risk of CVD in SLE patients. To do so, they recruited 210 SLE patients and 100 healthy controls of the same age (all women) in a prospective cohort study (*Predictors of Risk for Elevated Flares, Damage Progression and Increased Cardiovascular Disease in SLE -PREDICT*). The presence of the carotid plaque and intima-media thickening (IMT) were measured at the start of the study and follow-up. The carotid plaque was significantly associated with an age of over 48 years (OR= 4.1; *P*=0.002), the pro-inflammatory HDL levels (OR= 9.1; *P*<0.001), leptine levels < 34 ng/dl (OR= 7.3; *P*=0.001), plasmatic TWEAK levels > 373 pg/ml (OR= 28.8; *P*=0.004), and history of diabetes (OR= 61.8; *P*<0.001).

Case-control study
2+

At the present time, the recommendation is to consider SLE patients as patients with high or very high vascular risk, based on the high prevalence of cardiovascular events, as well as their early onset age with respect to the general population.[730] Therefore, it seems reasonable to periodically assess the cardiovascular risk of these patients, as recommended by EULAR.[10]

SR
2++

There are no specific scales that differ from those of the general population to assess vascular risk of SLE patients. Calculations using classical equations underestimate the risk and do not entail significant differences in the management of risk factors, as shown in the cohort study published in 2009 by O'Neill *et al*. In this work, they analysed the impact on the treatment of SLE patients after calculating their cardiovascular risk after 10 years. In those with a risk of more than 7.5%, an intervention was proposed, which derived in a similar management to what 96% of the patients received previously%. The authors concluded the need for risk scales that integrate classical cardiovascular risk factors with those related to the actual SLE.[755]

Case-control study
2-

Bartolini *et al*. published a work where they proposed a stratification of the cardiovascular risk in SLE patients into three categories, integrating variables related to the disease with those commonly identified in the general population. According to this scale, there would be no low risk patients. Those with inactive or little-active SLE would have a moderate risk. A high risk in the case of active SLE and/or treatment with glucocorticoids. Finally, a very high risk in the case of co-existence of SLE and any one or more of the following: established CVD, diabetes mellitus, active lupus nephritis, moderate or severe chronic kidney disease, score >10 and/or presence of atheroma plaque in carotid ultrasound.[756]

Non-analytical S.
3

The efficacy of this algorithm still has to be demonstrated in future work, as well as its possible implications in the intensity of the control of the risk factors, but it is possible that it may provide a better approach to the real risk of SLE patients, on integrating classical variables with other factors related to the actual disease.

The frequency with which we must assess the cardiovascular risk of SLE patients has not been established or analysed in any study. Other pathologies considered as equivalent in terms of vascular risk, such as diabetes mellitus, require a six-monthly control of the cardiovascular risk factors, if these are controlled well. If one or more risk factors are badly controlled, the assessment would be every three months.[757]

CPG
4

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**Summary of evidence**

| | |
|---|---|
| 2+ | SLE patients present an increase in risk of cardiac events[331,738] and coronary disease compared with the rest of the population.[736] More specifically, SLE patients present a risk of AMI that is between 2 and 10 times higher,[730,734] and between 1 and they have 1-3 times more probability of being admitted with congestive cardiac insufficiency than their matched controls by gender and age.[730]<br><br>SLE patients present a higher prevalence of atherosclerotic plaques and a more frequent abnormal aorta intima-medial thickness.[750] The atherosclerosis rate is between 2.4747 and 4.7 times greater[748] and the subclinical atherosclerosis rate may reach 18.8 times greater than the general population.[751]<br><br>The RR of suffering a CVA is increased,[730,734,735] and may even become seven times greater than what would be expected, depending on the vascular risk factors.[731] However, no differences in the peripheral vascular disease rates have been observed with the general population.[730] |
| 2+ | The risk factors associated with CVD include:<br>– High cholesterol.[733,736,739,745,747,751]<br>– Nicotine addiction.[733,744,753]<br>– High blood pressure.[733,745,747,751]<br>– Diabetes.[754]<br>– Male gender.[733,737,738,740,741,748]<br>– Age: advanced age is an independent predictor of CVD in SLE,[732,733,736,737,739-741,745-749,753,754] as well as the age at the time of the diagnosis.[749,750]<br>– The disease itself.[736]<br>– Disease activity.[733,753]<br>– Duration of the disease.[740,746,749]<br>– Accumulated damage.[737,741,746,751]<br>– APL.[733,735,740,744,753]<br>– C reactive protein.[741,744,746,752]<br>– Leptine and proinflammatory HDL.[754]<br>– Homocysteine, C3 and C5a.[749] |
| 2+ | The effect of different drugs on the risk of CVD is variable: More information exists about:<br>– Glucocorticoids: they decrease the systemic inflammation and atherogenesis, but flare up multiple traditional risk factors.[730] In patients who, at the time of the study, used 20 mg/day or more of glucocorticoids, there was a substantial increase in the risk of cardiac events.[738] The use of prednisone has been associated with calcification of the aorta valve.[752]<br><br>Anti-malarial drugs: they improve the lipidic and glycaemic profile, and reduce CVD events by 50-60%.[730,746] |

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|---|---|
| 2+ | With respect to the probability of suffering cardiac events depending on the ethnic group, the risk is greater in Afro-American patients, who have a larger number of risk factors compared with their Caucasian peers.[742-744] Differences in the risk presented by Caucasian and Hispanic patients have also been found, with a lower probability of appearance in the latter.[741,744] However, no ethnic differences have been observed in the risk of arterial or venous thrombotic events.[740] |
| 4 | The appropiate frequency to assess the cardiovascular risk of SLE patients has not been established or analysed in any study.[757] |
| 2- | There are no consolidated specific scales to assess the cardiovascular risk in SLE patients.[755] |

**Recommendations**

| | |
|---|---|
| √ | We suggest assessing the cardiovascular risk with the same frequency as recommended for other high cardiovascular risk diseases such as diabetes, using the instruments available for the general population until specific and validated instruments for SLE are available, and individualising the estimation according to specific risk-increase associated factors of SLE. |

## 8.1.2. Prevention of cardiovascular events

**Questions to be answered:**

- Is there evidence about specific cholesterol figure targets, or can we only transfer those recommended for other high cardiovascular risk pathologies such as diabetes?

Several studies have shown the association between SLE and premature arteriosclerosis, and it is broadly accepted that these patients have a high risk of suffering cardiovascular diseases, which cannot be explained entirely by classical risk factors, but rather, other factors related to the actual disease may also be involved, such as chronic systemic inflammation or treatment with glucocorticoids.[331,758]

Several observational studies, the majority performed on Caucasian populations, have shown a significantly greater prevalence of dyslipidemia in SLE patients, compared with healthy controls, and some authors refer to a "SLE dyslipidemia pattern" characterised mainly by high levels of triglycerides and very low density lipoproteins, and decreased levels of HDL.[758] Different authors suggest that dyslipoproteinemia in these patients may have a multifactoral origin, where factors such as steroid treatment, disease activity or renal impairment may intervene.[759-761] Hypercholesterolemia has been identified in several studies as a risk factor of coronary disease in SLE patients.[759,760]

No studies have been identified that afford revealing data with respect to the optimal figure of cholesterolemia in SLE patients.

Currently, the recommendations to prevent the cardiovascular risk in the general population establish some optimal values of cholesterol in blood, in agreement with the risk factors of the individuals. According to the 2012 guideline for the prevention of cardiovascular risk of the European Cardiology Society,[762] for people with low cardiovascular risk, the total cholesterol level recommended is less than 5 mmol/l (approximately 190 mg/dl) and the LDL less than 3

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mmol/l (115 mg/dl), while for individuals with a high risk, they recommend LDL of below 2.5 mmol/l (96.5 mg/dl), and if the risk is very high, 1.8 mmol/l (69.5 mg/dl). Although there are no specific recommendations established for SLE patients, they do include this pathology in the group of disease with increased cardiovascular risk.

On their part, the American Cardiology Association, in its 2013 recommendations[763], focused on hypolipemiant treatment, and referred to the values established previously by the NCEP (*National Cholesterol Education Program*), which established a desirable cholesterol level with a concentration of less than 200 mg/dl (but not optimal), and a LDL of between 100 and 129, the optimal being less than 100 mg/dl.[764]

Formiga *et al*., taking a total cholesterol level of over 200 mg/dl (5.2 mmol/l), as reference for hypercholesterolemia, obtained a prevalence of dyslipoproteinemia of 55% in a group of premenopausal women with SLE (n=53) compared with 30% in the control group of healthy premenopausal women (n=35) ($P$=0.03), with higher total cholesterol levels than in the healthy group (5.38 ± 1.2 mmol/l v. 4.86 ± 0.9 v; $P$=0.01), as well as of triglycerides ($P$=0.02) and apolypoprotein A and B ($P$=0.0001).[761] Observational S. 3

In another study (n=53), the average cholesterol level observed was more than 5.60 mmol/l in SLE patients without cardiovascular morbidity, and 5.9 mmol/l in patients with morbidity, compared with 4.9 mmol/l in healthy people ($P$<0.01); the figures of triglycerides and LDL were also higher in patients ($P$<0.001).[765]

Magadmi et al. did not find a significantly higher concentration of total cholesterol in SLE patients than in healthy people, but they did of triglycerides ($P$=0.02), as well as a lower level of HDL ($P$<0.01).[766]

The results of other identified studies, which focused their attention on the description and characterisation of the different subclasses of lipoproteins, suggest the presence of a more atherogenic lipid profile in SLE patients than in the general population.[759,767-770] Observational S. 3

McMahon *et al*. (n=154) revealed that HDL in SLE patients was more pro-inflammatory than in healthy people ($P$<0.0001) and that also the prevalence of this pro-inflammatory HDL was greater (44.7% v. 4.1%; $P$<0.001).[767]

Only two of these studies showed total cholesterol values and they did not observe significant differences between patients and healthy people; however both studies obtained higher levels of triglycerides ($P$<0.05, and $P$=0.004),[771,772] and one of them (50 healthy and 50 SLE) also found a significant increase in other atherogenic particles in participants with SLE.[768]

Higher levels of triglycerides ($P$=0.035) and lower levels of HDL ($P$=0.024) in SLE patients compared with healthy people were also observed in the study of Hua *et al*.[769]

Urquizu-Padilla *et al*. analysed the variations of the lipid profile between flares and remission phases of the disease (n=54, 88.5% women). Although a tendency was observed to obtain worse levels in absolute values of total cholesterol, HDL, LDL and triglycerides during the flare compared with the remission, no statistically significant differences were found. However, the total cholesterol/HDL and LDL/HDL ratios were greater during the flares than in remission phase ($P$=0.007 and $P$=0.015).[759]

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Other authors, although they do not focus their research on the subject of this question, establish some relationships between hypercholesterolemia and morbidity of SLE, based on some reference values.

Petri *et al*.[760] in an analysis of the *John Hopkins Lupus Cohort* (n=229) showed that 8.3% suffered some type of coronary disease and that these, compared with patients who did not suffer them, were more likely to have higher levels of cholesterol (mean: 271,2 vs. 214.9 mg/dl, *P*=0.0001) or a level of above 200 mg/dl (OR= 14.5; 95% CI: 1.9-112.1). Cross-cutting s. 3

In a second study on this same cohort, they reported that the most frequent cardiovascular risk profile was the presence of 2 risk factors, and within that profile, the most common one was a sedentary lifestyle plus hypercholesterolemia (defined as a serum concentration of more than 200 mg/dl). The cholesterol values assessed in one year were taken, observing that 56.3% of the patients had at least one measurement above that figure.[773]

A study of a Canadian cohort analysed the determinations of hypercholesterolemia carried out in the three years after the diagnosis of SLE, taking 200 mg/dl as reference value. Cohort S. 2+

They observed altered figures in 75.4% of patients in one or more determinations, of which 40% showed sustained hypercholesterolemia, defined as at least one high determination a year during that three-year period. They also found significant differences in coronary disease frequency (total 14.2%) between the different groups: 28% in patients with sustained hypercholesterolemia, 6.4% in variable hypercholesterolemia and 3% in normal values (*P*=0.005).[774]

The prevalence of cardiovascular events observed by Manzi et al. in a sample of 498 women (n=498, 76% Caucasians) was 7.3%, of whom 18% had hypercholesterolemia (value > 240 mg/dl) opposed to 4% who had not suffered it (RR= 3.35; 95% CI: 1.4-8.36).[739] Cohort S. 2+

Leong *et al*. carried out a study on 100 Chinese patients, finding a significant association between hypercholesterolemia (> 200 mg/dl) and renal damage and active SLE (both *P*<0.001).[775] Cross-sectional S. 3

**Summary of evidence**

| | |
|---|---|
| 3 | Existing evidence suggests that SLE patients have a greater prevalence of hypercholesterolemia and a more atherogenic lipid profile than the general population.[761,763-765,772] |
| 3 | Hypercholesterolemia is present in patients who suffered more frequent cardiovascular events than those who did not.[739,760,773,774] |
| | There is no available evidence on specific cholesterol target figures for SLE patients. |
| 4 | The European Cardiology Society includes SLE in the population group with increased risk of suffering cardiovascular events, for whom it recommends a LDL level lower than 2.5 mmol/l; this figure is recommended for diabetes type II patients without established arteriosclerotic disease, as well as a total cholesterol figure of 4.5 mmol/l (175 mg/dl).[762] |

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**Recommendations**

| | |
|---|---|
| √ | We recommend establishing the recommended cholesterol figures for people with increased cardiovascular risk as those desirable for SLE patients. |

## 8.1.3. Indication for aspirin

**Questions to be answered:**

- In which people with systemic lupus erythematosus is the use of aspirin indicated?

Anti-aggregate treatment with this drug at a dose of between 75 and 150 mg/day in patients with previous CVD produces a reduction of cardiovascular mortality and of major vascular episodes.[776]

In SLE patients, treatment with aspirin is usually indicated when there are risk factors such as the presence of some CVD or high blood pressure, diabetes mellitus, hyperlipidemia, presence of APL and/or in smokers.[777-779]

Two RCTs have been located and assessed, as well as one SR and a total of four observational studies that evaluated the use of aspirin as preventive treatment in SLE patients.

In the recent SR of Arnaud *et al,* 11 studies were included in a MA in order to assess the efficacy at low doses of aspirin for the primary prevention of thrombosis in patients with APL. Those observational and intervention studies were selected that compared the incidence of thrombosis in patients with APL treated with aspirin with patients with APL without this treatment. The average quality score of the studies included was 64 over 100. The MA was carried out using a random effect model and an OR 0.5 was obtained (95% CI: 0.27-0.93) for the risk of first thrombotic event when comparing the group of patients treated with aspirin (n=601) with the group of patients without treatment with aspirin (n=607).[694]

SR with MA
1+

Of the 11 studies assessed, eight included SLE patients (n=440). The analysis by subgroups according to the pathology revealed a significant protective effect of aspirin in SLE patients (OR= 0.55; 95% CI: 0.31-0.98).

In this same vein, the recent clinical trial, ALIWAPAS (A prospective, multi-centre, randomised trial comparing low-dose aspirin with low-dose aspirin plus low-intensity oral anticoagulation in the primary prevention of thrombosis in antiphospholipid antibody positive patients) with 5 years' follow-up and 232 patients with APL and SLE and/or APS, treated with low doses of aspirin (with or without anticoagulant treatment) than in those not treated.[780] In this study, the aim was to assess the efficacy of the treatment with low doses of aspirin plus low doses of warfarin in the primary prevention of thrombosis. Of the 232 patients, 166 were randomly assigned to two intervention groups, receiving treatment with low doses of aspirin (n=82) and treatment with low doses of aspirin as well as low doses of warfarin (n=84). The 66 patients who did not accept participating in the randomisation, were assigned to the control group. The incidence of thrombosis on randomised patients was 1.8 events/100 people-year (1.7 for the group treated with aspirin and 1.8 for the group treated with aspirin and warfarin), and 4.9 events/100 people-year in the observation group (HR= 2.43; 95% CI: 0.87-6.79).

RCT
1+

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| In addition, a more recent study with 33 SLE patients and nine healthy controls was carried out in order to determine the presence of resistance to aspirin. The result was that 19.2% of SLE patients (n=42) under regular treatment with aspirin (100 mg/day) develop resistance to this treatment.[777] | Case-control | S. 2- |

**Summary of evidence**

| | |
|---|---|
| 1+ | Prophylactic treatment with low doses of aspirin (75-100 mg/day) reduces the risk of suffering thrombotic events in patients with SLE and APL.[694,780] |
| 2++/2+ | SLE patients and sustained treatment with aspirin may develop resistance to the treatment.[777,778] |

**Recommendations**

| | |
|---|---|
| A | We recommend treating SLE patients who persistently present medium to high values of antiphospholipid antibodies with low doses of aspirin for the primary prevention of thrombosis. |
| D | We suggest treating SLE patients and previous cardiovascular disease with low doses of aspirin under the same terms as for the general population. |

## 8.1.4. Indication for high blood pressure drugs

**Questions to be answered:**

- Is there evidence that favours the use of certain high blood pressure drugs such as angiotensin blockers, in people with systemic lupus erythematosus?

The little scientific evidence identified related to the use of high blood pressure drugs in SLE patients is limited to the use of ACEI and ARA II.

Three observational studies were found that studied the effects of the use of ACEI and/or ARA II on renal impairment, proteinuria, clinical activity and other measures in SLE patients.[520,781,782]

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The study of Duran-Barragan[520] was a data sub-analysis of the LUMINA cohort,[49] which included SLE patients of less than 5 years' evolution from diagnosis, and belonging to different ethnic groups in the USA. The study analysed the influence of use of the inhibitors of the RCT in the development of renal impairment. They selected patients who, in the initial assessment, did not present this clinical manifestation and, within this subgroup of patients, compared those who used ACEIs (n=80) and those who did not use them (n=298) with respect to the development of nephritis. In agreement with their results, the probability of not suffering renal impairment after 10 years was 88.1% for inhibitor users and 75% for those who did not use them (*P*=0.0099). 7.1% of the patients who used ACEIs developed persistent proteinuria, whilst in those not exposed, this occurred in 22.9% of the cases (*P*=0.0016). Finally, using a Cox multivariate regression analysis, it was observed that patients treated with ACEIs presented a longer evolution time until the development of renal impairment than those not treated (HR= 0.27; 95% CI: 0.09-0.78). In an analysis performed on a subgroup of 288 patients of whom 18.8% were users of ACEI, it was observed, using a conditioned logistic regression model, that the use of these drugs was associated with a lower risk of presenting clinical activity of the disease (HR= 0.56: 95% CI: 0.34-0.94; *P*=0.026).

Observational
S.
2+

A case review study carried out in Hong Kong analysed effects of ACEI or ARA II in 14 patients with LN, two type III, six type ev and six type V, (average age: 38.3±9.1; 79% women), who had been receiving treatment for more than 18 months: Nine patients treated with ramipril (ACEI), three with enalapril (ACEI) and two with losartan (ARA II), as second-line treatment of high blood pressure or to reduce proteinuria. The changes observed in proteinuria, serum albumin, creatinine clearance and blood pressure before and after treatment were compared. The average follow-up was 52.1±35.7 months. The average level of proteinuria before starting treatment with ACEI or ARA II was 1.98 (95% CI: 1.10-6.90) and in the last determination, after treatment, it was 0.36 (95% CI: 0.00-1.35; *P*=0.043). The serum albumin level rose significantly (35.8±3.6 v. 41.3±2.2; *P*=0.023) and the systolic blood pressure dropped (137.6±10.9 v. 114.8±13.7). No significant differences were observe for other outcome measurements.[781]

Observational
S.
2-

Another historical study was carried out in Japan, analysing effects of losartan as additional treatment to the use of enalapril in only seven patients (average age 41.1±17.4; 100% women) with LN (two type III, three type ev and two type V) with persistent proteinuria despite the use of glucocorticoids and immunosuppressive treatment (at least for six months). Changes in the level of proteinuria and adverse renal effects associated with losartan over 12 months were analysed. The reduction in the level of proteinuria (expressed in % of baseline level) was 53.2±8.3% after three months, 62.7±5.6% after six months and 84.8±9.6% after 12 months, (*P*<0.01), The systolic and the diastolic blood pressure also dropped significantly (*P*<0.01), but no significant changes were observed in serum activity.[782]

Observational
S.
2-

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

**Summary of evidence**

| | |
|---|---|
| 2+ | In SLE patients without renal impairment, the use of ACEIs is associated with a lower probability of suffering renal impairment after 10 years as well as with a lower risk of clinical activity of the disease.[520] |
| 2- | In patients with LN, the use of ACEI or ARA II has been associated with a reduction of proteinuria.[781,782] |
| 2- | In LN with refractory proteinuria despite standard immunosuppressive treatment and the use of ACEI, the addition of ARA II may provide an added value.[781,782] |

**Recommendations**

| | |
|---|---|
| D | In patients with nephritis with proteinuria, we suggest the use of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers. |
| C | In patients with lupus and high blood pressure, we suggest the use of angiotensin converting enzyme inhibitors due to their possible added value in the primary prevention of renal impairment. |

# 8.2. Infection

## 8.2.1. Latent infection screening

**Questions to be answered:**

- What should the latent infection screening protocol be for people with systemic lupus erythematosus (tuberculosis, HCV, HBV, cytomegalovirus,...)?

SLE patients have a high risk of infections and these are an important cause of mortality and morbidity.[783]

The description of the screening protocols for latent infections such as tuberculosis, hepatitis B or C, cytomegalovirus, etc., has been based on the review of the EULAR consensus document for the follow-up of SLE patients in clinical practice[10] and the studies of Yilmaz *et al*.[784]

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

In a study with inter- and intra-subject design, the capacity of the *QuantiFERON Gold Test* (GFT-G) was compared with the *gold standard*, the tuberculin skin test (TST), on 78 SLE patients and 49 healthy participants. The objective of the study was to compare the differential capacity of QFT-G and TST to detect latent tuberculosis infection in SLE patients, given that it had been observed that the sensitivity of the TST is not high in immunosuppressed patients, in whom the risk of progressing to tuberculosis is greater. It was observed that the TST continued to show greater sensitivity in the diagnosis of tuberculosis at the standard cut-off point (5 mm). In this case, the agreement between QTF-G and TST was 64.4% (κ = 0.33) and there were fewer QFT-G TST results than TST (24.3 v. 50%, *P*=0.01). However, when the cut-off point was adapted for latent infection (10 m), the degree of agreement changed to 76.3% (k= 0,47) and, in the case of patients with moderate/high doses of glucocorticoids or immunosuppressants, to 72.9% (k= 0.40).[784] nRCT 1-

Lacking available scientific evidence, some of the recommendations that have been developed on this question are based on the EULAR consensus document for monitoring SLE patients in clinical practice. The different recommendations given in this work include those related to the reduction in impact of infections on the lives of SLE patients by risk and monitoring.[10] CPG 4

Regarding the control of latent infections in SLE patients, it is recommended that they be examined for: a) HIV, especially when risk factors appear; b) hepatitis C virus (HCV) and hepatitis B virus (HBV), based on the presence of possible risk factors, especially before the start of treatment with immunosuppressants, including with high dose glucocorticoids; c) tuberculosis, following local guidelines, and as with hepatitis B and C, paying special attention before the start of treatment with immunosuppressive drugs; d) Cytomegalovirus, which could be considered during treatment. (Level of evidence and degree of recommendation of the Oxford Centre for Evidence-Based Medicine: 2b, C; cost/risk assessment: Moderate/very low).

**Summary of evidence**

| | |
|---|---|
| 1- | There appears to be less agreement among tests on SLE patients, with infection by latent tuberculosis, in the cut-off values of TST <5. At the same time, QFT-G seems to be less influenced by prior vaccination and by immunosuppression. Therefore, it could be a more reliable test to detect latent infection both in vaccinated populations and in immunodepressed patients.[784] |
| 4 | SLE patients do not have a greater incidence of infection by HIV, HBV or HCV. However, due to the risks of reactivating latent infections after immunosuppressive therapy, especially with glucocorticoids at high doses, patients with any risk factor should be examined for HIV, HBV and HCV before administering these drugs. In addition, cytomegalovirus could be considered during the immunosuppressive treatment.[10] |

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

**Recommendations**

| | |
|---|---|
| √ | We cannot give a general recommendation on the indication or periodicity of repeated assessments of latent infection due to the human immunodeficiency virus, the hepatitis B virus, the hepatitis C virus and tuberculosis. Therefore these should be adapted to the clinical situation and the individual risk factors of each patient. |
| √ | We suggest examining all patients who are going to be submitted to immunosuppressive treatment for human immunodeficiency virus, hepatitis B virus, hepatitis C virus and tuberculosis, above all when this treatment involves high doses of glucocorticoids or biological therapies, regardless of the existence of risk factors. |
| D | For patients whose first tuberculin skin test is negative, we suggest carrying out a second test one week later to induce the immunological memory (*booster* effect) as false negatives are more frequent in the elderly and in immunosuppressed patients. |
| √ | The tuberculin skin test is the test of choice to detect tuberculosis thanks to its sensitivity in diagnosing tuberculosis in the standard cut-off point (5 mm). However, previous BCG vaccination and/or immunosuppression, could make the QFT-G a more reliable test for detecting latent infection. |

## 8.2.2. Pneumococcal vaccine

**Questions to be answered:**

- What is the safety and efficacy of a pneumococcal vaccine in people with systemic lupus erythematosus? Should this vaccine be administered to all patients?

Infections (especially respiratory ones, together with CVD are the major causes of death among SLE patients.[785,786]

According to the recommendations of the *Advisory Committee on Immunisation Practices* of the United States, patients with chronic diseases should receive pneumococcal and flu vaccinations.[787] Along this same line, the EULAR recommendations urge pneumococcal vaccination in patients with autoimmune inflammatory rheumatic diseases, even when they are treated with immunosuppressive drugs.[787-789] However, their safety and immunogenicity in rheumatologic patients has been disputed.[786] Encapsulated bacteria such as pneumococcus, haemophilus influenza, and meningococcus are the main infectious agents in patients with abnormal immunological response, as are SLE patients.[790]

The first double-blinded RCT was performed in the US in 1979 by Klippel *et al*., and included 40 SLE patients who received a pneumococcal vaccine intramuscularly (n=29) or placebo (n=20).[791] During a four-week follow-up no clinical or serological differences were observed between the intervention group and the control group, using a lupus activity index. Immunogenicity occurred in vaccinated patients, with a significant increase of anti-polysaccharide antibodies of the pneumococcus. ($P<0.001$). This increase was similar to the increase obtained in healthy subjects.

RCT
1+

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

A double-blinded RCT, performed in the US, studied the effect of treatment with CPM and/or AZA on immunogenicity of a 14-valent pneumococcal vaccine for six months.[792] The 77 SLE patients were stratified into a group without cytotoxics (n=60) or a group treated with cytotoxics (n=17), and randomly assigned to receive vaccination or placebo. The results showed that oral CPM, AZA or a combination of the two drugs, in low doses, had not effects on immunisation with pneumococcal vaccination. RCT 1+

One nRCT carried out in the US was described in two articles. 38 SLE patients were immunised, and 23 SLE patients who waivered vaccination and 22 healthy vaccinated volunteers as the control group.[793,794] During a six-month follow-up, the incidence of flares of SLE was similar in cases and controls. One death was recorded among vaccinated patients (fatal miocarditis after three months), and one death among the controls (pneumococcal meningitis). With respect to immunogenicity, one month after vaccination, the level of antibodies (the 12 tested serotypes) was significantly lower in SLE patients compared with healthy controls (918 ± 405 v. 1787±694 ng/ml, respectively; $P<0.001$). No differences were shown in antibody titres between patients with low doses of prednisone and patients with prednisone plus AZA. The long-term follow-up (one, two and three years) of 19 SLE patients and five healthy volunteers showed a lower level of antibodies in SLE patients, although the difference was only statistically significant in the first year. nRCT 1-

The studies did not use a valid disease activity index, so it was not possible to assess the effect of the vaccination on the global activity of SLE. Furthermore, the size of the control group in the long term was too small.

In another US nRCT, 24 SLE patients, 42 patients with RA and 20 healthy subjects were immunised with a 23-valent pneumococcal vaccine. Regarding safety, no differences were observed in clinical or laboratory variables, and only one patient suffered a flare after immunisation. One month later, both the SLE patients and those with RA showed a significant increase of the antibody concentrations, and the immunosuppressive drugs were not associated with the immunological response. However, 20.8% of SLE patients responded to one or none of the seven pneumococcal serotypes studied, while none of the healthy subjects failed in the response to the vaccination ($P=0.004$).[795] nRCT 1+

The last nRCT identified was conducted in Hungary on 18 SLE patients and nine healthy women, immunised with a 23-valent pneumococcal vaccine. Patients with lupus with SLEDAI>20 or with a recent activity flare were excluded from the study. During a four-week follow-up, no flare of SLE occurred, all the adverse effects were mild, the SLEDAI index remained almost the same, and no modifications were required in the treatment. The small size of the control group makes it difficult to interpret the results.[796] nRCT 1-

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

A non-controlled study was performed in the US with 73 SLE patients to determine the safety and immunogenicity of a combined administration of three vaccines: tetanus toxoid, pneumococcal and Haemophilus influenzae type B. No control was included. The majority of patients had a mild form of the disease and only 5% had renal impairment at the time of the vaccination.[797] During a 12-week follow-up no flares occurred among vaccinated patients, and the activity indices of the disease (SLEDAI or *Lupus Activity Criteria Count*) did no significantly increase. The authors concluded that simultaneous immunisation was safe for SLE patients. With respect to immunogenicity, the titres of pneumococcal antibodies increased by four in 47% of the SLE patients. However, a tendency towards a lower response of antibodies was observed in patients with immunosuppressive therapy or with active disease, although the difference was not statistically significant.

Observational
S.
2-

A study of a pre-post group, carried out in Israel, included 24 patient with SLE. Two months after immunisation, the SLEDAI index increased from 4.41±2.92 to 4.47±3.11, which did not represent a significant difference. At the time of vaccination, 10 patients had increased levels of anti-dsDNA, nine had anti-Ro, four anti-La, four aCL, IgG and IgM, and two had anti-RNP and anti-Sm antibodies. Two months after vaccination, no change was observed in the proportion of patients with anti-Sm, anti-RNP, anti-RO and aCL igM antibodies. Only one patient presented aCL IgG and another turned out to be anti-RNP negative.[798]

Observational
S.
2-

**Summary of evidence**

| | |
|---|---|
| 1+/2+ | SLE patients can be safely and successfully immunised against pneumococcus although they seem to present a lower seroconversion rate than healthy individuals.[791-794] |
| 1+/2+/2- | Immunosuppressive drugs were not significantly associated with the response to the vaccine.[792-795,797] |
| 2- | The simultaneous administration of multiple vaccines does not seem to affect safety, and the therapy does not significantly affect immunogenicity.[797] |
| 1+/1-/2- | The activity of the disease (incidence of flares, SLEDAI) does not change after immunisation with the pneumococcal vaccination,[791,795-797] although the studies systematically excluded patients suffering a flare or with severe disease. |
| | No evidence has been found on the immunisation of SLE patients during pregnancy. |

**Recommendations**

| | |
|---|---|
| √ | We suggest administering the pneumococcal vaccine to SLE patients. |
| √ | We suggest administering the pneumococcal vaccine, preferably, during a stable phase of the disease. |
| √ | For pregnant women with SLE, we suggest following the existing recommendations for pregnant women in the general population, if any. If there are none, we suggest not vaccinating until there is available scientific evidence. |

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# 8.3. Cancer

**Questions to be answered:**

- What are the most frequent types of cancer in people with systemic lupus erythematosus? Should specific screening be carried out for this type of patients?

The association between cancer and SLE has been studied for years. Since the 1970s many reports have appeared that suggest an increased risk in suffering cancer in SLE patients.[799]

According to different studies performed on different cohorts it appears that SLE patients have up to 25% more risk of developing some neoplasia (RR: 1.15-1.25), especially in the case of non-Hodgkin lymphoma, in which the prevalence seems to be up to three times greater than that of the general population. Other neoplasias more represented in SLE patients are: lung cancer, hepatobiliary cancer and cervical uterine cancer.[800]

Moreover, it seems that exposure to cytotoxic and immunosuppressive drugs may increase the susceptibility of these patients.[799]

In order to determine the estimations of the risk of cancer in SLE with relation to the general population, an international cohort of SLE patients (n=16409) was selected and compared with the general population.[801] A slight increase in the risk of cancer was observed in SLE patients (SIR = 1.14; 95% CI: 1.05-1.23). However, some types of cancer increased substantially, included, haematological type cancers (lymphomas, leukaemia, and multiple myeloma (SIR = 3.02; 95% CI: 2.48-3.63), more specifically, non-Hodgkin's lymphoma (SIR= 4.39: 95% CI: 3.46-5.49), Hodgkin's type lymphoma (SIR0 2.28; 95% CI: 0.92-4.70) and leukaemia (SIR= 1.75; 95% CI: 1.04-2.76). Other types of cancer that increased were cancers of the vulva (SIR= 3.78, 95% CE: 1.52-7.78), lung (SIR= 1.30; 95% CI: 1.04-1.60), thyroid (SIR= 1.76; 95% CI: 1.13-2.61), and liver (SIR= 1.87; 95% CI: 0.97-3.27). On the other hand, a decrease in the risk of breast cancer (SIR= 0.73; 95% CI: 0.61-0.88), endometrium (SIR= 0.44; 95% CI: 0.23-0.77), and ovary (SIR= 0.64; 95% CI: 0.34-1.10) was observed.

Observational
S.
2++

Another identified study assessed the possible association between malignancy and SLE, comparing a sample of SLE patients (n=2150) with a cohort of healthy controls (n=17207).[802]

In SLE patients, the overall risk of developing cancer in general was greater (marginal significance, HR= 1.26; 95% CI: 0.99-1.59) and the risk of developing prostate cancer was significantly higher (HR= 3.78; 95% CI: 1.30-11.0; *P*=0.05).

Observational
S.
2+

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| | |
|---|---|
| One study determined the incidence of cancer on SLE patients (n=914, 100% women) compared with the general population of Korea (data compiled from the National Cancer Registry). The prevalence of cancer was 1.75% and the SIR for cancer was 1.45 (95% CI: 0.74-2.16). The risk for non-Hodgkin's lymphoma (SIR= 15.2, 95% CI: 2.9-37.7) and bladder cancer (SIR= 43.5, 95% CI: 8.21-106.8) was significantly greater than expected. The most frequent cancer was cervix cancer, however the increase of the SIR was not statistically significant. The data showed a higher cumulative risk of the incidence of cancer in SLE patients with disease duration of more than 10 years (SIR= 4.3; 95% CI: 1.19-14.6; *P*<0.001), with organ damage (HR= 3.03; 95% CI: 1.04-8.83; *P*=0.002) and/or haematological participation (*P*=0.041). On the other hand, high accumulated doses of CPM were associated with a greater risk of cancer (*P*=0.017).[803] | Observational S. 2+ |
| A cross-sectional study with 173 SLE patients, and 217 women without SLEcited for routine cervix cancer screening, was carried out to determine the prevalence of the human papilloma virus (HPV) in SLE patients, and to assess the associated risk factors, including the use of immunosuppressants. The prevalence of the HPV was significantly greater in SLE patients than in the control women (20.2 v. 7.3%, *P*=0.0001). The genotypes of high risk HPV were detected in 42.9% of SLE patients (genotypes 58, 45, 66, 33, 16 and 68), and in 40% of the controls (genotypes 18, 16 and 58) (*P*=0.82) among all the cases in which HPV genotyping was possible. In women with SLE, the intensive use of immunosuppressants was found as a risk factor for cervical infection by HPV (283% v. 12.5%, when there was no immunosuppression) (OR= 3.45; 95% CI: 1.28-3.29; *P*<0.006), as well as a history of four or more sexual partners in life (32.8% v. 13.9%, with less than four sexual partners) (OR= 3.26; 95% CI: 1.39-7.61; *P*<0.006), and a history or previous infection by HPV (40% v. 17.6%, when there was no history of previous HPV) (OR= 3.55; 95% CI: 1.20-10.43; *P*<0.02).[804] | Cross-sectional S. 3 |
| To determine if the incidence of the development of intraepithelial cervical neoplasia increased in immunosuppressed women with SLE with a previous abnormal cervical smear, a sample of 89 patients was recruited, 61 of whom satisfied the inclusion criteria. Routine screening for cervix cancer was carried out on them at the start of the study, after three and after seven years; and the data were analysed depending on the treatment they were receiving. The overall incidence after three years of intraepithelial cervical neoplasia was 9.8% in patients treated with intravenous CPM 15%. A relationship between the 1 g increase of iv CFM and the 13% increase of the risk of cervical neoplasia (*P*=0,04) was observed.[805] | Observational S. 2+ |
| To compare the prevalence of autoimmune diseases (SLE, RFA, Sjögren's syndrome, and autoimmune haemolytic anaemia), 44,350 cases of lymphoid malignancy (≥ 67 years) and 122,531 controls based on the population, were selected. In the case of SLE patients, a strong association with non-Hodgkin's lymphoma was observed (OR= 1.5; 95% CI: 1.2-1.9; *P*<0.0002), as well as with Hodgkin's type lymphoma (OR= 3.5; 95% CI: 1.9-6.7; *P*=0.0002).[806] | Case-control study 2+ |

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

| | |
|---|---|
| In order to analyse the morbidity, mortality and type of neoplasia in SLE patients, a historical study was carried out with 860 Hungarian patients. The results were compared with data from the general population, matched by age and gender, and also with data from literature. The prevalence of cancer observed was 4.3% (SIR= 0.89; 95% CI: 0.6-1.2). The rate of mortality associated with cancer was 2% (18/860). This accounted for 11% of the deaths (SMR= 1.64). In an analysis of the type of malignant tumours, breast cancer was the most frequent (29.7%), followed by tumours of the digestive tract (21.6%), cervical cancer (13.5%), haematological malignant neoplasias (13.5%) and lung cancer (10.8%). Other types of cancer ocurred more frequently as was the case of bladder, skin, hepatobiliary or ovarian cancer (2.7%, respectively). The SIRs were higher for the non-Hodgkin's lymphomas (SIR= 3.5; 95% CI: 0.4-12.5) and cervical cancer (SIR= 1.7, 95% CI: 0.6-4.1).[807] | Observational S. 2+ |
| The main objective of another identified study (n=165) was to establish the frequency at which SLE patients are submitted to cancer screening (mammograms, colorectal cancer detection and Papanicolaou cervical tests); as well as to determine if that frequency corresponds to the established patterns, comparing this with the available figures for the general population. 53% of women with SLE had had a mammogram in the last 12 months (95% CI: 38-68), compared with 74% of women of a similar age from the general population (95% CI: 73-75). Only 18% of SLE patients over the age of 50 reported having undergone a colorectal screening (hidden blood in faeces with or without endoscope), within the recommended interval, compared with 48% (95% CI: 45-51) of the general population. Only 33% of the SLE patients under the age of 30 had had a Papanicolaou test in the last 12 months (95% CI: 19-52), compared with a general population rate of 56% (95% CI: 53-59) for women of a similar age.[808] | Cross-sectional S. 3 |
| A longitudinal study was carried out to compare the receipt of health services, more specifically of cancer screening procedures by women with SLE (N=685), compared with a general population sample (n=18013), and other conditions with non-rheumatic chronic diseases (n=4515). Preventive care in SLE was similar in both comparison samples. 70% of the SLE patients reported they had undergone cervical cancer screening and mammograms in the year prior to the study (in women over 40 years of age); and 62% (of women over 50 years of age) reported having undergone tests to detect colon cancer (one colonoscopy in the last 10 years or a flexible sigmoidoscopy, plus hidden blood in faeces in the last five years).[809] | Observational S. 2+ |

**Summary of evidence**

| | |
|---|---|
| 2++/2+ | Only a slight increase in the risk of cancer in general is estimated in SLE compared with the general population. However, there is a greater risk of haematological type cancer (lymphomas and leukaemia),[801] especially for non-Hodgkin's lymphoma.[801,803,806,807] Other types of cancer with greater risk are lung cancer,801 hepatobiliary cancer,[801] vulva cancer,[801] cervix cancer,[807] prostate cancer,[802] thyroid cancer,[801] and bladder cancer.[803] |

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| | |
|---|---|
| 2++ | Regarding the risk of SLE patients developing breast cancer, this has been seen to be slightly lower,801 or even similar to that of the general population, except when they present a positive expression of the oestrogen receptor.[800] |
| 2+ | Finally, it seems that the risk of suffering cancer is greater in SLE patients whose disease has been ongoing for more than 10 years, with organ damage, haematological participation, and high accumulated doses of CPM.[803] |
| 2+/3 | Although some studies show that the global receipt of cancer detection procedures in SLE patients is relatively high and comparable with the general population,809 other studies reveal that mammograms, colorectal cancer detection, and Papanicolaou tests may be neglected within the follow-up routine of SLE.[808] |
| 2+/3 | In this sense, there is evidence that SLE patients present a higher prevalence of infection by HPV, which is even greater with the use of immunosuppressants, a history of four or more sexual partners and/or a history of previous infection by HPV.[804] Furthermore, treatment with intravenous CPM and an increase in its dosage has been associated with the development of intraepithelial cervical neoplasia.[805] |

**Recommendations**

| | |
|---|---|
| C | We suggest maximising early cancer detection measures in patients with long-lasting SLE, organ damage and/or haematological participation, especially in patients treated with high doses of cyclophosphamide. |
| D | We suggest that SLE patients should undergo a cervical cancer screening programme more frequently than recommended for the general population, especially in presence of associated risk factors such as the use of immunosuppressants, a history of four or more sexual partners and/or a history of prior infection by HPV or of dysplasia. |

# 8.4. Osteoporosis

## 8.4.1. Indication of bone densitometry

**Questions to be answered:**

- Should bone densitometry be carried out on all people with systemic lupus erythematosus? If so, how often?

The prevalence of osteopenia and osteoporosis in SLE patients varies between 25-46% and 4-23%, respectively.[810,811] SLE per se represents an independent risk factor for low BMD, but there are additional risk factors that may concur, such as therapy with glucocorticoids and the high prevalence of vitamin D deficiency, among others.[810,811]

The determination of the BMD by means of bone densitometry permits detecting osteoporosis, and thus, start up efficient treatments and preventive measures, increasing the bone mass and/or avoiding ulterior losses, and reducing the risk of fracture.[811]

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A study was performed that compared BMD and bone geometry (macroarchitecture) of two cohorts, one of SLE patients: The SOLVABLE cohort (*Study of Lupus Vascular and Bone Long Term Endpoints*) (n=153), and another cohort of controls from NHANES III (*Third National Health and Nutrition Examination Survey*) (n=4920).[812] It was shown, both in Caucasian and in Afro-American women, that there was a decrease in BMD with respect to controls of a similar age and gender in the different sub-regions of the femoral neck analysed (e.g., 0.80 v. 0.94 g/cm$^2$ in the intertrochanteric region, $P<0.0001$- subgroup of white women). Furthermore, using a software that permits carrying out different analyses of the hip geometry (hip structure analysis) a decrease was observed of the cross-section of the bone in all the hip regions studied (narrow neck, etc.), suggesting, together with other estimations such as the increase of the buckling ratio, etc., the presence of greater bone fragility in SLE patients compared with controls.[812]

Cases-controls
2+

A case-control study selected 32 women treated with prednisone and 16 women who had never been treated with glucocorticoids in order to analyse the heterogeneity of the reduction of the BMD in women with SLE under treatment with glucocorticoids.[813] During the follow-up, in the group of SLE patients, the bone mass loss in the lateral column was 5.54% a year, of 3.59% in the hip, and 0.33% in the forearm, compared with losses of 1.30% in the column, 0.83% in the hip, and 0.11 in the forearm, in the control group.

Case-control study
2+

In a case-control study, 47 premenopausal SLE patients and healthy control women of the same age were selected in order to determine bone loss associated with SLE. Among the results, it was observed that patients who had never received glucocorticoids had a significantly higher lumbar BMD than patients who had received them ($P<0.05$; $P<0.001$ patients with glucocorticoids v. healthy controls). It was also observed that patients not treated with glucocorticoids had a lower BMD in the hip than controls ($P=0.05$). A negative correlation was also observed between the lumbar BMD (r= -0.403; $P<0.05$) and hips (r= -0.516; $P<0.01$) of patients treated with glucocorticoids and accumulated dose of oral prednisolone. It was confirmed, through a multivariate analysis, that treatment with glucocorticoids was associated with bone loss regardless of factors such as age, height, weight, BMI or duration of the disease.[814]

Case-control study
2+

In a group of 126 patients, one study longitudinally assessed the long-term changes of BMD and associated factors in SLE. The loss of BMD in the lumbar spine was significantly associated with medium-high doses of glucocorticoids ($P=0.004$) and with lower baseline levels of 25-hydroxyvitamin D ($P=0.030$). The loss of BMD of the hip was associated with lower levels of 25-hidroxyvitamin D at the start of the study ($P=0.040$), with reduction of BMI ($P=0.030$) and with the use of anti-malarial drugs at start ($P=0.006$).[815]

Observational S.
2+

A case-control study selected 38 women with SLE under treatment with glucocorticoids (17 premenopausal and 11 postmenopausal and 160 healthy women 858 premenopausal, 102 postmenopausal) to assess the bone change in SLE patients submitted to long-term treatment with glucocorticoids (treatment duration 90.8 ± 78.5 months). The BMD and the bone mineral content were lower in postmenopausal women, both in SLE patients ($P<0.01$ and $P<0.05$, respectively), and in the women from the control group.[816]

Case-control study
2+

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30 SLE patients who had not taken glucocorticoids were selected, as well as 30 SLE patients who had taken them for a long period, and 60 healthy controls to measure the effect of SLE on BMD and bone strength.[817] SLE patients without glucocorticoids had a lower BMD in the femoral neck (9.2%) and total hip (7.9%) and a reduction of total radial volumetric BMD, of the cortical area, of the volumetric BMD and of the bone thickness, by 81.3%, 8%, 2.7% and 9.2%, as well as greater compromise of the bone strength (rigidity, tensile strength and apparent elasticity modulus). Similar alterations were found in SLE patients with glucocorticoids compared with controls.

Case-control study
2+

Another case-control study was carried out to assess the alterations of the bone quality in a cohort of women with SLE who had taken glucocorticoids over a long period of time (n=180), compared with healthy control (n=180).[818] The prevalence of osteoporosis in SLE patients was 3.9% in the total hip and 5.6% in the lumbar spine, compared with 0 and 2.2% in the controls ($P$=0.015 and $P$=0.014, respectively). Furthermore, the cortical area, the mean volumetric BMD and the cortical volumetric BMD were reduced by 5.3, 5.7 and 1.9% in SLE patients, respectively.

Case-control study
2+

In order to compare the risk of fracture in 10 years between SLE patients (n=45) and healthy individuals (n=45) a case-control study was carried out, using the FRAX (*Fracture Risk Assessment Tool*) prediction tool.[819] More SLE patients than control patients had a high risk of fracture after 10 years, in agreement with the criteria of the *National Osteoporosis Foundation* (NOF) (16 v. 2%, $P$=0.026). The increase in age, the decrease of BMD of the hip, the accumulated doses of glucocorticoids and anti-dsDNA level were independent predictors of the risk of fracture in SLE patients.

Case-control study
2+

To determine the prevalence of low BMD and the risk of fractures in women with SLE, a cohort of 271 patients without a history of fractures was selected.[820] Osteoporosis was diagnosed in 14.6% of the sample and low BMD in 8.8%. Probability of fracture after 10 years was seen to be more than 20% in 5.3% of the population. The probability of hip fracture after 10 years was more than 3% in 9.4% in patients. The buckling deformity ratio (curvature) of the femoral neck positively correlated with the probability of fracture after 10 years, the duration of SLE and the duration of the use of glucocorticoids.

Cohort S.
2+

**Summary of evidence**

| | |
|---|---|
| 2+ | Although some authors suggest that severe osteoporosis is not very common in SLE patients,[813] others reveal rates of between 39% and 41.8% for osteopenia and between 3.9% and 14.6% for osteoporosis.[818] It seems that in SLE, it is related not only to a decrease of BMD, but also to changes in the bone geometry, with an increase in bone fragility, and therefore, to the risk of fracture.[812] |
| 2+ | The heterogeneity of the reduction of BMD among different SLE patients, emphasises the need for the selective use of BMD in SLE patients, especially in those treated with glucocorticoids.[813] |
| 2+ | SLE patients suffer trabecular and cortical bone loss, regardless of the treatment with glucocorticoids and indicative of a greater risk of fracture.[813,814] |

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| | |
|---|---|
| 2+ | The relationship between treatment with glucocorticoids and low BMD,[813,814,817,818] in agreement with the dose,[815] the accumulated dose of drug,[819] and the duration of treatment,[820] suggests that women with SLE under treatment with glucocorticoids could benefit from regular monitoring of the BMD. |
| 2+ | Other risk factors of low BMD in SLE patients are low BMI,[815] postmenopause,[816] vitamin D deficiency,[815] duration of the disease,[817,820] and the use of anti-malarial drugs.[815] These results underline the importance of preventing and treating vitamin D deficiency and osteoporosis in SLE, especially in postmenopausal patients under treatment with glucocorticoids.[815] |
| 2+ | The risk of fracture in SLE patients increases with age, the duration of SLE, the reduction of BMD of the hip, the duration of the use of glucocorticoids and accumulated doses.[819,820] |

**Recommendations**

| | |
|---|---|
| D | Given the lack of evidence, we do not recommend carrying out a BMD test on all SLE patients. |
| √ | For the estimation of fracture risk, including BMD, we suggest following the recommendations applied to the general population, with special diligence in case of additional risk factors such as chronic treatment with glucocorticoids or menopause. |

## 8.4.2. Prevention of steroid-induced osteoporosis

**Questions to be answered:**

- Which measures should be taken to prevent steroid-induced osteoporosis in people with systemic lupus erythematosus?

For decades, glucocorticoids have been extensively used to treat SLE patients to control the disease. However, the use of these drugs, together with the actual pathology, has proven to be an important factor in the reduction of BMD, and in the increase of the risk of fractures.[811] Despite the complexity of the pathogenesis of steroid-induced osteoporosis, it could be summed up as follows:[811,821]

- *Alteration of the homeostasis of calcium*. Glucocorticoids produce a reduction in the absorption of calcium in the gastrointestinal tract, as well as an increase in its renal excretion. If it is not corrected, this alteration of the calcium metabolism may stimulate the parathyroid hormone, originating an increase in bone remodelling and the subsequent bone loss.
- *Reduction in bone formation*. Glucocorticoids inhibit the production, proliferation, maturing and activity of osteoblasts, which are the bone matrix production cells, at the same time as they increase the apoptosis of mature osteoblasts and osteocytes. The inhibition of the bone formation may also be due to the reduction in the production and action of different bone factors and different cytokines.
- *Hypogonadism*. The reduction in the production of sexual hormones, through multiple mechanisms, also plays an important role in the bone loss produced by glucocorticoids, contributing to the increase in bone resorption, both in men and in women, and at any age.

The effect of glucocorticoids on the bone takes place in two stages: initially they cause a

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rapid phase when bone reabsorption increases,[815,822,823] followed by a slower and more progressive phase when the bone formation is reduced.[821,824] The fastest bone loss rate occurs between the 6th and 12th month of treatment, and is similar in lumbar spine and femoral neck. The speed of this decrease is two-fold or three-fold in patients with long-term treatment with glucocorticoids, determining a greater risk of vertebra and non-vertebra fractures.[824]

Thus, and bearing in mind that effective prevention could significantly reduce morbidity and mortality related to steroid-induced osteoporosis,[825] bone protection should be considered in SLE patients treated with glucocorticoids.

In a RCT performed on 81 premenopausal women with SLE, carried out in China, the effect of calcitriol and calcium on BMD was studied.[826] Thus, participants were randomly assigned to the following three arms: calcitriol (0.5 µg/day) plus calcium (1200 mg/day), calcium (1200 mg/day); and placebo. The patients, despite receiving treatment with glucocorticoids (≥7.5 mg/day of prednisone), did not present a significant loss of bone mass during the two years the study lasted. Likewise, the use of calcitriol and calcium increased the BMD of the lumbar spine compared with the baseline moment, although the existing difference with the exclusive use of calcium, or the control group was not significant at the end of the study.

RCT
1+

A study carried out in China analysed the effects of raloxifene on BMD, in 33 post-menopausal women with SLE receiving treatment with glucocorticoids (prednisone ≤ 10 mg/day).[827] In 12 months, the BMD of the femoral neck and in lumbar spine decreased considerably in the control group, treated only with calcium (1200 mg/day), while it remained stable in the group treated with raloxifene (60 mg/day) and calcium. The difference in BMD of the lumbar spine between both groups was significant ($P<0.05$). There were no fractures in any of the groups. No thrombosis was observed.

RCT
1+

In another RCT performed in Malaysia with 98 premenopausal women with SLE receiving long-term treatment with glucocorticoids (prednisone ≥ 7.5 mg/day), the changes suffered in the BMD were compared in three intervention arms: alendronate (70 mg/week) plus calcium (1 g/day); calcitriol (0.5 µg/day) plus calcium (1 g/day); and only calcium (1 g/day).[824] After two years of study, no noticeable changes were found in the BMD in the calcitriol group, while in the group treated with calcium there was a reduction in the hip of 0.93% compared with the baseline situation ($P<0.001$). In contrast, the group with alendronate showed an increase of 2.69% in the BMD of the lumbar spine and of 1.41% in the BMD of the hip, compared with the state at the start of the study (both differences $P<0.001$). No comparative analysis was carried out between the groups.

RCT
1-

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The efficacy of the hormone replacement therapy (HRT) to prevent steroid-induced osteoporosis was studied in another RCT carried out on Chinese women (n=28) with hypogonadism and SLE receiving treatment with prednisone (≥ 10 mg/day). The patients were randomised to receive HRT (0.625 mg/day of conjugated equine oestrogens for three weeks, and 5 mg/day of medroxyprogesterone acetate for 12 days) or to receive calcitriol (0.5 µg/day). Patients from both arms received calcium carbonate each day (1 g).828 After two years' follow-up, it was observed that lumbar BMD ($P<0.05$) and distal BMD of the radius ($P<0.02$) had decreased in the group treated with calcitriol, compared with the baseline moment. In contrast, the group treated with HRT showed a significant increase in BMD of the lumbar spine respect to the baseline moment ($P<0.05$). Ccomparing both treatment groups, the HRT obtained a more beneficial effect than calcitriol on the BMD both in the lumbar area ($P<0.03$), and in the radius ($P<0.05$). RCT 1-

In addition, some bone remodelling biochemical markers were studied in both arms. At the end of the study, the urinary NTx (bone resorption marker) was reduced with HRT and increased with calcitriol; however, the differences observed between the groups were not statistically significant. However, serum osteocalcine (bone formation marker) did show a significant increase in both arms after 24 months with respect to the baseline situation ($P<0.05$). During the course of the study, there were no notable changes in the activity of SLE or fractures.

A final RCT, carried out in premenopausal women in Belgium, assessed if steroid-induced osteoporosis could be prevented in autoimmune diseases. The participants (n=21 with SLE from a total of 30) were randomised to two arms: the experimental arm that received disodium pamidronate (100 mg/day) and another one that acted as control. Both groups received calcium salts (500 mg/day) and vitamin D (25000 units/month). They also followed a standardised glucocorticoid regime (0.5 equivalent mg of prednisone/kg/day for one month, reducing it by 2.5 mg every two weeks until a maintenance dose of 7.5 equivalent mg of prednisone/day were reached).[829] After one year's follow-up, lumbar BMD had not varied significantly in the group treated with disodium pamidronate, the opposite to what occurred in the control group, where the decrease was statistically significant ($P<0.01$). However, for the hip, a statistically significant bone loss was verified in both groups compared with the baseline situation ($P<0.05$ for the group with disodium pamidronate; $P<0.01$ for the control group). On the other hand, remodelling markers were measured such as C-terminal telopeptide of type I collagen (bone resorption marker) and the intact parathyroid hormone (secondary hyperparathyroidism) in serum. During the course of the study, no outstanding changes took place in these markers in any of the groups. RCT 1-

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In a study carried out in the Netherlands, the follow-up of a cohort of 126 SLE patients (89.7% women) was carried out for an average of 6.7 years in order to assess the changes that occurred on the BMD and identify the factors related to these changes.[815] On the one hand, it was observed that a prednisone dose of ≥ 7.5 mg/day was associated with bone loss at lumbar level ($P$=0.05), while the hip was not affected. Likewise, low serum levels of calcitriol (*25(OH) vitamin D3*) were related to a decrease of BMD, both in the lumbar spine and in the hip. On the other hand, the baseline use of immunosuppressive agents (excluding glucocorticoids and anti-malarial drugs) was associated with an increase of BMD in the lumbar spine ($P$<0.016), while a high serum level of calcitriol ($P$<0.03) was linked to BMD gain, both in the spine and in the hip. These results underline the importance of vitamin D deficiency and osteoporosis screening, especially in the use of high doses of glucocorticoids, to prevent alterations of the BMD in SLE.

Cohort S. 2+

In 2010, the ACR published a detailed guide on prevention and treatment of steroid-induced osteoporosis. It identified different risk factors (including low weight, smoking, family history of fractures) to be added to the treatment with glucocorticoids. In general, doses at which intervention is recommended starts at 7.5 mg/day, even 5 mg/day in patients with high risk profile.[830]

There is also a consensus document, updated in 2011, on osteoporosis from the Spanish Rheumatology Society, which includes a section on the management of steroid-induced osteoporosis.[831]

CPG

**Summary of evidence**

| | |
|---|---|
| 1+ | The combined use of calcium (1200 mg/day) and calcitriol (0.5 µg/day) and the exclusive use of calcium showed a protective, but not significant, effect compared with placebo, on the BMD in premenopausal women with SLE receiving treatment with glucocorticoids (≥7.5 mg/day of prednisone).[826] |
| 1+ | The combination of raloxifene (60 mg/day) and calcium (1200 mg/day) maintains the BMD of the lumbar spine and the femoral neck stable in postmenopausal women receiving treatment with glucocorticoids (≤10 mg/day of prednisone).[827] |
| 1- | Treatment with calcitriol (0.5 µg/day) and calcium (1 g/day) stabilised BMD of the lumbar spine in premenopausal SLE patients receiving long-term treatment with glucocorticoids (prednisone ≥ 7.5 mg/day), while alendronate (70 mg/week) administered with calcium increased the BMD in the lumbar spine and the hip.[824] |
| 1- | The administration of calcitriol (0.5 µg/day) and calcium (1 g/day) in women with hypogonadism receiving treatment with prednisone (≥ 10 mg/day) did not protect from the reduction of BMD at lumbar and distal level of the radius. However, lumbar BMD improved with the use of equine oestrogens (0.625 mg/day for three weeks), combined medroxyprogesterone (5 mg/day for 12 days) and calcium.<br>Both HRT and calcitriol increased the serum level of osteocalcine, indicating the existence of bone formation.[828] |

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| | |
|---|---|
| 1- | The use of vitamin D supplements (25000 units/month) and calcium (500 mg/day) in women of childbearing age did not protect from the reduction of BMD in the lumbar spine. In one study. Conversely, the addition of disodium pamidronate (100 mg/day) preserved the BMD at the same level.[829] |
| 2+ | Prednisone dose ≥ 7.5 mg/day caused BMD loss at lumbar level, although not in the hip. On the other hand, low serum levels of calcitriol (25-hydroxyvitamin-D) were associated with a reduction of BMD, while high levels presented an increase, both at lumbar level and in the hip. The baseline use of immunosuppressive agents (except for glucocorticoids and anti-malarial drugs) was also associated with an increase in BMD of the lumbar spine.[815] |
| CPG | There are CPGs that recommend specific prevention and treatment measures for steroid-induced osteoporosis depending on the daily dose of prednisone and the presence of other risk factors that are applicable to SLE.[830] |

**Recommendations**

| | |
|---|---|
| B | The use of calcium in monotherapy is not recommended to prevent steroid-induced osteoporosis. |
| C | In order to reduce the risk of steroid-induce osteoporosis in SLE, we suggest avoiding long-term sustained doses of prednisona > 5mg/day in SLE. If it is necessary, steroid-saving drugs such as immunosuppressants should be used. |
| √ | We suggest recommending an adequate diet, resistance exercises, periodic measurement of BMD if prednisone > 5 mg/day or equivalent are used for ≥ 2-3 months, calcium and vitamin D supplements, and evaluation of the need for pharmacological prophylaxis of osteoporosis with antiresorptive therapy. |
| √ | We suggest following the CPG for treatment of steroid-induced osteoporosis. |

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# 9. Dissemination and implementation

## Dissemination and implementation strategy

CPGs are useful to improve the quality of healthcare and outcomes in patients. The great challenge today is to achieve professionals' adherence to the recommendations of these guidelines. An implementation strategy, aimed at overcoming the existing barriers in the medium where it is going to be applied is therefore essential.

The CPG is comprised of two versions for health professionals: full and abridged. Both have information for patients. All the CPG versions are published in electronic format, available on the GuiaSalud website (www.guiasalud.es).

The dissemination and implementation plan of the guideline on SLE includes the following interventions:

1. Official presentation of the guideline by the health authorities to the media.
2. Presentation of the guideline to the directorates and sub-directorates for Primary Care and Specialised Care of the different Health Services.
3. Forwarding of e-mail to entities and resources to inform about the CPG, as well as to the professional groups involved (general practitioners and specialists in Rheumatology, Nephrology, Haematology, Internal Medicine, Immunology, Dermatology, nurses, midwives) to facilitate dissemination.
4. Effective distribution aimed at the professional groups involved (specialists in Rheumatology, Nephrology, Haematology, Internal Medicine, Immunology, Dermatology, nurses) to facilitate dissemination.
5. Dissemination of the guideline on electronic format on the websites of the Ministry of Health, Social Services and Equality, of GuiaSalud, of the Canary Island Health Service Assessment Service, and of the societies involved in the project.
6. Publication of the guideline in scientific magazines.
7. Presentation of the guideline at scientific activities (conferences, congresses, meetings).

## Indicator proposals

Measuring adherence to or implementation of the CPG recommendations by monitoring and/or auditing can improve its use. The AGREE II instrument manual includes the importance of developing indicators, where item 21 on the applicability dimension is the one that deals with this aspect.[42] Consequently, a CPG should offer a list of clear and quantifiable quality indicators or criteria, which are derived from the key recommendations included in the guideline. The most well-known classification of indicators, and used in this guideline is the Donabedian[832] classification, which groups them into: structure, process and results. To determine and evaluate compliance with the recommendations considered to be most important, the assessment of some process variables and most important clinical results is proposed.

The indicators proposed by the guideline development group are listed and described below. They are classified according to the clinical area, type of indicator, dimension of the quality they address and the healthcare level where they may be applied (primary care and/or specialised

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care). It is important to bear in mind that the indicators are a proposal and are only an approach. As they are quantitative measures, if they are obtained with certain regularity, the evolution can be analysed in time (monitoring).[832] The authors' purpose has not been to design a comprehensive and detailed assessment that entails using all the proposed indicators. On the contrary, the aim is to provide stakeholders and clinicians with a tool that may be useful in the specific design of the care assessment. The people responsible for assessing the impact of the CPG and for caring for patients should choose the most suitable information sources and most advisable period of time that each indicator refers to.

Proposed indicators

| Area | Type of indicator | Name of indicator | Quality dimension | Healthcare Level* |
|---|---|---|---|---|
| Treatment | Process | % of patients receiving anti-malarial treatment | 90% | 1.2 |
| Treatment | Process | Daily average dose of prednisone throughout the follow-up | ≤7.5 mg/day | 1.2 |
| | Result | % of SLE patients who smoke | < 10% | 1.2 |
| Diagnosis | Process | % of LN diagnosed by biopsy | >80% | 2 |
| Treatment | Process | % of proliferative LN treated with immunosuppressants. | >90% | 2 |
| Treatment | Process | % of proliferative LN treated with initial doses of prednisone ≤30 mg/day. | >90% | 2 |
| | Process | % of pregnancies in women with SLE with prior preconception consultation | >80% | 2 |
| | Process | % of pregnancies in women with SLE controlled in multidisciplinary clinics | >80% | 2 |

** 1: Primary Care; 2: Specialised care; 3: Social-Health Care.*

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# 10. Future research lines

The following areas of priority uncertainties were identified throughout the development process of this guideline:

## Diagnosis

Role of the new SLICC criteria for SLE in the clinical diagnosis.

## Management of comorbidities

Safety and efficacy of the pneumococcal conjugate vaccine in SLE patients.

Predictor models to estimate cardiovascular risk in SLE patients.

Indications of chemoprophylaxis against Pneumocystis jirovecii.

Risk factors of thrombosis in SLE patients.

## Treatment

Strategies and other general aspects:

- T2T strategy in SLE.
- Impact of treatment of SLE on HRQoL.
- Impact of treatment of SLE on damage.
- Risk-benefit of treatment in early stages of SLE, possible opportunity window.

Glucocorticoids:

- Oral glucocorticoid attack dose in serious patients.
- Efficacy and safety of glucocorticoid pulses in active SLE.
- Optimal glucocorticoid reduction regimens.
- Safety of low maintenance doses of glucocorticoids.

Anti-malarial drugs:

- Doses of anti-malarial drugs for baseline treatment of SLE.
- Ideal ocular toxicity monitoring regimen by antimalarial drugs in SLE.

Biological therapies:

- Long-term safety of ablation therapy B with RTX.
- Role of belimumab in LN and other severe manifestations.

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## Specific manifestations

Duration of maintenance treatment of LN.

Role of thrombopoietin agonists in managing thrombocytopenia associated with SLE.

APS:

- Duration of anticoagulation in patients with APS associated with SLE and thrombotic events.
- Role of the new anticoagulants in APS.
- Role of control of vascular risk factors in the development of thrombosis in SLE and APS.

Develop a specific tool to evaluate arthritis in SLE or validate DAS28 in these patients.

Given the importance of contraception in women with SLE due to the risks entailed by pregnancy, and on the other hand, the cardiovascular risks associated with this disease, we recommend conducting good quality studies that provide more information about the role exercised by hormone contraceptives.

A certain dispersion of active groups in clinical research into Lupus has been detected in our country, so the group of experts of this guideline recommends making an effort to converge, seeking possible synergies and avoiding redundant projects and research lines.

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# Appendices

## Appendix 1. Declaration of interest

In agreement with procedure established in the SNS CPG Programme (available at www.guiasalud.es), each of the members participating in the development and review of the CPG on SLE has made a declaration of interest, submitted later on to assessment. The declaration of interest of each of the members of the guideline development group, expert collaborators and expert reviewers, are summarized and presented below, together with the results of the assessment process. The complete declaration of interest is available (on request) for consultation at the Canary Island Health Service Assessment Service.

The following people have declared a lack of conflict of interests:

Abraham Pérez de la Rosa, Adoración Martín Gómez, Amelia Carbonell, Ana Isabel González, Ana Mª de Pascual y Medina, Angel Robles Marhuenda, Antonia Rodríguez Hernández, Begoña Bellas Beceiro, Carlos Romero Gómez, Carolina Guerra Marrero, Cristina Valcarcel Nazco, Daniel Pacheco Rodriguez, Elisa Trujillo Martín, Graciela S. Alarcón, Hugo Saavedra, Ignacio Abaitúa Borda, Ignacio García-Doval, Inmaculada Alarcón Torres, Isabel Arceo Fernández, Isabel del Cura González, Isidro Jarque Ramos, Iván Ferraz Amaro, Jaime Nogueiras Pérez-Santamarina, Jeannette Pérez Ramos, Josefina Panetta Monea, Juan Antonio López Rodríguez, Juan José Bethencourt Baute, Laura García Hernández, Leticia Cuellar Pompa, Lorena Expósito Pérez, Lucio Pallares Ferreres, Mª del Mar Trujillo Martín, Mª Dolores Rodríguez Huerta, Mª José Torijano Castillo, Mª Teresa Martínez Ibáñez, Manuel Hens Pérez, María Ángel Valcárcel de la Iglesia, María Delia Almeida González, María Galindo Izquierdo, María García González, María Paz Carrillo Badillo, María Prieto Blanco, María Terol Claramonte, Nelida Gómez Corzo, Noemí Martínez López de Castro, Norberto Ortego Centeno, Pedro Serrano Aguilar, Pilar Pazos Casal, Pritti M. Melwani, Rafael García Rodríguez, Raúl Quirós López, Renata Linertová, Ricardo Rodríguez Barrientos, Silvia García Díaz, Tasmania Mª del Pino Sedeño.

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| DIRECT PERSONAL INTERESTS OF A FINANCIAL NATURE | |
|---|---|
| Type of interest declared | Author-Details |
| Financing for meetings and congresses, attendance at courses (registrations, travel bags, accommodation, …) | Iñigo Rua-Figueroa Fernández de Larrinoa: MSD, Roche and Glaxosmithkline<br>Jaime Calvo Alen: UCB Pharma<br>José María Pego-Reigosa: Pfizer and Glaxosmithkline<br>Miguel Ángel Frutos Sam: Roche<br>Antonio Fernández Nebro: MSD, Pfizer and Roche– ACR, EULAR and SER Congresses<br>Francisco Javier López Longo: Sanofi, Roche, UCB Pharma, Actelion, Pfizer and Abby<br>Luis Caminal Montero: GEAS, H Clinic, GSK<br>Gerard Espinosa Garriga<br>Luis Sáez Comet: Acthelion, Glaxosmithkline, Esteve, Menarini y Novartis<br>Amaia Ugarte Núñez: Glaxosmithkline<br>María José Cuadrado Lozano: Glaxosmithkline |
| Fees as speakers (conferences, courses,...). | Iñigo Rua-Figueroa Fernández de Larrinoa: Roche and Glaxosmithkline<br>José María Pego-Reigosa: Glaxosmithkline<br>José Mario Sabia Sánchez: Simule and GEAS Master<br>Loreto Carmona Ortells: Pfizer, Roche and Abbvie<br>Ricard Cervera Segura: Glaxosmithkline, Novartis, Rubió, Roche and UCB Pharma<br>Antonio Fernández Nebro: Glaxosmithkline and Roche<br>Francisco Javier López Longo: Actelion<br>Luis Caminal Montero: MSD<br>Gerard Espinosa Garriga<br>Luis Sáez Comet: Acthelion, Glaxosmithkline, Novartis<br>Juan Jiménez Alonso: Phadia<br>María José Cuadrado Lozano: SER |
| Funding for educational programmes or courses (recruitment of personnel, rental of facilities,...) | Ricard Cervera Segura: Glaxosmithkline, Novartis, Rubió and Roche<br>Antonio Fernández Nebro: Glaxosmithkline, Pfizer and Roche<br>María José Cuadrado Lozano: Glaxosmithkline and Roche |
| Funding for participating in a research | Ricard Cervera Segura: Glaxosmithkline<br>Gerard Espinosa Garriga |

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| | |
|---|---|
| Advisory and consultancy work for a pharmaceutical company or others | Iñigo Rua-Figueroa Fernández de Larrinoa: Glaxosmithkline –Consultant<br>Jaime Calvo Alen: Lilly and Grünenthal Pharma –Consultant<br>José María Pego-Reigosa: Glaxosmithkline –Consultant<br>Loreto Carmona Ortells: Bristol-Myers Squibb and MSD –Consultant<br>Ricard Cervera Segura: Glaxosmithkline, UCB Pharma, Lilly, Werfen, Cephalon and Immunomedics –Consultant<br>Antonio Fernández Nebro: Glaxosmithkline, Pfizer and Roche –Consultant<br>Francisco Javier López Longo: Pfizer and GSK –Consultant |

| DIRECT PERSONAL INTERESTS OF A NON-FINANCIAL NATURE | |
|---|---|
| Type of interest declared | Author-Details |
| Occupying a post in a professional organisation or support group with direct interest in the topic considered. | Loreto Carmona Ortells – Scientific Director of the Musculoskeletal Health Institute. |

| INDIRECT INTERESTS RELATED TO THE PROFESSIONAL FIELD | |
|---|---|
| Type of interest declared | Author-Details |
| Significant endowment of material to unit or services | Iñigo Rua-Figueroa Fernández de Larrinoa: Abbot<br>Luis Sáez Comet: Acthelion |
| Recruitment or financial aid to recruit personnel in the unit or services | Iñigo Rua-Figueroa Fernández de Larrinoa: Bristol<br>Luis Sáez Comet: Acthelion |
| Economic aid for funding research | Iñigo Rua-Figueroa Fernández de Larrinoa: Novartis, MSD, Glaxosmithkline, Bristol and UCB Pharma<br>José María Pego-Reigosa: Pfizer, Novartis, Glaxosmithkline, UCB Pharma, MSD and Roche<br>Loreto Carmona Ortells: Musculoskeletal Health Institute |
| Funding for educational programmes or courses for the unit | Guillermo Ruíz Irastorza: Glaxosmithkline<br>Iñigo Rua-Figueroa Fernández de Larrinoa: Pfizer and Roche<br>Luis Sáez Comet: Acthelion<br>Manuel Posada de la Paz: Merck and ISCIII |

After assessing the declaration of interest of each of the members of the CPG it was considered that there had been no conflicts of interest with respect to the content of this CPG in any of the cases.

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# Appendix 2. Recommendations to favour shared decision-making

To determine the strength of each one of the formulated recommendations, the development group of this guideline has considered the level of available evidence, and the equilibrium between desirable and undesirable consequences of making the recommendation.[1] In this sense, with respect to decisions in which the benefits clearly exceed the risks, or vice versa, it is reasonable to consider that practically all the patients will make the same choice, and therefore a "strong" recommendation is offered. In contrast, in situations in which the benefits are balanced with the risks or there is considerable uncertainty about the magnitude of both, it is likely that patients or relatives may take different decisions depending on their individual values and preferences. In these cases, we recommend that the decisions taken should be based on a process whereby the health professional informs the patient in detail about the risks and benefits of each option (including no action), and the patient expresses his/her values and preferences on the issue, to ensure that the final decision is consistent with these. Therefore, this shared decision-making (SDM) process between professional and patient[2] should always take place based on grade C and D recommendations, and on "good practice" recommendations. However, in certain recommendations, with a higher level of evidence (grade A and B), such as those where the options have very different risk and benefit profiles, the benefits of both options are equivalent, the effect of the option depends on the patient's adherence, or it is related to his/her lifestyle, the patient's opinion is also desirable. In order to promote and facilitate the SDM process between health professionals and SLE patients and their relatives, the guideline development group identified the following grade A and B recommendations, which, under their criterion, are more sensitive to the values and preferences of the patients, and therefore, with respect to which the SDM process should be favoured:[3]

5. General management of systemic lupus erythematosus

5.2. General therapeutic approach

5.2.5. Preventing reactivation of disease

| | |
|---|---|
| A | We recommend prolonged treatment with antimalarial drugs, even during pregnancy, to prevent reactivations of SLE. |

6. Managing specific clinical manifestations

6.1. Lupus nephritis

6.1.5. Maintenance treatment

6.1.5.2. Suspension of maintenance treatment

| | |
|---|---|
| B | We recommend prolonging this maintenance treatment for 2 to 3 years at least. |

7. Sexual and reproductive health

7.1. Pregnancy

7.1.3. Treatment with antimalarial drugs

| | |
|---|---|
| B | We recommend maintaining hydroxychloroquine during pregnancy. |

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7.2. Fertility and contraception

7.2.2. Contraception methods

| | |
|---|---|
| B | In women with positive antiphospholipid antibodies, we recommend avoiding combined hormone contraceptives due to them having a greater risk of suffering arterial and venous thrombotic phenomena. |


1. Montori V, Devereaux P, Straus S, Haynes R, Guyatt G. Decision making and the patient. In: Guyatt G, Rennie D, Meade M, Cook D (eds). *Users' Guides to the Medical Literature*: *A Manual for Evidence-Based Clinical Practice*. McGraw-Hill: New York, NY, 2008.
2. Edwards A, Elwyn E. *Shared decision-making in health care*: *Achieving evidence-based patient choice*. Second edi. Oxford University Press: New York, NY, 2009.
3. Van der Weijden T, Pieterse AH, Koelewijn-van Loon MS, Knaapen L, Légaré F, Boivin A *et al*. How can clinical practice guidelines be adapted to facilitate shared decision making? A qualitative key-informant study. *BMJ Qual Saf* 2013; 22: 855-63.



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# Appendix 3. System Lupus Erythematosus classification criteria

Classification criteria for diagnosing system lupus erythematosus (SLE), revised in 1997.[37]

| | |
|---|---|
| 1. Malar rash | Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds. |
| 2. Discoid rash | Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring occurs in older lesions. |
| 3. Photosensitivity | Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation. |
| 4. Oral ulcers | Oral or nasopharyngeal ulceration, usually painless, observed by a physician. |
| 5. Arthritis | Non-erosive arthritis involving two or more peripheral joints, characterised by tenderness, swelling or effusion. |
| 6. Serositis | a) Pleurisy: History of pleuritic pain, rub or pleural effusion<br>or<br>b) Pericarditis: Documented by ECG or rub or evidence of pericardial effusion. |
| 7. Renal disorder | a) Persistent proteinuria > 0.5 g per day or >3+ if quantification is not performed<br>or<br>b) Presence of cellular casts in urine sediment (red cell, granular, tubular or mixed) |
| 8. Neurological disorder | Seizures or psychosis, in the absence of medication toxicity and metabolic derangements (uraemia, ketoacidosis, or electrolyte imbalance). |
| 9. Haematological disorder | a) haemolytic anaemia with reticulocytosis<br>or<br>b) Leucopoenia: <4000/mm$^3$ on 2 or more occasions<br>or<br>c) Lymphopenia: <1500/mm$^3$ on 2 or more occasions<br>or<br>b) Thrombocytopenia: <100,000/mm$^3$ on 2 or more occasions in the absence of medication toxicity |

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| | |
|---|---|
| 10. Immunological disorders | a) High native antiDNA antibody titres<br>or<br>b) Presence of anti-Sm antibodies<br>or<br>c) Positive finding of APA based on:<br>-High levels of IgG or IgM anticardiolipin antibodies<br>-Presence of lupus anticoagulant proven using standard methods<br>-False positive tests for syphilis on 2 occasions separated by at least 6 months, confirmed by treponema immobilisation tests or by the fluorescent treponemal antibody absorption test (FTA–ABS) |
| 11. ANA | Presence of abnormal titre of antinuclear antibody (ANA) by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs associated with the «drug-induced lupus» syndrome. |

Note: To classify an individual as a patient with SLE they must meet 4 or more of the 11 criteria at any moment in the history of their disease. APL: antiphospholipid antibodies

Classification criteria of SLE, reviewed in 1982.

| All the criteria are the same as those reviewed in 1997, except criterion 10 (immunological disorders) | |
|---|---|
| Criteria reviewed in 1982 | Criteria reviewed in 1997 |
| a) Positive LE phenomenon<br>or<br>b) High native antiDNA antibody titres<br>or<br>c) Presence of anti-Sm antibodies<br>or<br>d) False positive tests for syphilis on 2 occasions separated by at least 6 months, confirmed by treponema immobilisation tests or by FTA-ABS | a) High native antiDNA antibody titres<br>or<br>b) Presence of anti-Sm antibodies<br>or<br>c) Positive finding of APA based on:<br>- High levels of IgG or IgM anticardiolipin antibodies<br>- Presence of lupus anticoagulant proven using standard methods.<br>- False positive tests for syphilis on 2 occasions separated by at least 6 months, confirmed by treponema immobilisation tests or by FTA-ABS |

To classify an individual as a patient with SLE they must meet 4 or more of the 11 criteria at any moment in the history of their disease.

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SLE classification criteria proposed by the SLICC group.[38]

| **A. Clinical criteria** | |
|---|---|
| 1. Acute cutaneous lupus or subacute cutaneous lupus | Malar rash (does not count if malar discoid), bullous lupus, toxic epidermal necrolysis (variant of SLE), maculopapular lupus rash, photosensitive lupus rash in the absence of dermatomyositis.<br>or<br>Subacute cutaneous lupus: Nonindurated psoriaform and/or annular polycyclic lesions, that resolve without scarring, although occasionally with post-inflammatory dyspigmentation or telangiectasias. |
| 2. Chronic cutaneous lupus | Classic discoid rash above the neck (localised) or above and below the neck (generalised), hypertrophic (verrucous) lupus), lupus panniculitis (profundus), mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/ lichen planus overlap. |
| 3. Oral ulcers | In oral cavity or tongue or nose, in the absence of other causes such as vasculitis, Behcet's disease, infection (herpes virus), inflammatory bowel disease, reactive arthritis and acidic foods. |
| 4. Nonscarring alopecia | Diffuse thinning or hair fragility with visible broken hairs, in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia. |
| 5. Joint disorder | Synovitis in 2 or more joints, characterised by swelling or effusion.<br>or<br>b) tenderness in 2 or more joints and at least 30 minutes of morning stiffness. |
| 6. Serositis | a) Pleurisy: Typical pleuritic pain for at least one day or pleural rub or pleural effusions.<br>or<br>b) Pericarditis: Typical pericardial pain (pain with recumbence improved by sitting forward) for at least one day, or pericardial effusion or pericardial rub or pericarditis shown by ECG, in the absence of other causes such as infection, uraemia and Dressler's pericarditis. |
| 7. Renal disorder | a) Urine protein–to-creatinine ratio (or 24-hour proteinuria) of over 500 mg/day<br>or<br>b) Presence of red blood cell casts in urine sediment. |
| 8. Neurological disorder | Seizures, psychosis, mononeuritis multiplex(in the absence of other known causes such as primary vasculitis), myelitis, peripheral or cranial neuropathy (in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus), acute confusional state (in the absence of other causes, including toxic/metabolic, uraemia, drugs) |
| 9. Haemolytic anaemia | |
| 10. Leucopoenia | a) Leucopoenia less than 4.000/mm$^3$ at least once: In the absence of other known causes such as Felty's syndrome, drugs, and portal hypertension.<br>or<br>b) Lymphopenia of less than 1000/mm$^3$ at least once, in the absence of other causes such as corticosteroids, other drugs and infection. |

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| | |
|---|---|
| 11. Thrombocytopenia | Less than 100,000/mm$^3$, at least once, in the absence of other causes such as drugs, portal hypertension and thrombotic thrombocytopenia purpura. |

| **B. Immunological criteria** | |
|---|---|
| ANA | Titres above laboratory reference range |
| Anti-nDNA | Titres above laboratory reference range (or 2-fold the reference range if determined by ELISA). |
| Anti-Sm antibodies | |
| Antiphospholipid antibodies | a) Lupus anticoagulant<br>b) False-positive test result for rapid plasma reagin<br>c) Medium or high-tire anticardiolipin antibody level (IgA, IgG or IgM)<br>d) Presence of anti-ß2-glycoprotein I antibodies (IgA, IgG or IgM) |
| Complement | Low levels of C3, C4 or CH50 |
| Positive Direct Coombs test | In absence of haemolytic anaemia |

Anti-nDNA: Native anti-DNA antibodies; ANA: antinuclear antibodies; ELISA: Enzyme-linked immunosorbent assay; SLE: systemic lupus erythematosus

The criteria are cumulative and they need not all be present at the same time. For an individual to be classified as SLE: a) they should meet at least four criteria, including at least one clinical criterion and one immunological criterion, or b) have proven LN via biopsy in presence of ANA or native anti-DNA antibodies.

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# Appendix 4. Other major manifestations in patients with System Lupus Erythematosus

Other frequent major manifestations in SLE patients and how to detect them:[242,244,833-835]

| Manifestation | Detection/management |
|---|---|
| Acute pneumonia (1-9%) | Serious system, similar to pneumonia infectious<br>Rule out infection<br>Chest Rx/CT<br>Bronchofibroscopy |
| Alveolar haemorrhage (25) | Cough+dyspnoea+haemoptisis<br>Chest CT<br>Bronchofibroscope with bronchoalveolar lavage (siderophages)<br>Rule out associated infection |
| DILD (3%) | Progressive dyspnoea:<br>Chest Rx/CT (high resolution<br>Complete RFTs<br>Biopsy in doubtful cases |
| Shrinking lung (0.5%) | Dyspnoea<br>xR+ complete RFTs<br>Phrenic n. stimulation studies |
| Myocarditis (≈7%) | Congestive cardiac insufficiency symptoms<br>Rule out toxicity due to HCQ or ischemic cardiopathy<br>xR+Echocardio+ECG+enzyme pattern |
| Endocarditis (50% subclinical, 4% clinical) | Dyspnoea, cardiac murmur, thrombotic phenomena<br>Echocardio (transoesophageal)<br>Rule out 2º APS |
| Myelopathy (1%) | Acute establishment<br>MRI and CSF<br>Rule out ischemic origin (2º APS) |
| Psychosis (8%) | Clinical Dx<br>MRI and CSF<br>Rule out secondary to drugs |
| Seizures (6%) | Clinical Dx<br>MRI + electroencephalogram |
| Ictus (5-18%) | Focal deficiency:<br>Rule out: 2º APS, arteriosclerosis, PTT, vasculitis, endocarditis,<br>MRI and CSF |
| Aseptic meningitis | Meningeal syndrome<br>Rule or infectious origin or by drugs (AZA, ibuprofen)<br>CSF |
| Acute confusion status (4.7%) | Rule out infectious and/or metabolic causes, drugs and PTT<br>MRI + CSF |
| Cranial neuropathy (3-16%) (includes optical neuritis, NO) | MRI<br>Evoked potentials (NO) |

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| | |
|---|---|
| Peripheral neuropathy (2-3%) | Clinical patterns: PNP, moneuritis, polyradiculopathy<br>EMG<br>CSF (if polyradiculoneuritis) and nerve biopsy (selected cases) |
| Posterior reversible encephalopathy | Confusion+crisis+blindness<br>Relationship with high blood pressure, immunosuppression<br>MRI |
| Peritonitis (up to 67% in autopsies) | Paracentesis |
| Lupus enteropathy | Possibilities: Vasculitis, thrombosis (APS). Protein-losing E.<br>CT with contrast, arteriography, angioMRI<br>Marked albumin / -1 antitrypsin in faeces |
| Lupus pancreatitis | Possibility of being drug-induced (AZA, diuretics, steroid)<br>Analytics: Amylase, lipase<br>ECHO/CT |
| Lupus hepatitis | Increase in hepatic transaminase without any other cause<br>Liver biopsy if persistent |

APS: Antiphospholipid syndrome; AZA: Azathioprine; CSF: Cerebrospinal fluid; DILD: Diffuse interstitial lung diseases; HCQ: Hydroxychloroquine; RFTs: Respiratory function tests.

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# Appendix 5. Auto-antibodies as serological markers in System Lupus Erythematosus: Detection techniques and clinical meaning

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- Anti-nuclear antibodies

The technique of choice to detect this is IIF on HeP-2 cells.

Not specific of SLE. Presented in other SADs.

- Anti-dsDNA antibodies

Specific SLE marker antibody. 40-70% in active disease and lupus nephropathy. Homogeneous nuclear IIF pattern with peripheral reinforcement.

- Anti-U1-RNP antibodies

30-40% of all lupus cases. Associated with Raynaud's phenomenon and mixed connective tissue disease.

Thick mottled nuclear IIF pattern.

- Anti-Sm antibodies

Specific SLE marker antibody. 15-30% of all cases.

Thick mottled nuclear IIF pattern.

- Anti-SSa antibody (Ro)

24-60%. Associated with LCSA (70-90%), photosensitivity, neonatal lupus (>90%), C2 and C4 deficiencies (90%) and in the majority of patients with Sjögren's syndrome associated with SLE.

Fine mottled nuclear IIF pattern, at times ANA may be negative or present a cytoplasmatic pattern in cell HEp-2.

- Anti-SSb antibody (La)

9-35%; neonatal lupus syndrome (75%).

Fine mottled nuclear IIF pattern.

- Anti-histone antibody

95% in drug-induced lupus; 50-70% other lupus; low AR titre (5-14%); homogeneous nuclear IIF pattern.

- Anti-ribosomal P antibody

Possible association with psychosis and lupus hepatitis; 10% of all lupus cases. Specific of SLE.

Diffuse cytoplasmatic IIF pattern in HEp-2 cell.

- Antiphospholipid antibodies: Lupus anticoagulant, anticardiolipin IgG and IgM, and anti-beta2 glycoprotin I, class IgG and IgM

25-30%; associated with thrombosis, recurrent foetal losses, thrombocytopenia, livedo reticularis and haemolytic anaemia. Not determined by IIF.

# Appendix 6. Histopathological classifications of lupus nephritis and its clinical repercussion

### A6.1. LUPUS NEPHRITIS (LN) Classification according to the International Nephrology Society and the Renal Pathology Society ISN/RPS (2003) (Mittal adaptation 2005)[493,513]

| | |
|---|---|
| **CLASS I** | Minimal mesangial LN (normal glomeruli by light microscopy, but with deposits in IF) |
| **CLASS II** | Mesangial proliferative LN (any degree of purely mesangial hypercellularity or mesangial matrix expansion by light microscopy with positive immune deposits. Few subepithelial or subendothelial deposits may be visible by IF or EM, but not by light microscopy) |
| **CLASS III** | Focal LN (endo- or extracapillary glomerulonephritis involving <50% of the glomeruli, with subendothelial deposits with or without mesangial alterations). |
| CLASS III (A) | Active lesions: Focal proliferative LN |
| CLASS III (A/C) | Active and chronic lesions: Focal proliferative LN and sclerosis |
| CLASS III (C) | Chronic inactive lesions with glomerular sclerosis: Focal LN with sclerosis |
| **CLASS IV** | Diffuse LN (endo- or extracapillary glomerulonephritis involving □50% of the glomeruli, with diffuse subendothelial deposits with or without mesangial alterations) |
| CLASS IV-S (A) | Segmental (<50% glomeruli) and with active lesions: Diffuse segmental proliferative LN |
| CLASS IV-G (A) | Global (<50% glomeruli) and with active lesions: Diffuse global proliferative LN |
| CLASS IV-S (A/C) | Segmental and with active lesions, and chronic/sclerosing: Diffuse segmental proliferative and sclerosing LN |
| CLASS IV-G (A/C) | Global and with active lesions, and chronic/sclerosing: Diffuse global proliferative LN and sclerosis |
| CLASS IV-S (C) | Segmental and with chronic inactive cicatricial lesions sclerosing: Diffuse LN segmental Sclerosis |
| CLASS IV-G (C) | Global and with chronic inactive cicatricial lesions sclerosing: Diffuse LN with global sclerosis |
| **CLASS V** | Membranous LN (global/segmental subepithelial immune deposits) or their morphological sequelae by light microscopy and IF/EM, with/without mesangial alterations).<br>May occur in combination with class III or IV, in which case both will be diagnosed (Class V and III, or V and IV) |
| **CLASS VI** | LN with Advanced sclerosis (□90% of glomeruli with globally sclerosing inactive residual lesions) |

Sample conditions:

Light Microsopy with at least 6 glomeruli

IF Study with 1-2 glomeruli.

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### A6.2. Activity and chronicity indices[507]

| Index | Quality | Points |
|---|---|---|
| ACTIVITY (0-24) | Endocapillary hypercellularity | 0-3 |
| | Leukocyte infiltration | 0-3 |
| | Subendothelial hyaline deposits | 0-3 |
| | Fibrinoid necrosis/karyorrhexis | (0-3) x 2 |
| | Epithelial crescents | (0-3) x 2 |
| | Interstitial inflammation | 0-3 |
| CHRONICITY (0-12) | Glomerular sclerosis | 0-3 |
| | Fibrous crescent | 0-3 |
| | Tubular atrophy | 0-3 |
| | Interstitial fibrosis | 0-3 |

### A6.3. Clinicopathological correlation and prognosis according to prevailing histological class in first renal biopsy[494,504,836,837]

| Class | Incidence | Clinical | Prognosis |
|---|---|---|---|
| **I** | <5% | None or mild microhaematuria, proteinuria | Very good |
| **II** | 10-15% | Mild-moderate proteinuria. Microhaematuria. No CKD or high blood pressure | Good |
| **III** | 10-30% | Moderate proteinuria. Microhaematuria. Nephritis syndrome ≤20%. | Good in absence of KD, except if evolves to class IV |
| **IV** | 40-60% | Nephrotic syndrome Active sediment. KD+high blood pressure 40-50% (nephrotic-nephritic syndrome) | May progress to CKD, mainly in refractory cases |
| **V** | 10-30% | Nephrotic syndrome Inactive sediment. | May evolve to CKD in patients with persistence of nephritic proteinuria |
| **VI** | <5% | CKD Residual proteinuria. | Evolves ACKD, RRT |

KD: kidney deficiency; CKD: chronic kidney deficiency; ACKD: advanced chronic kidney disease (stage 4-5); RRT: renal replacement treatment (dialysis or transplant); RAS: Renin Angiotensin system

Note: Vascular lesions are not included in the WHO-ISN/RPS classification: 1. Lupus vasculopathy (immune deposits in small arteries or arterioles, not inflammatory): asymptomatic or mild. 2. TMA (Thrombotic microangiopathy: alone or accompanying any class): worse prognosis. 3. Necrotising vasculitis (more rarely, but may accompany proliferative, above all): worse prognosis.

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### A6.4. Suggested indications for repeated renal biopsies in SLE patients

| Situation |
|---|
| - Unexplained increase of serum creatinine at any time. |
| - Refractoriness after 3-6 months of induction treatment or in maintenance phase, after 12 months without reaching complete remission for classes III and IV. |
| - Uncertainty about degree of chronicity of kidney lesions. |
| - Increase or reappearance of nephrotic proteinuria or active sediment |
| - Suspected nephropathy de novo not related to Lupus (e.g., Diabetes, thrombotic microangiopathy, etc.) |

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# Appendix 7. Most commonly used available tools to assess the disease status

**SELENA-SLEDAI activity index form**

| Weighting | Present | Descriptor | Definition |
|---|---|---|---|
| 8 | | Seizure | Recent (last 10 days). Exclude metabolic, infection or drug cause. Exclude seizure due to irreversible CNS damage. |
| 8 | | Psychosis | Altered ability to function in normal activity due to severe disturbance in perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganised or catatonic behaviour. Exclude uraemia and drug causes. |
| 8 | | Organic brain syndrome | Altered mental function with impaired orientation, memory or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment, plus at least 2 of the following: Perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infection or drug cause. |
| 8 | | Visual disturbance | Retinal change of SLE. Include cytoid bodies, retinal haemorrhages, serous exudate or haemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection or drug cause. |
| 8 | | Cranial nerve disorder | New onset of sensory or motor neuropathy, involving cranial nerves. Include vertigo due to SLE. |
| 8 | | Lupus headache | Severe persistent headache: May be migrainous, but must be refractory to opioids. |
| 8 | | CVA | New onset of cerebrovascular accident(s). Exclude arteriosclerosis or hypertensive causes. |
| 8 | | Vasculitis | Ulceration, gangrene, tender finger nodules, periungual infarction, splinter haemorrhages, or biopsy or angiogram proof of vasculitis. |

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| | | | |
|---|---|---|---|
| 4 | | Arthritis | > 2 joints with pain and signs of inflammation (tenderness, swelling or effusion). |
| 4 | | Myositis | Proximal muscle aching/weakness, associated with elevated CPK/aldolase or EMG changes or a biopsy showing myositis. |
| 4 | | Urinary casts | Haeme-granular or red blood cell casts. |
| 4 | | Haematuria | >5 red blood cells/field. Exclude stone, infection or other cause. |
| 4 | | Proteinuria | New onset or recent increase of more than 0.5g/24 hours. |
| 4 | | Pyuria | >5 white blood cells/field. Exclude infection |
| 2 | | Rash | Ongoing inflammatory rash |
| 2 | | Alopecia | Ongoing abnormal, patchy or diffuse loss of hair. |
| 2 | | Mucosal ulcers | Ongoing oral or nasal ulcerations, due to active SLE. |
| 2 | | Pleurisy | Classic and severe pleuritic chest pain or pleural rub or effusion, or new pleural thickening due to SLE. |
| 2 | | Pericarditis | Classic and severe pericardial pain or rub or effusion, or ECG confirmation. |
| 2 | | Low complement | Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory. |
| 2 | | Increased DNA binding | >25% binding by Farr assay or above normal range for testing laboratory. |
| 1 | | Fever | >38ºC. Exclude infection |
| 1 | | Thrombocytopenia | <100,000 platelets/mm$^3$. |
| 1 | | Leucopenia | <3,000 white blood cells/mm$^3$. Exclude drug causes. |
| | **TOTAL** | | |
| Note: CPK: Creatinine phosphokinase | | | |

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## BILAG activity index form

**Indicate findings that are present:**

1 Improving
2 Same
3 Worse
4 New

**Yes/No or value (where indicated)**
**❑ Indicate if <u>not due to SLE activity</u>**

**0 Not present**

CONSTITUTIONAL
1. Temperature–documented > 37.5º C ( )
2. Weight loss–unintentional > 5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

MUCOCUTANEOUS
5. Skin eruption–severe ( )
6. Skin eruption–mild ( )
7. Angio-oedema–severe ( )
8. Angio-oedema–mild ( )
9. Mucosal ulcers–severe ( )
10. Mucosal ulcers–mild ( )
11. Panniculitis/Bullous lupus–severe ( )
12. Panniculitis/Bullous lupus–mild ( )
13. Major cutaneous vasculitis/thrombosis ( )
14. Digital infarcts or nodular vasculitis ( )
15. Alopecia–severe ( )
16. Alopecia–mild ( )
17. Periungual erythema/chilblains ( )
18. Splinter haemorrhages ( )

NEUROPSYCHIATRIC
19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional status ( )
24. Psychosis ( )
25. Polyradiculoneuropathy acute vinflammatory demyelinating ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizures ( )
31. Status epilepticus ( )
32. Cerebrovascular Disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache–severe unremitting ( )
38. Headache from IC hypertension ( )

MUSCULOSKELETAL
39. Myositis–severe ( )
40. Myositis–mild ( )
41. Arthritis (severe) ( )
42. Arthritis (moderate)/Tendonitis/Tenosynovitis ( )
43. Arthritis (mild)/Arthralgia/Myalgia ( )

CARDIORESPIRATORY
44. Myocarditis–mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Pleurisy/Pericarditis ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/vasculitis ( )
52. Interstitial alveolitis/pneumonitis ( )
53. Shrinking lung syndrome ( )
54. Aortitis ( )
55. Coronary vasculitis ( )

GASTROINTESTINAL
56. Lupus peritonitis ( )
57. Abdominal serositis or ascites ( )
58. Lupus enteritis/colitis ( )
59. Malabsorption ( )
60. Protein losing enteropathy ( )
61. Intestinal pseudo-obstruction ( )
62. Lupus hepatitis ( )
63. Acute lupus cholecystitis ( )
64. Acute lupus pancreatitis ( )

OPHTHALMIC
65. Orbital inflammation/myositis/proptosis ( )
66. Keratitis–severe ( )
67. Keratitis–mild ( )
68. Anterior uveitis ( )
69. Posterior uveitis/ retinal vasculitis–severe ( )
70. Posterior uveitis/ retinal vasculitis–mild ( )
71. Episcleritis ( )
72. Scleritis–severe ( )
73. Scleritis–mild ( )
74. Retinal/choroidal vaso-occlusive disease ( )
75. Cotton–wool spots (cytoid bodies) ( )
76. Optic neuritis ( )
77. Anterior ischemic optic neuropathy ( )

RENAL
78. Systolic Blood Pressure (mmHg) Value ( ) ❑
79. Diastolic Blood Pressure (mmHg) Value ( ) ❑
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) ❑
82. Urine albumin-creatinine ratio mg/mmol ( ) ❑
83. Urine protein-creatinine ratio mg/mmol ( ) ❑
84. 24-hour urine protein (g) value ( ) ❑
85. Nephrotic syndrome Yes/No ( )
86. Creatinine (plasma/serum) µmol/l ( ) ❑
87. GFR (calculated) ml/min/1.73 $m^2$ ( )
88. Active urinary sediment. Yes/No ( )

**Weight (kg):**
**Serum urea (mmol/l):**
**African ancestry: Yes / No**
**Serum albumin (g/l):**

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## SLICC / ACR DI damage index form

| | Points | Date |
|---|---|---|
| **OCULAR** | | |
| Cataract(s) at any time in either eye (documented by ophthalmoscope) | 1 | |
| Retina changes or optic atrophy (documented with ophthalmologic examination) | 1 | |
| **NEUROPSYCHIATRIC** | | |
| Cognitive impairment (for example: Memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language,…) or major psychosis | 1 | |
| Seizures requiring therapy for 6 months | 1 | |
| Cerebrovascular accident or surgical resection (for non-malignant cause) (***score 2 if >1***). | 1 2 | |
| Cranial or peripheral neuropathy (excluding optic) | 1 | |
| Transverse myelitis | 1 | |
| **RENAL** | | |
| GFR (estimated/measured) <50% | 1 | |
| Proteinuria ≥ 3.5g/24 hours | 1 | |
| or | | |
| End-stage renal disease (regardless of dialysis or renal transplant) | 3 | |
| **PULMONARY** | | |
| Pulmonary hypertension (right ventricular prominence or loud P2) | 1 | |
| Pulmonary fibrosis (physical examination and radiograph) | 1 | |
| Shrinking lung (radiograph) | 1 | |
| Pleural fibrosis (radiograph) | 1 | |
| Pulmonary infarction (radiograph) or surgical resection (due to non-malignant cause) | 1 | |
| **CARDIOVASCULAR** | | |
| Angina or coronary bypass | 1 | |
| Myocardial infarction (***score 2 if > 1***) | 1 2 | |
| Cardiomyopathy (ventricular dysfunction) | 1 | |
| Valvular disease (diastolic or systolic murmur > 3/6) | 1 | |
| Pericarditis for 6 months, or pericardiectomy | 1 | |
| **PERIPHERAL VASCULAR** | | |
| Claudication for 6 months | 1 | |
| Minor tissue loss (pulp space) | 1 | |
| Significant tissue loss (finger or limb) (***score 2 if > 1***) | 1 2 | |
| Venous thrombosis with swelling, ulceration or clinical evidence of venous statis | 1 | |
| **GASTROINTESTINAL** | | |
| Infarction or intestinal resection below duodenum, spleen, liver or gall bladder, for any cause (***score 2 if > 1***) | 1 2 | |
| Mesenteric insufficiency | 1 | |
| Chronic peritonitis | 1 | |
| Stricture or upper gastrointestinal tract surgery | 1 | |
| Pancreatic insufficiency requiring enzyme replacement | 1 | |
| **MUSCULOSKELETAL** | | |
| Muscle atrophy or weakness | 1 | |
| Deforming or erosive arthritis (including reversible deformities, excluding avascular necrosis). | 1 | |
| Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis) | 1 | |
| Avascular necrosis (diagnosed by radiological image) (***score 2 if > 1***) | 1 2 | |
| Osteomyelitis (with microbiological evidence) | 1 | |
| Tendon breakage | 1 | |
| **SKIN** | | |
| Scarring chronic alopecia | 1 | |
| Extensive scarring or panniculum (other than scalp and pulp space) | 1 | |
| Skin ulceration for > 6 months (excluding thrombosis) | 1 | |
| **PREMATURE GONADAL FAILURE** (secondary amenorrhea before the age of 40) | 1 | |
| **DIABETES MELLITUS** (regardless of treatment) | 1 | |
| **MALIGNANCY** (excluding dysplasia) (***score 2 if > 1 site***) | 1 2 | |

Assessment Dates:

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Fatigue Severity Scale (FSS) Form

| **Statement** | **Degree of agreement** | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 1. My motivation is lower when I am fatigued | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. Exercise brings on my fatigue | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. I am easily fatigued | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. Fatigue interferes with my physical functioning | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. Fatigue causes frequent problems for me | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. My fatigue prevents sustained physical functioning | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7. Fatigue interferes with carrying out certain duties and responsibilities | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8. Fatigue is one of my three most disabling symptoms. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9. Fatigue interferes with my work, family or social life | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| **Total Score** | | | | | | | ☐ |

The scale from 1 to 7 represents the degree of agreement: From 1, indicating strongly agree, to 7, indicating strongly disagree.

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## Form of the health-related quality of life questionnaire, specific of SLE: Lupus QoL (McElhone y cols)

**(Version adapted and validated by Peralta-Ramirez & Col)**

**Name_____Age:_____Date_____**

**This questionnaire is designed to find out how lupus affects your life. Read each question and then circle the answer, which will be the one that is closest to how you feel. Please try to answer all the questions as honestly as possible.**

**How often has this occurred to you over the last 4 weeks.**

1. **Because of my lupus I need help to do hard physical work such as dig the garden, paint and/or decorate, move furniture,…**
   All the time Most of the time Sometimes Occasionally Never
2. **Because of my lupus I need help to do moderate physical work such as vacuum cleaning, ironing, going shopping, cleaning the bathroom,…**
   All the time Most of the time Sometimes Occasionally Never
3. **Because of my lupus I need help to do light physical chores such as cooking or preparing the meal, opening a can, dusting, combing my hair or attending to my personal hygiene,…**
   All the time Most of the time Sometimes Occasionally Never
4. **Because of my lupus, I am unable to do daily tasks or do my work, care for the children or household chores as well as I would like.**
   All the time Most of the time Sometimes Occasionally Never
5. **Because of my lupus I find it difficult to walk upstairs.**
   All the time Most of the time Sometimes Occasionally Never
6. **Because of my lupus I have partly lost my independence and I am more dependent on others.**
   All the time Most of the time Sometimes Occasionally Never
7. **I have to do things at a slower pace because of my lupus.**
   All the time Most of the time Sometimes Occasionally Never
8. **Because of my lupus my sleep pattern has been disturbed.**
   All the time Most of the time Sometimes Occasionally Never

**How often has this occurred to you over the last 4 weeks.**

9. **I have been prevented from carrying out jobs that I like because of the pain produced by lupus.**
   All the time Most of the time Sometimes Occasionally Never
10. **Because of my lupus, the pain that I experience interferes with the quality of my sleep.**
    All the time Most of the time Sometimes Occasionally Never
11. **The pain produced by lupus is so severe that it limits my mobility.**
    All the time Most of the time Sometimes Occasionally Never
12. **Because of my lupus I avoid planning to attend future events.**
    All the time Most of the time Sometimes Occasionally Never
13. **Because of the lack of predictability of my lupus, I am unable to organise my life efficiently.**
    All the time Most of the time Sometimes Occasionally Never
14. **My lupus changes from one day to the next making it difficult for me to commit myself to social events.**
    All the time Most of the time Sometimes Occasionally Never
15. **Because of the pain I suffer due to lupus I am less interested in sexual relations.**
    All the time Most of the time Sometimes Occasionally Never
16. **Because of the lupus I am not interested in sex.**
    All the time Most of the time Sometimes Occasionally Never
17. **I am concerned that my lupus is stressful for people around me.**
    All the time Most of the time Sometimes Occasionally Never
18. **Because of my lupus I am concerned that I may cause problems for people close to me.**
    All the time Most of the time Sometimes Occasionally Never
19. **Because of my lupus I feel that I am a burden for my friends and/or my family.**
    All the time Most of the time Sometimes Occasionally Never

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**Over the last 4 weeks, I have found that my lupus makes me**

**20. Resentful**
All the time Most of the time Sometimes Occasionally Never

**21. Fed up and that nothing can liven me up.**
All the time Most of the time Sometimes Occasionally Never

**22. Sad.**
All the time Most of the time Sometimes Occasionally Never

**23. Anxious.**
All the time Most of the time Sometimes Occasionally Never

**24. Worried.**
All the time Most of the time Sometimes Occasionally Never

**25. With loss of self-confidence.**
All the time Most of the time Sometimes Occasionally Never

**How often has this occurred to you over the last 4 weeks.**

**26. My physical appearance, produced by lupus, interferes with my way of enjoying life.**
All the time Most of the time Sometimes Occasionally Never

**27. Because of my lupus, my appearance (e.g., rashes, weight loss or gain) makes me avoid social situations.**
All the time Most of the time Sometimes Occasionally Never

**28. Skin rashes caused by lupus make me feel less attractive.**
All the time Most of the time Sometimes Occasionally Never

**How often has this occurred to you over the last 4 weeks.**

**29. The hair loss I have experienced because of my lupus makes me feel less attractive.**
All the time Most of the time Sometimes Occasionally Never

**30. The increase in weight loss I have experienced because of the lupus treatment makes me feel less attractive.**
All the time Most of the time Sometimes Occasionally Never

**31. Because of my lupus, I cannot concentrate for long periods of time.**
All the time Most of the time Sometimes Occasionally Never

**32. Because of my lupus I feel exhausted and slow.**
All the time Most of the time Sometimes Occasionally Never

**33. Because of my lupus I need to go to bed early.**
All the time Most of the time Sometimes Occasionally Never

**34. Because of my lupus I often feel exhausted in the mornings.**
All the time Most of the time Sometimes Occasionally Never

**Please feel free to make any additional comments**

**Please check that you have answered all the questions**

**Thank you very much for completing this questionnaire**

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# Appendix 8. Measures to prevent cardiovascular events in patients with System Lupus Erythematosus

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**Types of measures:**

1. Class I: Supported by scientific evidence
2. Class II: Recommended but without sufficient scientific evidence
3. Class III: Not recommended

**CLASS I MEASUREMENTS**

1. General measures:
    a. Stop smoking
    b. Balanced diet
    c. Physical exercise
    d. Avoid being overweight
2. Blood Pressure: Therapeutic intervention if:
    a. > 149/90
    b. > 130/80 if kidney disease or diabetes mellitus
3. LDL: Therapeutic intervention if:
    a. ≥ 130 mg/dl
    b. > 100 mg/dl (diabetes mellitus, cardiac disease, chronic kidney disease)
4. Anti-aggregation if:
    a. Cerebrovascular disease (> 65 years)
    b. Cardiac disease
    c. Atrial fibrillation
    d. Positive antiphospholipids

**CLASS II MEASURES**

1. Treatment with omega-3 (1800 mg/24h)
2. Reach LDL<70 mg/dl (women with risk factors)
3. Treatment with niacine and/or fibrates to reach HDL>50 mg/dl
4. Glycaemic control (HbA<7)

**CLASS III MEASURES**

1. Hormone replacement therapy or SERMS (as protective treatment against cardiovascular risk)
2. Use of anti-oxidants
3. Folic acid
4. Routine anti-aggregation in < 65 years

# Appendix 9. Classification, properties and side effects of sun filters

## CLASSIFICATION OF SUN FILTERS

1) **Organic filters:** They absorb UV RADIATION of a certain wavelength depending on their chemical structure.

a. UVB filters:
   i. Para-aminobenzoic acid (PABA) and byproducts (Padimat O)
   ii. Cinnamates (Octinoxate, Cinoxate)
   iii. Salicylates (Octisalate, Homosalate, Trolamaine salicylate)
   iv. Others: Octocrylene, Ensulizole

b. UVA filters:
   i. Benzophenones (Oxybenzone, Sulisobenzone, Dioxybenzone)
   ii. Avobenzone
   iii. Meradimate

c. Broad spectrum photoprotectors (UVA + UVB):
   i. Ecamsule (Mexoryl SX)
   ii. Silatriazol (Mexoryl XL)
   iii. Bemotrizinol (Tinosob S)
   iv. Bisoctrizol (Tinosorb M)

2) **Inorganic filters:** They work by reflecting, dispersing or absorbing UV radiation. The most commonly used are zinc oxide and titanium dioxide.

Organic filters act by absorbing UV radiation and converting it into heat. PABA is the most powerful UVB filter and it is water-resistant, but it has been replaced by by-products with less capacity to produce contact allergy and without the PABA property of staining the skin, such as Padimate O.[838,839] Cinnamates are less sensitising and they do not stain but they are less water resistant and they require frequent reapplications.[839,840] Salicylates are less powerful but safer, and they are used at high concentrations to use the photostability of other ingredients, but octocrylene also does this. The advantage of ensulizol is that it is hydrosoluble and can be incorporated into daily moisturising creams.[840]

Benzophenones provide a broad protection spectrum against UVA and UVB, but they are photo-unstable and require being formulated with other ingredients that make them more stable.[840]

Mexoryl SX is a broad spectrum filter, able to reduce pigmentation, the formation of pyrimidine dimers, the accumulation of p53, the alteration of the density of Langerhans cells and photodermatosis.[841]

Inorganic agents act by UV light and IR radiation. Zinc oxide offers greater protection against UVA radiation, whilst titanium dioxide does so against UVB radiation.[842] Due to their reduced cosmetic properties, these filters were not very popular until new formulations based on nanoparticles (10-50 nm) appeared.[839] Due to their photostability, they are the filters of choice for children and for people who are predisposed to contact dermatitis.[840] They are also able to protect against visible light in diseases that are accompanied by photosensitivity.[843]

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In addition to the organic and inorganic filters (also called chemical and physical filters, respectively), secondary photoprotection consists in adding active agents that interfere or interact in the photochemical process that might lead to harm in the DNA. These are the antioxidants (Vitamins C and E, polyphenols), osmolites (taurine13, ectoine14 and DNA repairing enzymes).[844]

## PROPERTIES OF SUN FILTERS

When sufficient quantity is applied (2 mg/cm$^2$), photoprotectors are efficient in preventing acute sunburn and tanning; it has also been proven that they can reduce immunosuppression, photocarcinogenesis and photoageing.[1]

**Photoprotection indices**[845]

1) Sun Protection Factor (SPF) or Protection Index (PI)

This tells us the number of times that the photoprotector increases the skin's natural capacity to protect itself against erythema or reddening prior to burning, so it is giving us information about protection against UVB.

The cosmetic industry uses different methodologies to determine the SPF, so, depending on the origin of the cosmetics, we can find different indices that cannot be compared to each other:

- ➔ FDA or American, in force in the United States
- ➔ DIN or German. Protection index whose value is half the previous value. Currently not in use.
- ➔ SAA or Australian, resulting from the combination of FDA and DIN
- ➔ COLIPA o European method, which is the most broadly used today.

To calculate the SPF, the minimal dose of UV radiation that produces the first perceived erythematic reaction on human skin (MED) is evaluated. The MED is determined with and without photoprotection. The relationship between the two is the SPF.

Current trends, using the COLIPA method, classify the products into different types or categories, depending on the SPF.

| TYPE OF PHOTOPROTECTOR | SPF |
|---|---|
| **Low** | 2-4-6 |
| **Medium** | 8-10-12 |
| **High** | 15-20-25 |
| **Very high** | 30-40-50 |
| **Ultra** | 50 + |

2) UVA protection

There are several methods to evaluate UVA protection indices, although there is no official or recommended evaluation method. In vivo methods, or methods based on the capacity to produce immediate pigment darkening (IPD) or persistent pigment darkening (PPD) are used. There are also in vitro methods based on the radiation transmittance capacity on the product (DIFFEY).

3) IR protection

There are no official or recommended methods to assess this protection index.

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### Water resistance

There are two degrees that reflect the skin protection capacity when entering into contact with a humid medium.

*Water resistant*: When the photoprotection has not lost its protection capacity after being immersed in water for 40 minutes.

*Waterproof*: When the photoprotection has not lost its protection capacity after being immersed in water for 80 minutes.

## SIDE EFFECTS OF SUN FILTERS

1) Contact dermatitis: Although an itchiness feeling is usually a relatively frequent subjective symptom,[846] real contact dermatitis is infrequent or perhaps underdiagnosed. PABA and oxybenzone are the most commonly involved photoallergens, followed by avobenzone, sulisobenzone, octinoxate and padimate O.[847] Salicilates, Mexoryl SX and inorganic agents cannot penetrate the corneal stratum and therefore rarely act as photosensitisers.[82,840]
   There are opposing opinions regarding the penetration capacity of nanosomate particles. Some authors state that they increase the production of free radicals,[848] while for others, these particles remain on the surface of the skin.[849]
2) Effects on Vitamin D synthesis: 90% of the Vitamin D required is synthesised through exposure to UVB radiation.[850]
   The adequate use of a SPF 15 sunscreen can reduce Vitamin D synthesis by 98%. Some authors suggest that the regular use of high photoprotectors may cause vitamin D insufficiency. However, others consider that it does not affect the serum levels, probably because part of the vitamin D is ingested in the diet, because usually a sufficient amount of photoprotector is not normally used and because part of the UVB radiation is able to penetrate the skin despite the use of the photoprotector.[851,852] However, in people at risk, it is recommendable to measure the Vitamin D levels and supplement them if necessary.[853]
3) Hormone effects: Some photoprotectors (oxybenzone, avobenzone, octinoxate, padimate O) have presented oestrogen/antiandrogen effects in animal models. Further studies on humans are required to be able to verify these effects.[848]

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# Appendix 10. Topical corticosteroids

<table>
<tr><th colspan="2">POWER OF CORTICOSTEROIDS854</th></tr>
<tr><td>CLASS 1: Superpotent<br>➔ Betamethasone dipropionate 0.05%, optimised vehicle<br>➔ Clobetasol propionate 0.05%<br>➔ Diflorasone diacetate 0.05%<br>➔ Fluocinonide 0.1%, optimised vehicle<br>➔ Flurandrenolide, 4 mg/cm2<br>➔ Halobetasol propionate 0.05%</td><td>CLASS 4: Mid-strength:<br>➔ Betamethasone valerate 0.12%<br>➔ Clocortolone pivalate 0.1%<br>➔ Desoximetasone 0.05%<br>➔ Fluocinolone acetonide 0.025%<br>➔ Flurandrenolide 0.05%<br>➔ Hydrocortisone probutate 0.1%<br>➔ Hydrocortisone valerate 0.2%<br>➔ Prednicarbate 0.1%<br>➔ Triamcinolone acetonide 0.1%</td></tr>
<tr><td>CLASS 2: High potent<br>Amcinonide 0.1%<br>Betamethasone dipropionate 0.05%<br>Desoximetasone 0.25%<br>Desoximetasone 0.5%<br>Diflorasone diacetate 0.05%<br>Fluocinonide 0.05%<br>Halcinonide 0.1%<br>Mometasone furoate 0.1%</td><td>CLASS 5: Lower mid-strength<br>Betamethasone dipropionate 0.05%<br>Betamethasone valerate 0.1%<br>Fluocinolone acetonide 0.025%<br>Flurandrenolide 0.05%<br>Fluticasone propionate 0.05%<br>Hydrocortisone butirate 0.1%<br>Hydrocortisone valerate 0.2%<br>Prednicarbate 0.1%<br>Triamcinolone acetonide 0.1%</td></tr>
<tr><td>CLASS 3: Upper mid-strength<br>Amcinonide 0.1%<br>Betamethasone dipropionate 0.05%<br>Betamethasone valerate 0.1%<br>Diflorasone diacetate 0.05%<br>Fluocinonide 0.05%<br>Fluticasone propionate 0.005%</td><td>CLASS 6: LOW POTENT<br>Alclometasone dipropionate 0.01%<br>Desonide 0.05%<br>Fluocinolone acetonide 0.01%</td></tr>
<tr><td colspan="2">CLASS 7: Least potent<br>Topical agents in dexametasone, flumetasone, hydrocortisone<br>Methylprednisolone, prednisone</td></tr>
</table>

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# Appendix 11. Health needs and priorities of people with System Lupus Erythematosus

## Results of the SR of literature

With respect to physical health, the most relevant problems that can be drawn from the SRs, were intense fatigue; muscle and joint pains, headaches, concerns for physical aspect (skin lesions and rashes), photosensitivity, problems with exposure to cold or heat, mouth sours, weight and hair loss, chronic lumbalgia and dental problems.

The most important problems that affect psychic well-being are confined to mood disorders and more importantly to depression and reduction in self-esteem.

Problems are also identified in the family environment, which mainly have to do with the need for support in all aspects related to daily life, and especially, with alterations in sex life.

With regards to the economic consequences of SLE, practically all the studies from North America and Europe point to considerable economic repercussions that have to do with the use of services that are not covered by the public administrations or medical insurance. In these same studies, attention is drawn to the limited satisfaction with the health services that patients receive. The most commonly mentioned reasons are: Lack of understanding and limited sensitivity of health personnel, as well as difficulty to access consultations with specialists. 20% of the SLE patients consult physiotherapists and alternative health professionals such as acupuncture specialists, naturopaths or quiropractitioners.

Demands for information and little satisfaction with the answers received are very frequent, especially when the information comes from specialist physicians. This information was frequently insufficient and confusing for patients. Almost half the patients demand more information to self-manage the disease, about healthy lifestyles (exercises, diet), and about medical treatment alternatives. Patients expect this information to be available in different formats, with greater scientific quality and to be more accessible.

## Result of consultation with patients (Spanish context)

Out of the contributions from more than 100 people affected by SLE who completed the three Delphi consultation rounds, the following final results were obtained:

The prioritised health problems were joint pains, intense fatigue, photosensitivity, mood disorders (depression/anxiety), kidney damage, generalised pains and lack of concentration, and loss of memory.

With respect to the health care offered by the public health services for problems such as fatigue, generalised pains, mood disorders (depression/anxiety), and skin lesions derived from photosensitivity (due to the cost of the photoprotectors); patients considered them to be not very satisfactory. Patients are aware that these manifestations of the disease do not limit life expectancy, so they may not be of maximum priority for the professionals; however, they demand better health-care responses due to the important limitation that they produce on their quality of life. Furthermore, they consider that organisational improvements are very necessary, which will contribute to the coordination between the different specialists who intervene in their care, and between these and the general practitioner; suggesting the possibility of considering and assessing the possible role of "comprehensive units". Another frequent demand is to include psychological therapy among the benefits they receive. These improvements in organisation and in the service

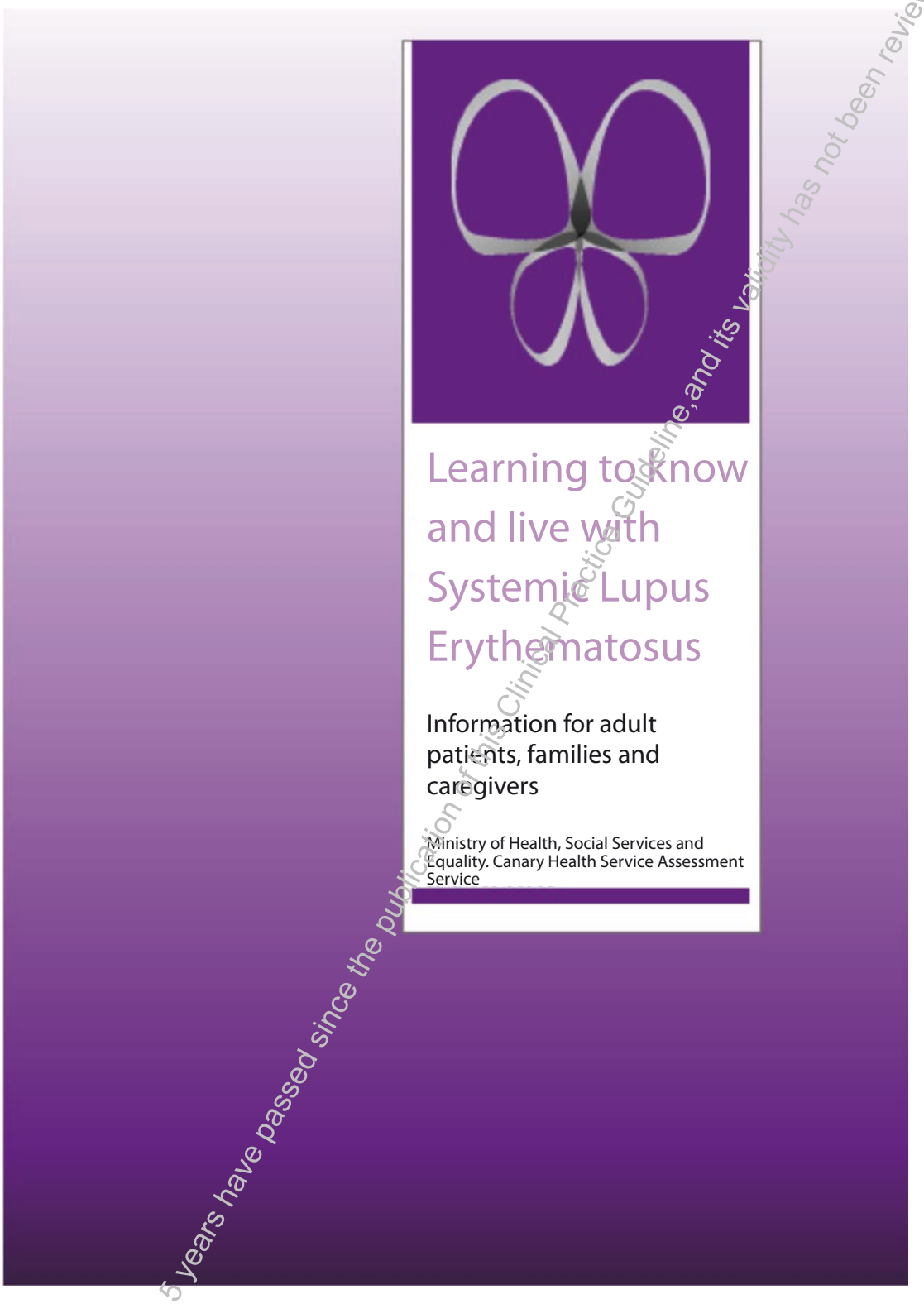
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offer should help improve health-care quality and reduce patients' waiting times.

Finally, regarding the therapeutic alternatives that SLE patients would like to have better access to, they emphasise the need to receive clear and valid recommendations on food, exercises and other healthy lifestyles, as well as clear and reliable recommendations (that do not vary from one health professional to another) about self-care of SLE. They point out the need to improve access to physiotherapy and psychotherapy services, and they would like to be able to have access to homeopathic care.

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# Appendix 12. Patient information




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## Declaration of interest

The financing entity has had no influence on the content and management of the recommendations given in this document.

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This *Information for adults with Systemic Lupus Erythematosus, relatives and/or caregivers* forms part of the document:

Clinical Practice Guideline on Systemic Lupus Erythematosus. (Spanish) Ministry of Health, Social Services and Equality. Assessment Service of the Canary Is. Health Service; 2013 Clinical Practice Guidelines in the SNS (Spanish National Health System. SESCS No. 2012/02.

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This information as well as the full version and abridged version of the aforementioned Clinical Practice Guideline, is also available in electronic format on the Guia-Salud website (www.guiasalud.es) and on the Canary Health Service Assessment Service website (SESCS) (www.sescs.es).

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## Presentation

This document is aimed at people who have Systemic Lupus Erythematosus and it may also be helpful for their families and caregivers.

The information in this guide will help provide a better knowledge of the basic issues of Systemic Lupus Erythematosus, contributing to improve the knowledge and self-care of people affected, with the aim of improving their quality of life. This document includes information about the diagnosis and treatment of Systemic Lupus Erythematosus, advice on how to manage the disease on a day-to-day basis, and other useful resources such as contacts of patients' associations or online resources. This information does not substitute the opinion or evaluation of your doctor or other health professionals. The aim of the information provided is to complement that offered by the health team that cares for you, and will act as a guide so you can learn more about your health problems, based on the best available scientific evidence.

The recommendations contained in this guideline are based on scientific studies published. The best methodological quality studies were selected and then the information agreed by the group that has developed the guideline was extracted. A group of people affected by Systemic Lupus Erythmatosus was also consulted in order to provide information about their needs and preferences with respect to the disease.

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## What is Systemic Lupus Erythematosus?

Systemic Lupus Erythematosus (from hereinafter only Lupus) is a chronic inflammatory, non-contagious, disease of the immune system, which affects and attacks healthy cells and tissues. The immune system is responsible for combating external aggressions or foreign substances in the body, such as bacteria and virus. When there is an autoimmune disease, the immune system is out of control and the body starts to attack its own cells. In Lupus, more specifically, the organism creates antibodies that appear in the blood flow, causing inflammation and damaging the actual tissue.

Lupus is a disease that may affect many parts of the body (practically any organ or system), although the most frequently involved areas are the joints, the skin, kidneys, lungs and the nervous system. It appears in a different way in each person. If you have Lupus, several parts of your body may be affected; however, it is practically impossible for all the organs of a person to be affected.

The disease usually progresses with activity flares that can be treated and, in many cases, prevented.

It is estimated that, in Spain, 9 out of every 10,000 inhabitants have Lupus, 90% of whom are women, mainly aged between 15 and 55 years of age. In general, patients with Lupus, in our environment, present a mild or moderate severity of the disease.

Over the last years, the survival of patients with Lupus has gradually come on a par with that of the general population, so Lupus is considered as a chronic autoimmune disease.

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## What are the symptoms?

Lupus presents a wide variety of symptoms, and its evolution and prognosis are very variable.

In general, Lupus appears with a mixture of muscle, joint, skin or haematological symptoms, and of the immune system, in addition to general symptoms such as fatigue or fever. There are patients in whom Lupus is manifested through the impairment of different organs (kidney or brain, for example). In general, the main symptoms over the first years of the disease tend to continue later one.

The symptoms that may arise due to Lupus are described below, both at the onset and during the evolution of the disease:

### ► General symptoms

**Fever**, **fatigue** and **weight loss** are the so-called "general symptoms", which are present in the majority of patients with Lupus.

### ► Symptoms of organ or system impairment

The most frequent are:

✓ **Arthritis** (joint swelling) and **arthralgia** (joint pain). More than 90% of patients present one of these two symptoms through the evolution of the disease.

✓ **Skin and mucosa impairment**. This occurs in 60% of patients at onset of the disease, and up to 80% during the evolution of the disease. By order of frequency, the following are manifested:

- **Malar rash**, which consists of swelling and reddening of the nose and cheeks, which may cause pain, a burning feeling and taut skin. It usually has a butterfly shape, and is normally related to exposure to the sun. It is the most typical symptom of Lupus.
- **Other skin conditions** include discoid, chronic and scarring Lupus; sub-acute Lupus or other different skin rashes.
- Alopecia or **unusual hair loss** (especially in the scalp).
- **Ulcers or aphtas** (open and painful ulcers) in the mouth.
- Purpura (**purple**-coloured **spots** on the skin) and **urticaria**, although they are much less frequent.

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✓ **Raynaud's phenomenon.** This is a very normal symptom, especially at the onset of the disease, and it is characterised by the presence of **paleness, numbness and coldness of the fingers**. Sometimes, the fingers can go from white to blue. When the episode ends, the blood circulates again, the fingers turn red and a tingling, burning sensation appears.

✓ **Kidney disease.** This is an important manifestation in Lupus and it occurs in 50-70% of the patients. The kidney swells, losing proteins (proteinuria) and it cannot eliminate waste from the organism properly, so this accumulates in the blood.

✓ **Neuropsychiatric impairment and cerebrovascular manifestations.** This usually appears during the first years of the disease (28% of patients with Lupus). The most frequent neuropsychiatric symptoms are **headaches, depression, seizures, anxiety** and **reduction of cognitive functions** (orientation, language, memory,…). On the other hand, the **cerebrovascular disease** usually appears in a thromboembolic manner, above all, (presence of a blood clot or "thrombus" that obstructs the blood flow to certain parts of the brain). The presence of these symptoms can only be attributed directly to Lupus in one out of every three people.

✓ **Pulmonary manifestations.** In the course of Lupus, **pleurisy** (swelling of the membrane that covers the lungs), **interstitial pneumonitis** (swelling with scarring of the lungs) and **pulmonary hypertension** (higher pressure than normal in lung arteries) can appear. The last two are not very frequent but pleurisy occurs in half the patients with Lupus throughout the disease, although it rarely appears at the onset of the illness. These symptoms usually appear as **chest pain accompanied by difficulty in breathing.**

✓ **Gastrointestinal symptoms.** These are frequent in patients with Lupus, but they are usually more associated with the treatment rather than the disease itself. Noteworthy are **gastritis** (inflammation or swelling of the stomach coating) and **peptic ulcer** (sore in the mucosa that coats the stomach), related to non-steroid anti-inflammatory drugs and/or glucocorticoids.

✓ **Haematological manifestations.** These appear at the onset of the disease in 23% of the patients; however, during the course of Lupus, they may affect 80% of the patients. The most frequent haematological manifestations include: **reduction** in number of white blood cells, followed by reduction of **red blood cells** (anaemia) and of **platelets** (thrombocytopenia).

✓ **Antiphospholipid syndrome.** This syndrome is associated with the presence of **thrombi** (blood clots) in arteries and veins. In pregnant women

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it is usually associated with complications such as **spontaneous repetition miscarriages**, foetal deaths, premature births and preeclampsia (serious form of high blood pressure, induced by pregnancy).

The symptoms described tend to appear and disappear. When the symptoms appear they are called «**flares**». The flares vary from mild-moderate to strong. New symptoms may appear at any time.

**REMEMBER:**

**Recognising the alert signs before a flare occurs may help you prevent or reduce the intensity of it.**

**Visit your doctor when symptoms appear, such as:**

**Exhaustion, pain, skin lesions, fever, swelling of joints or feet, dizziness...**

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## What are the causes?

The cause or causes of Lupus are unknown. Research shows that genetics play an important role, but genes alone do not determine who suffers from Lupus. Sometimes, Lupus is repeated in families, which indicates the existence of a hereditary predisposition. Even so, this predisposition does not mean that you are going to develop Lupus. There are probably several factors that contribute to the origin of this disease. These may include hormone, infectious and environmental factors (exposure to sun, medication, stress…).

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## How is it diagnosed?

In clinical practice, the combination of symptoms and immunological alterations typical of Lupus are normally taken into account when making the diagnosis.

The different forms of presentation of Lupus and the many different clinical characteristics during its evolution mean that it is generally complicated to diagnose.

The confirmation diagnosis of Lupus will require the presence of suggestive symptoms that affect two or more organs or systems. After the presence of these symptoms, the health professional will proceed to carry out blood analyses that will help confirm or rule out this disease. Obtaining a diagnosis may be difficult and it may take months or years. This difficulty is due to the fact that the manifestations required to establish the diagnosis do not usually appear at the same time, but rather, they appear gradually over time.

To obtain a diagnosis, your doctor should consider, among other things: 1'

- ✓ Your clinical history
- ✓ A complete examination
- ✓ Blood tests
- ✓ Biopsy of the skin or of the kidneys

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## Which are its most frequent complications?

Some complications may appear during the course of Lupus. One of these problems is atherosclerosis (obstruction of the arteries). This problem increases the risk of heart attacks, cardiac insufficiency, and cerebral vascular accidents. For this reason, special attention should be paid to risk factors (high blood pressure and cholesterol levels, overweight, sedentary lifestyle, smoking,..), fostering healthy living habits (for example, doing exercise and following a balanced diet).

Lupus may also cause damage to the kidney and derive in renal insufficiency (possibly requiring dialysis). You can help prevent these severe problems by consulting your doctor when the first symptoms appear. These include:

- ✓ High blood pressure
- ✓ Swelling of feet and hands
- ✓ Swelling around the eyes
- ✓ Changes in urine (presence of blood or foam in the urine, need to urinate more at night, having difficulties or feeling pain when urinating)

It seems that Lupus and its treatment may also increase the risk of suffering osteoporosis (decalcification of the bones), so your bones become less dense and more likely to break. You should try to maintain a balanced diet, rich in calcium and vitamin D, doing physical exercise on a regular basis, and consulting your doctor if you are a candidate to bone density test (especially if receiving treatment with corticosteroids.

Patients with Lupus have a high risk of infections. Certain vaccines may help reduce the risk of some infections.

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## What treatments exist? What are its risks and benefits?

Lupus has no cure today, so its treatment focuses on controlling its manifestations. As Lupus may affect different organs of the body, which vary depending on the patient, treatment will be personalised. It should be taken into account that the treatments applied may become very aggressive and generate considerable side effects.

There are five main objectives of treating Lupus:

1. Controlling symptoms as soon as possible

2. Reducing flares

3. Avoiding irreversible damage to organs

4. Reducing the risk of complications associated with the disease

5. Reducing the risk of side effects of the medication

When treating the manifestations of Lupus, these can be divided into two blocks:

1. **Minor manifestations or those that do not endanger the patient's life**. This block includes fever, joint swelling (arthritis), skin lesions and inflammation of different membranes.

2. **Major manifestations or that may be life-threatening for the patient**. Noteworthy among these are impairment of the kidney, central nervous system, blood cells (in form of anaemia or reduction of platelets), lung and heart.

Depending on the severity, the doctor may choose from among the drugs indicated below, adjusting the treatment and its possible toxicity to the affect that the disease has. It is very important to bear in mind that we should avoid producing more harm with the treatments than the harm that Lupus could cause.

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**BEAR IN MIND THAT:**

**Lupus is manifested in different ways, so the treatment will depend on the symptoms, severity and duration.**

The drugs that are normally recommended for treating Lupus include:

► Non-steroid anti-inflammatory drugs

Non-steroid anti-inflammatory drugs are drugs that combat inflammation. However, in Lupus, their use is restricted to short symptomatic treatments, basically in cases with joint conditions, as, in general, they cannot control the disease by themselves. They are usually well-tolerated, but it may be recommendable to use them together with gastric protectors, especially if taken together with corticosteroids.

Although the most important side effects of these drugs are digestive-related, there is also a risk of adverse effects at kidney and cardiovascular level (high blood pressure and cardiac insufficiency in susceptible patients).

**REMEMBER:**

**Consult your doctor before taking any non-prescribed medication for treating lupus**

► Glucocorticoids

This is an important group of drugs used to control many of the manifestations of Lupus. Glucocorticoids are anti-inflammatory and they have a powerful and generally fast effect, so they are very useful in acute flares of the disease. However, they also have many and very serious adverse effects, with capacity to product irreversible organ damage at several levels (diabetes, high blood pressure, osteoporosis, bone infarcts –destruction of part of the bone due to lack of vascularisation–, etc.), producing infections and changes in physical aspect (obesity, increase of body hair, stretch marks), which may condition the lives of patients as much or more so than the actual Lupus. Over the last few years it has been established that high doses of oral glucocorticoids (prednisone) should be avoided whenever possible, limiting the administration time as much as possible. Prolonged treatments with more than 5 mg a day are unadvisable.

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**BEAR IN MIND THAT:**

**There are measures that might reduce the risk of adverse effects of glucocorticoids, ask your doctor about them.**

**REMEMBER:**

**It is essential for glucocorticoids to be used sensibly, enabling us to take advantage of their great anti-inflammatory power, and minimising their considerably potential toxicity.**

### ► Anti-malarial drugs

As their name implies these are drugs that were initially synthesised for treating malaria. However, their regulating effect on the immune system has been known for some time, and they form one of the most commonly used groups of drugs in Lupus, especially hydroxychloroquine.

Although it has been considered for years that hydroxychloroquine was only indicated in minor manifestations of Lupus, recent studies have shown a large variety of beneficial effects. Nowadays it is considered that hydroxychloroquine is the essential baseline treatment for Lupus, so its prolonged administration is recommended in all patients who have no contraindications. Its excellent safety profile permits its use during pregnancy, too, so it should not be discontinued during this period.

Retinal toxicity is the most serious adverse effect. Fortunately, it is not very frequent in patients treated with hydroxychlorquine (not so, though, with chloroquine), and it can be prevented if detected early on. That is why annual ophthalmological examinations are recommended.

**DO NOT FORGET...**

**Keep your appointments with the ophthalmologist when you are taking anti-malarial drugs.**

### ► Immunodepressants

Immunodepressants are a heterogeneous group of drugs with capacity to

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inhibit the immune response and, therefore, they can be used to treat several autoimmune diseases, including Lupus. There are old immunodepressive drugs (such as cyclophosphamide, azathioprine or methotrexate) and other more recently introduced ones (such as mycophenolate or tacrolimus).

They are considered as alternative drugs that are used in cases of severe manifestations (for example, in nephritis or lupus psychosis), but they are also used in more mild forms of Lupus that require maintenance therapy with prednisone, so that the dose of the latter can be reduced. Although these are drugs that are considered as potentially toxic, if properly indicated, if their doses are controlled well and their adverse effects are properly monitored, their safety profile is good, above all considering that they help us control severe manifestations of Lupus and minimise the toxicity associated with glucocorticoids.

Many of them are contraindicated in pregnancy; however, azathioprine and tracrolimus can be used relatively with relative tranquillity during this period.

**REMEMBER:**

**Your doctor will prepare a treatment plan in agreement with your symptoms. You and your doctor should review the results of your treatment plan on a regular basis.**

**If new symptoms appear, if they increase in frequency or intensity, immediately inform your doctor; he/she will indicate if your treatment has not been modified.**

**DO NOT FORGET...**

**Follow the treatment, keep your medical appointments, get analyses done and follow your doctor's instructions. These measures help keep your disease under control as much as the treatments do.**

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## Professionals involved in Lupus

Lupus is an example of a multi-system disease, so it is important for its management to be shared by multidisciplinary teams. These teams should be led and coordinated by doctors with training and experience, and who are specifically dedicated to autoimmune disease. In Spain these are mainly rheumatologists and internists. Furthermore, depending on the type of specific manifestations in each patient, the participation of other specialities may be necessary:

- ✓ Nephrologists
- ✓ Dermatologists
- ✓ Haematologists
- ✓ Neurologists
- ✓ Immunologists
- ✓ Pneumologists
- ✓ Cardiologists
- ✓ Endocrinologists
- ✓ Obstetricians and gynaecologists
- ✓ Psychiatrists

It is also very important for Primary Care doctors to be involved, and for them to coordinate appropriately with hospital doctors. Likewise, nurses, psychologists, physiotherapists, social workers, etc. are becoming more and more involved in the care of patients with Lupus.

It is very important for the work of the different professionals to be coordinated, ensuring easy accessibility and fast responses in patients' situations of need.

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**REMEMBER:**

**Visit your doctor on a regular basis. These visits will help you and your doctor to:**

- √ **Detect changes in symptoms**
- √ **Prevent flares and complications of lupus**
- √ **Adjust the treatment plan**
- √ **Detect side effects of the treatment**

**On many occasions, several specialists should intervene and act together in your treatment plan and follow-up.**

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## Pregnancy and contraceptives

Women with Lupus can have healthy babies. It is important to involve the medical care team during your pregnancy, in close collaboration with the gynaecologist/obstetrician. There are some considerations to be taken into account if you are thinking of getting pregnant:

✓ Pregnancy, in women with Lupus, is considered high risk; however, the majority of women have complication-free pregnancies.

✓ Although the pregnancy is high risk, this is not the same in all the cases, as this depends on the severity of the disease, personal characteristics or treatment received.

✓ Pregnant women with Lupus should make more regular visits to the doctor.

✓ A flare of Lupus could occur at any time during pregnancy but, with good planning, they are usually mild.

✓ Careful planning before pregnancy is important, aiming for this to occur after a period of 6 to 12 months of well-controlled disease, with low treatment levels.

**REMEMBER:**

**If you are considering getting pregnant, do not hesitate to consult with your doctor. Your doctor will help you plan your pregnancy and will advise you during the gestation.**

**With respect to contraceptive measures, you should take the following aspects into account.**

✓ Women with Lupus who do not want to get pregnant or who are taking medication that might be harmful for the baby may want a reliable birth control method. Recent studies have shown that some oral contraceptives (pill) are practically harmless for women with inactive Lupus and without other factors of risk of thrombosis, like antiphospholipid antibodies or smoking, providing that the doses of oestrogens they contain are low.

✓ The benefits of the pill may exceed the risks in many patients. In any case, it should be your regular doctor and your gynaecologist who make an assessment of your case and inform you of the most appropriate measures for you.

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**REMEMBER:**

**If you are thinking of starting contraceptive measures, do not hesitate to consult this with your doctor. Your doctor can help you and give you valuable advice regarding contraception.**

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## Lifestyles and self-care

Lifestyles and self-care habits can improve your quality of life and the control of your disease. Bear the following advice in mind:

✓ Practice aerobic exercise (walking, swimming, cycling, etc.) on a regular basis (2 or 3 times per week, in 30 to 60-minute sessions, depending on your possibilities).

✓ Avoid being overweight and a sedentary lifestyle.

✓ Avoid smoking, thus you will help reduce the activity of Lupus, increasing the efficacy of some of the treatments, and reducing the risk of cardiovascular diseases.

✓ If you consume alcohol, do so with moderation and consult your doctor if there is any interaction with your normal treatment.

✓ Follow a diet low in saturated fats and rich in omega-3 fatty acids (blue fish, seafood, almonds, walnuts).

✓ If you decide to plan a diet, do not forget to consult your doctor. He/she may assess possible deficiencies of some elements such as iron, folic acid, vitamin B12, calcium and vitamin D.

✓ Avoid excessive exposure to the sun.. Prolonged exposures may worsen your disease and even trigger a severe flare. Protect yourself every day (even on cloudy days) with quality sunscreens (SPF 50+) and renew application throughout the day (especially if you perspire and after swimming in the sea/swimming pool). Use clothing that covers the more sensitive areas. Try not to go to the beach at hours around midday, when the sun is at its most harmful. Some patients may be very sensitive to the sun and require more drastic protection measures. Consult your regular specialists to individualise these measures.

✓ Develop living habits that will help you reduce stress (adapt the activities or your daily objectives to your physical condition, practice relaxation techniques, rest at midday, etc.).

✓ Rest sufficiently (sleeping an average of 7 to 8 hours/day is recommended).

✓ Develop a support system, surround yourself with people who you trust, who are able to understand your health process (family, friends, patient associations, etc.).

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√ Adopt a participative, active and collaborative attitude regarding your illness and do not place responsibility exclusively on your doctor, family and caregiver for your state.

**DO NOT FORGET...**

**Patients who are informed and activity participate in their treatment:**

- √ **Take their medication in a more adequate manner**
- √ **Have less pain**
- √ **Need to visit the doctor less**
- √ **Have greater confidence in themselves**
- √ **Remain more active**

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## Role of family and caregivers

Patients with Lupus may experience difficult moments. At times, the family should adapt to changes in their daily activities and leisure. Families should have a good understanding of the disease and its possible limitations, as well as the most suitable lifestyle to be followed. Maintaining a good family climate is very positive. Thus, sharing your fears and feelings may help you.

The following advice may be useful for families, caregivers, or people who live with patients with Lupus, to help them:

✓ Try not to be overprotective. You cannot give them their health back but being overprotective may make the person affected feel unable to cope by themselves.

✓ Try to be positive and control catastrophic anticipations related to the disease. There will be bad days, but do not get discouraged. Remember that negative thoughts are just that, thoughts, they are not facts.

✓ Try to understand possible sudden mood changes in the person affected. Lupus, depending on the severity, may generate quite a significant impact on the lives of people, forcing them to change their daily habits and, on many occasions, lose their autonomy. Faced with this change of reality, people with Lupus often feel frustrated and express rage, among other emotions. Be patient and compassionate; it is nothing personal towards you.

✓ Look for reliable information about Lupus on sites of Medical Societies or Patient Associations (more information at Where can I get more information? Mistrust websites that offer a cure for your disease or do not have the backing of experts.

✓ If you consider that you need guidance or information about other help available, look for the advice of a social worker at your health centre, hospital or town council.

✓ You can find support and advice from people with similar experiences in patients' associations.

**If the person affected is your partner** bear in mind that:

✓ You should try to prevent the disease from governing your lives. Your partner is not a victim, nor are you. You are not responsible for the Lupus of your partner. Be honest with your partner and with yourself.

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✓ Make a list of activities that you can enjoy together.

✓ Take time for yourself, finding things that stop you thinking about your partner's disease.

✓ Find a moment to take a rest or break, too, carrying out some recreational activity outside the home. To replace you in the care, ask family, friends or a patients' association for help. In this way you will not feel so oppressed by leaving your partner alone.

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## What should I take into account when I visit my doctor?

During your visit to the health centre or hospital, in the assessment, diagnosis, treatment, and follow-up process of your disease, you are going to deal with different professionals. To facilitate the relationship and communication with them, the following suggestions can be taken into account:

✓ Before your appointment prepare what you want to say. You are the person who knows your symptoms the best, and your information can be very valuable for the professionals attending you. What you tell your doctor about your symptoms, problems, activities, family and lifestyle will help him/her determine the best plan to be followed.

✓ Preparing a list with the answer to the questions mentioned below may be helpful:

- What symptoms have you got?
- When did the symptoms start and what makes them get worse or improve?
- Have you received any treatment for Lupus before this? If so, what was it?
- Are you receiving treatment for any other disease? Or, what medication do you normally take?

✓ Remember that you should always take the treatment that you are receiving with you as well as available report.

✓ Warn about any allergy to medications that you may have.

✓ You should inform about any substance, medication, herbal products or alternative medicine that you are taking for your health problems.

✓ Do not be afraid of asking questions if everything is not clear.

✓ Ask them to give you the information in simple and understandable language.

✓ You may want to be accompanied to your medical appointment by a relative or friend. Take notes if this helps or ask for information in writing.

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**REMEMBER:**

**You are the most important part of this process, so you should express your needs and preferences both during the diagnosis and with the different treatment options.**

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## Where can I get more information?

Apart from the health centre or hospital where you keep your regular appointments, there are other organisations, such as patients' and family associations, which may offer you advice and help. There are also websites on the Internet where you can find additional information about Lupus.

### Associations of patients

| MADRID NATIONAL | |
|---|---|
| Name: | FELUPUS (Spanish Lupus Federation) |
| Field of action: | National |
| Address: | C/ Moreto nº 7, 5º derecha, despacho 5 |
| PC: | 28014 |
| Town: | Madrid |
| Province: | Madrid |
| Telephone(s): | 918 251 198 / 674 250 527 / 674 250 474 |
| E-mail: | felupus@felupus.org |
| Website: | www.felupus.org |

| ANDALUSIA | |
|---|---|
| Name: | ALAL (Association of autoimmune people and Lupus of Almeria) |
| Field of action: | Provincial |
| Address: | Antigua Plaza de Abastos de Regiones s/n (entrada por C/ Santa Marta) |
| PC: | 04006 |
| Town: | Almeria |
| Province: | Almeria |
| Telephone(s): | 950 228 082 / 659 965 694 / 619 271 728 |
| E-mail: | asociaciondelupusalal@hotmail.com |
| Website: | www.alal.es |
| | |
| Name: | ACOLU (Support for Living with Lupus in Cordoba) |
| Field of action: | Provincial |
| Address: | Centro cívico Norte. Avda. Cruz de Juárez, s/n |

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|---|---|
| PC: | 14006 |
| Town: | Cordoba |
| Province: | Cordoba |
| Telephone(s): | 622 630 102 |
| E-mail: | acolu@hotmail.com |
| Website: | Not available |

| | |
|---|---|
| Name: | LUPUS GRANADA (Granada Lupus Association) |
| Field of action: | Provincial |
| Address: | C/ Escultor Navas Pareja, local 2 |
| PC: | 18006 |
| Town: | Granada |
| Province: | Granada |
| Telephone(s): | 958 819 118 |
| E-mail: | granadalupus@telefonica.net |
| Website: | facebook.com/asociacion.granadinadelupus |

| | |
|---|---|
| Name: | HULUA (Huelva Lupus Association) |
| Field of action: | Provincial |
| Address: | C/ Virgen de la Esperanza Coronada nº 8, bajo |
| PC: | 21001 |
| Town: | Huelva |
| Province: | Huelva |
| Telephone(s): | 959 280067/ 959 253 462 |
| E-mail: | huelvahulua@gmail.com |
| Website: | Not available |

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|---|---|
| Name: | ALUJA (Jaen Lupus Association) |
| Field of action: | Provincial |
| Address: | C/ Virgen de la Cabeza nº 10, bajo Izq. |
| PC: | 23008 |
| Town: | Jaen |
| Province: | Jaen |

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|---|---|
| Telephone(s): | 953 883 528 / 616 593 704 |
| E-mail: | aluja2001@hotmail.com |
| Website: | www.aluja.org |

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|---|---|
| Name: | ALA (Malaga Lupus Association) |
| Field of action: | Provincial |
| Address: | C/ Lagunillas nº 25, locales 3 y 4 |
| PC: | 29012 |
| Town: | Malaga |
| Province: | Malaga |
| Telephone(s): | 952 266 504 |
| E-mail: | lupusmalaga@gmail.com |
| Website: | Not available |

| | |
|---|---|
| Name: | ALUS (Autoimmune and Lupus Association of Seville) |
| Field of action: | Provincial |
| Address: | C/ Ronda de Capuchinos nº 2, local 16, E2 |
| PC: | 41003 |
| Town: | Seville |
| Province: | Seville |
| Telephone(s): | 954 531 155 |
| E-mail: | alusevilla@alusevilla.org |
| Website: | www.alusevilla.org |

## ARAGON

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|---|---|
| Name: | ALADA (Aragon Lupus Association) |
| Field of action: | Regional |
| Address: | C/ Honorio García Condoy nº 12, bajo |
| PC: | 50007 |
| Town: | Zaragoza |
| Province: | Zaragoza |
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| Website: | alada-lupus.blogspot.com |

## ASTURIAS

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|---|---|
| Name: | ALAS (Asturias Lupus Association) |
| Field of action: | Regional |
| Address: | C/ Instituto nº 17, 2º A |
| PC: | 33201 |
| Town: | Gijon |
| Province: | Asturias |
| Telephone(s): | 985 172 500 |
| E-mail: | lupusasturias@telefonica.net |
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## BALEARIC ISLANDS

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|---|---|
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| Field of action: | Regional |
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| Province: | Palma de Mallorca |
| Telephone(s): | 971 498 777 |
| E-mail: | aiblupus@hotmail.com |
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## CANARY ISLANDS

| | |
|---|---|
| Name: | CANALUP (Canary Is. Lupus Association) |
| Field of action: | Regional |
| Address: | C/ Dr. José Juán Megías nº 8 |
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| Telephone(s): | 677 216 769 |
| E-mail: | canariaslupus@hotmail.com |
| Website: | http://www.canalup.org/ |

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## CANTABRIA

| | |
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## CATALONIA

| | |
|---|---|
| Name: | ACLEG (Catalan Association of Generalised Lupus Erythematosus) |
| Field of action: | Regional |
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| PC: | 08024 |
| Town: | Barcelona |
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## CASTILE – LA MANCHA

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|---|---|
| Name: | ALMAN (La Mancha Lupus Association) |
| Field of action: | Regional |
| Address: | Apartado de Correos nº 176 |
| PC: | 13080 |
| Town: | Ciudad Real |
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## CASTILE LEÓN

| | |
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| Name: | ALELYSA (Leon Association of Lupus and Antiphospholipid Syndrome) |
| Field of action: | Provincial |
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| PC: | 24009 |
| Town: | Ceas de Armunica |
| Province: | León |
| Telephone(s): | 636 563 138 |
| E-mail: | alelysa @gmail.com |
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| | |
|---|---|
| Name: | ASALU (Salamanca Lupus Association) |
| Field of action: | Provincial |
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| PC: | 37006 |
| Town: | Salamanca |
| Province: | Salamanca |
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| | |
|---|---|
| Name: | ASVEL (Valladolid Association of Lupus Patients) |
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## EXTREMADURA

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| PC: | 06011 |
| Town: | Badajoz |
| Province: | Badajoz |
| Telephone(s): | 644 549 491 |
| E-mail: | agal@lupusgalicia.org |
| Website: | http://www.aluex.es/ |

## GALICIA

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| Name: | AGAL (Galicia Lupus Association) |
| Field of action: | Regional |
| Address: | Rúa Solís, s/n. Eirís de Arriba (detrás del CHUAC) |
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| Town: | La Coruña |
| Province: | La Coruña |
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## MADRID

| | |
|---|---|
| Name: | AMELYA (Madrid Lupus and Antiphospholipid Association) |
| Field of action: | Regional |
| Address: | C/ Martínez Izquierdo nº 40 |
| PC: | 28028 |
| Town: | Madrid |
| Province: | Madrid |
| Telephone(s): | 913 558 726 |
| E-mail: | info@lupusmadrid.com / rrss@lupusmadrid.com |
| Website: | www.lupusmadrid.com |

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| | |
|---|---|
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| PC: | 28231 |
| Town: | Madrid |
| Province: | Madrid |
| Telephone(s): | 916 378 093/ 636 375 329 |
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## MURCIA

| | |
|---|---|
| Name: | AMLEA (Murcia Association of Lupus and other Similar Diseases) |
| Field of action: | Regional |
| Address: | C/ Galicia nº 11. Molina de Segura |
| PC: | 30500 |
| Town: | Molina de Segura |
| Province | Murcia |
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## NAVARRE

| | |
|---|---|
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| Field of action: | Regional |
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| PC: | 31001 |
| Town: | Pamplona |
| Province: | Navarre |
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## COMMUNITY OF VALENCIA

| | |
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| Website | www.lupusvalencia.org |

## BASQUE COUNTRY

| | |
|---|---|
| Name: | ADELES–VIZCAYA (Association of Aid to Lupus Patients of Vizcaya) |
| Field of action: | Provincial |
| Address: | Apartado de Correos 20175 |
| PC: | 48004 |
| Town: | Bilbao |
| Province: | Vizcaya |
| Telephone(s): | 636 799 617 |
| E-mail: | lupus_bizkaia@yahoo.es |
| Website: | Not available |

| | |
|---|---|
| Name: | ADELES–ALAVA (Association of Lupus Patients of Alava) |
| Field of action: | Provincial |
| Address: | C/ Pintor Vicente Abreu nº 7, Bajo |
| PC: | 01008 |
| Town: | Victoria Gasteiz |
| Province: | Álava |
| Telephone(s): | 945 225 454 |
| E-mail: | lupusalava@euskalnet.net |
| Website: | www.adeles.es |

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## Online resources

### SPANISH LUPUS FEDERATION

http://www.felupus.org/felupus.php

### SPANISH CENTRE FOR INFORMATION DISTRIBUTION OF THE NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES (NIAMS)

http://www.niams.nih.gov/portal_en_espanol/Informacion_de_salud/Lupus/default.asp

### SPANISH RHEUMATOLOGY SOCIETY

http://www.ser.es/

### NATIONAL INSTITUTES OF HEALTH / INSTITUTOS NACIONALES DE SALUD

http://www.nih.gov/

### LUPUS COMPANION

https://itunes.apple.com/us/

### THE LUPUS APP

https://play.google.com/store/apps/details?id=com.svtech.lupus&hl=es

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Ministry of Health, Social Services and Equality. Canary Health Service Assessment Service

# Appendix 13. Glossary

**Absolute risk reduction:** Epidemiological measurement obtained in intervention studies, resulting from subtractingv the incidence of the disease or effect observed of the control group (standard treatment, placebo or non-intervention) from the incidence of the disease or effect observed of the group with intervention.

**Analysis by protocol (or of valid cases):** Analysis that is limited to including only patients who have completed the study, about whom all the data foreseen are available and with no irregularities or violations of the protocol. It is closer to the effect of the treatment in optimal conditions of use. If this type of analysis reaches the same conclusions as the intention to treat analysis, we can consider that the results of the trial are more reliable.

**Asthenia:** Tiredness following minimal effort, decrease of functional capacity, weakness defined as an advanced feeling of inability to start any activity, decrease of the capacity of concentration, memory disturbance and emotional incontinence.

**Before-after (or pre-post) study:** This is based on measuring and comparing the response variable before and after exposing the individual to the experimental intervention. Before-after designs with one single group allow researchers to manipulate the exposure, but they do not include a comparison group. Each individual acts as his/her own control. There is a greater risk of selection bias in quasi-random trials where the allocation is not adequately masked, compared with controlled clinical trials with adequate allocation concealment.

**Bias:** This is an error or systematic deviation in the results or inferences of a study due to factors that depend on the collection, analysis, interpretation, publication or review of the data, and which might lead to incorrect conclusions or are systematically different to the truth about the objectives of a research. In studies on the effects of healthcare, biases may arise from systematic differences in the characteristics of the groups that are compared (selection bias), in the care given or the exposure to other factors, apart from the intervention of interest (execution bias), in the abandonment or exclusions of people initially included in the study (wear bias) or in the assessment of the outcome variables (detection bias). Biases do not necessarily represent an imputation of prejudice, as they could also be the researchers' preferences for some specific results, which is different to the traditional use of this word to refer to a partisan point of view. Many varieties of biases have been described. (See also methodological quality, validity).

**Blinding (synonym:** see Masking). Preserving secrecy, with respect to the participants in the study or the researchers, about the assignment to each group (e.g., treatment or control). Blinding is used as protection against the possibility that the knowledge of the assignment might affect the patient's response to the treatment, the behaviour of the health professionals (execution bias) or the evaluation of the results (detection bias). Blinding is not always possible (e.g., when a surgical treatment is compared with a pharmacological treatment). The importance of blinding depends on how objective the result measurement is. Blinding is more important for less objective result measurements, such as pain or quality of life. (Also see simple blind, double blind and triple blind.).

**Blind study:** A study where some of those involved do not know which person is receiving one treatment or another, or placebo. Treatment concealment is used to prevent the results of the research being "influenced" by the placebo effect or by the bias of the observer. To correctly evaluate the blinding, it is necessary to know who in the study has been blinded (patients, researchers, health professionals, results and/or statistic awarders).Cohort study (synonyms: follow-up, incidence, longitudinal study): An observational study where a defined group of people (the cohort) is monitored in time and where the results or outcome are compared between the subgroups of the cohort that were or were not exposed (or exposed to different levels) to an intervention or another factor of interest. The measurement of association that is used in these studies is relative risk and absolute risk. Cohorts can be formed on the spot and monitored prospectively (a concurrent cohort study) or identified based on historical records and monitored in time forwards from

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that moment to now (a historical cohort study). As a random distribution is not used, a pairing or a statistical alignment should be used to guarantee that the comparison groups are as similar as possible.

**Bone densitometry:** Non-invasive diagnostic tests that measure the bone mass in different parts of the skeleton, by means of techniques that may or may not use ionising radiation, are included in this definition. Ionising techniques include those that use gamma rays, such as simple photonic densitometry, dual photonic densitometry, neutron activation analysis and Compton radiation count; these last two are still in experimental phase. In contrast, X-rays are ionising radiations that use radiogrammetry and photodensitometry, which are currently obsolete, simple radiological densitometry, dual radiological densitometry (DXA) and quantitative computerised tomography.

**Bone mineral density (BMD):** To diagnose osteoporosis, we recommend measuring BMD, measured by central dual radiological densitometry (DX), evaluating the T-score (comparing the patient's value with the reference value of the young adult population of the same sex and same race) and applying the WHO criteria.2 The comparison is established between the individual BMD and the BMD of young healthy adults (20-35 years old) of the same sex. It is obtained based on the patient's BMD value minus the mean value of the BMD in young adults, divided by the standard deviation of BMD of young adults of the same sex. A T-score is assigned to the patient, which is the number of standard deviations (SD) above or below the mean BMD for normal young adults, as indicated below:

Normal BMD: A T-score ≥ -1.0.

Osteopenia (low BMD): T-score between -1.0 and -2.4.

Osteoporosis: T-score ≤ -2.5.

**Caregiver:** A person that provides unselfish and voluntary support to people affected, who either live with the patient or else devote part of their time (over 20 hours a week) to caring for the patients.

**Case and control study (synonyms:** case control study, case referent study): Observational epidemiological study in which individuals with a certain disease or outcome of interest (cases) are selected, and compared with an appropriate control group without the disease or outcome of interest (controls), or in relation to the prior exposure of possible risk factors associated with the disease. The relationship between a factor (intervention, exposure or risk factor) and the outcome of interest is examined by comparing the frequency or level of this factor in the cases and in the controls. The measurement that is used to quantify the association is the odds ratio. Case and control studies are retrospective, as they are always developed looking backward in time.

For example, to determine if thalidomide was the cause of birth defects, a group of children with these malformations (cases) was able to be compared with a group of children without those defects (controls). Then, both groups were compared with respect to the proportion of those exposed to thalidomide in each one of them by their mothers taking that medication.

**Clinical Practice Guideline (CPG):** Set of systematically developed instructions, directives, statements or recommendations, whose purpose is to help professionals and patients take decisions about the most appropriate healthcare modality for specific clinical circumstances.

**Clinical series (also case series):** Uncontrolled observational study that includes an intervention and a result of more than one person, where the experience with a group of patients with a similar diagnosis, with no comparison group, is described.

**Clinical trial (synonyms:** therapeutic trial, intervention study): Experimental study to evaluate the efficacy and safety of a treatment or other intervention. This general term includes randomised controlled clinical trials and controlled clinical trials.

**Clinical trial in parallel:** Type of randomised clinical trial in which some patients are allocated to receive control treatment, whilst other patients are allocated to receive experimental

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treatment. Thus, each patient only receives 1 of the study treatments. It is the most commonly used design to assess the comparative efficacy of the drugs.

**Cochrane library:** A series of databases, produced by the Cochrane Collaboration, published on disc and CD-ROM and updated every three months, which contains *the Cochrane Database of Systematic Reviews*, *the Cochrane Controlled Trials Register*, *the Database of Abstracts of Reviews of Effectiveness*, *the Cochrane Review Methodology Database* and information about the Cochrane Collaboration.

**Cochrane review:** Systematic and updated review of the most reliable scientific evidence about the benefits and risks of health care. Cochrane reviews try to help take practical decisions. This is also the name given to a systematic review carried out according to the Cochrane Collaboration methodology and published in the Cochrane Library. For a review to be called "Cochrane review" it should be included in the Parent database maintained by the Cochrane Collaboration. The Parent database (database of reference) is comprised of review modules sent by the Review Collaborator Groups that are registered in the Cochrane Collaboration. The reviews included in one of the modules that comprise the Parent database are reviewed by the publishing team of the Review Collaborator Groups, as described in the different modules of each one of the groups. The reviewers follow the guidelines published in the Cochrane Manual for Reviewers. The specific methods used in a review are described in the text. Cochrane reviews are prepared using the Review Manager (Revman) software, provided by the Collaboration and that adapts to a structured format.

**Comorbidity:** Presence of several added or associated diseases.

**Confidence Interval (CI):** Interval in which the real magnitude of the effect (never known exactly) is found, whose possible existence is estimated with a certain degree of certainty. Margin of values within which the real value of the population can be expected with a certain likelihood. Specific likelihood is called level of confidence, and the endpoints of the confidence interval are called confidence limits (upper and lower). Confidence intervals with a likelihood of 95% are generally used, although sometimes 90% or 99% are used.

**Note:** confidence intervals represent the likelihood of committing random errors, but not committing systematic errors (biases).

**Consistency:** This refers to the extent to which the results obtained by a measurement procedure can be reproduced. Lack of consistency may arise from differences between observers or measurement instruments, or due to lack of stability of the variable measured.

**Control:** In clinical trials that compare two or more interventions, a control is a person from the comparison group that receives a placebo, no intervention, traditional care or any other type of service.

In case and control studies, a control is a person in the comparison group without the disease or outcome of interest.

In statistics, controlling means adjusting or bearing in mind the external influences or observations.

Programmes aimed at reducing or eliminating a disease are also called control, especially when applied to transmissible diseases (infectious).

**Controlled clinical trial:** This refers to a study that compares one or more intervention groups with one or more comparison groups (control). Although not all the controlled studies have a random distribution, all the clinical trials are controlled.

**Correlation:** Degree of relationship between two variables. The measurement used is the correlation coefficient (r) that quantifies the linear relationship between exposure and disease.

**Cost effectiveness analysis:** Assessment of the results obtained in terms of increase in therapeutic benefit derived from the extraordinary costs. This analysis evaluates if the benefits

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provided offset the added cost. The result is expressed as a ratio between cost and effectiveness, measuring the costs in monetary units and the benefits in terms of effectiveness units, such as life years gained.

**Crossed clinical trial:** Type of randomised clinical trial in which the individuals receive two or more treatments in successive periods that have been randomly determined, enabling each individual to carry out his/her own control. On reducing variability, these trials are more efficient and their statistical power is greater. To prevent the effects of the first treatment of the sequence from being expressed in the second period, lavage periods are usually included between treatments to avoid residual effects.

**Cross-sectional study or prevalence study:** Study that examines the relationship between the diseases (or other health characteristics) and other variables of interest that might exist in a defined population at a specific moment in time: the temporary cause-effect sequence cannot necessarily be established in a cross-sectional study.

**Delphi method:** Qualitative research technique of consensus, aimed at a comprehensive and dynamic explanation, and the analysis of certain phenomena with the purpose of generating ideas, sharing experiences and sensing tendencies for the future. It purports to analyse a reality, reaching agreements on the phenomena regarding which there is no conclusive information. It is especially useful when working with very subjective elements, when it is difficult to determine their intrinsic value. The method is applied by phases. The problem is formulated and a panel of trained experts is selected to contribute to the study with their knowledge and experience. The questions that will be submitted to study are determined and posed to the members of the panel. An anonymous questionnaire posed to the members of the panel in successive rounds until a consensus is reached. The study concludes with the preparation of a report containing the final results of the survey.

**Diagnostic test study:** Studies on diagnostic tests may satisfy two objectives. Firstly, evaluate the impact of one or several diagnostic strategies on clinical decisions or on outcome in patients. This assessment is carried out by clinical trials or non-experimental comparative studies. This type of proposal, although ideal, is available on very few occasions. The second objective, traditionally more frequent, is to determine the diagnostic capacity of a test (capacity to classify a person as healthy or sick). In this section, we refer to this second objective. Its design is based on a comparison between the test that is studied and the gold standard, which are applied to a group of patients, assessing the results in terms of sensitivity, specificity, predictive value or odds ratios.

**Double blind:** Clinical trial where neither the participants nor the researchers are aware of which intervention has been administered to the participants. The purpose of blinding the participants (both receivers and suppliers of the care) is to prevent performance bias. The objective of "blinding" the researchers (the assessors of the outcome, who may be the suppliers of the care) is to prevent detection bias. (Also see blinding, simple blind, triple blind, and allocation concealment).

**Effect estimation (synonym:** therapeutic effect): In studies on the effects of health care, this is the name given to the relationship observed between an intervention and an expressed outcome, for example, such as the number of patients needed to treat, odds ratio, risk difference, relative risk, standardised mean difference or weighted mean difference.

**Effectiveness:** Extent to which a diagnostic, preventive or therapeutic intervention when applied in normal practice and in non-experimental conditions, achieves a beneficial result. For this reason, what is effective for the participants of a clinical trial may not be effective in the general population, due to conditioning factors such as therapeutic compliance or the actual characteristics of the population.

Clinical trials that evaluate effectiveness are sometimes called clinical management trials. (Also see the term "intention to treat").

**Efficacy:** Extent to which a diagnostic, preventive or therapeutic intervention produces a beneficial result under ideal conditions, experimental and/or controlled conditions, such as within the framework of a clinical trial.

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Clinical trials that evaluate efficacy are sometimes called explanatory trials and their participation is restricted to people who cooperate fully.

**Efficiency:** Extent to which an intervention produces a beneficial result with respect to the effort required, in terms of human resources, materials and costs. In general, it refers to the use of the strictly necessary resources that produce maximum effectiveness.

**Embase:** European (Dutch) database produced by Excerpta Medica with clinical medicine and pharmacology content.

**Established osteoporosis (severe):** This describes patients with a T-score of less than 2.5, who also have fracture due to fragility.

**Evidence:** Synonym of scientific tests. Incorrect translation into Spanish of the English, evidence.

**Evidence-based Medicine:** Medicine based on scientific tests.

**Glucocorticoid-induced secondary osteoporosis:** This is the most frequent cause of secondary osteoporosis. It is multifactor, due to the direct action of the glucocorticoids on the bone and mineral metabolism, in addition to the catabolic effect on the muscle, which causes deterioration of the muscular mass, strength and resistance, and a loss of the trophic effect on the bone. There is also an increase in instability and risk of falls. The daily dose and administration time (cumulative dose) affect the bone loss. In adults, doses of over 7.5 mg/day of prednisone or equivalent, administered for prolonged periods, reduce the BMD in the backbone and in the hip. The minimum dose below which no bone loss occurs cannot be established with precision. For some, doses of under 10 mg/day do not increase physiological bone loss, but others have verified that, with an average dose of 7.5 mg. an abnormal decrease of BMD already occurs. This reduction occurs above all during the first six months' treatment

**Glucocorticoids:** Chemical compounds that are used as pharmacological agents and are used very frequently. They are irreplaceable for the medical treatment of many and very varied disorders of different organs and systems due to their anti-inflammatory and immunosuppressive effects. Their effectiveness is indisputable, but their use entails the risk of producing many adverse effects, of which osteoporosis is the most frequent and concerning.

**Gold standard:** Method, procedure or measure that is broadly accepted as the best available to act as a reference and comparison with respect to new interventions. It is especially important in studies on the precision of diagnostic tests. For example, a manual review is often used as a gold standard to identify clinical trials and act as a reference for electronic searches in databases, such as, for instance, MEDLINE.

**GuíaSalud:** Library of Clinical Practice Guidelines (CPG) of the (Spanish) National Health System (SNS). It is a body pertaining to the SNS, which the 17 autonomous communities participate in to promote the development and use of CPGs and other tools, as well as scientific evidence-based products. Its mission is to foster the offer of resources, services and products based on scientific evidence, to support the decision-making of professionals and patients in the SNS, as well as to boost the creation of networks of collaborators and cooperation between entities related to the CPGs and evidence-based medicine.

**Healthcare Levels:** Different clinical care modalities that are provided to people depending on the type of care and the place where this care is provided.

**Heterogeneity:** Within the context of a systematic review, it is the variability or difference between studies in terms of effect estimations. Sometimes a distinction is made between "statistical heterogeneity" (differences in reported effects), "methodological heterogeneity" (differences in the study design) and "clinical heterogeneity" (differences between the studies referring to key characteristics of participants, to interventions or to result measurements). The statistical heterogeneity tests are used to evaluate if the clinical variability in the results of the studies (the effect magnitude) is greater than the variability that would be expected to have randomly occurred.

**Incidence:** Number of new cases of a disease that are developed in a population during a

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certain period of time. It tells us the likelihood of a disease-free individual developing it in a certain period of time.

**Intention to treat analysis:** Analysis of the results of all the patients included in a study, maintaining the random assignment intact. This avoids the bias that occurs on excluding all those patients who have had incomplete follow-up, or on changing the initially assigned group. Intention to treat analyses are recommended in the assessment of effectiveness, as they reflect the lack of compliance and changes in treatment that probably occur when the intervention is used in clinical practice.

**Likelihood ratios (positive and negative):** Combined result of sensitivity and specificity of a diagnostic assay. The "positive likelihood ratio" (LR+) expresses how likely a positive result is among patients in contrast to non-patients. The "negative likelihood ratio" (LR-) expresses how likely a negative result is among patients in contrast to non-patients. The likelihood ratios permit transforming pre-test likelihood, that is, the likelihood of an individual having the disease before applying the test (estimated based on patient history and on prior tests), into a post-test likelihood. Although there is no fixed rule, it is estimated that the changes that can cause these ratios according to its results are:

LR + > 10 or LR - < 0.1 = high capacity to confirm and/or rule out the diagnosis.

5 < LR + < 10 or 0.1< LR - < 0.2 = moderate capacity.

2 < LR + < 5 or 0.2< LR - < 0.5 = low capacity.

1 < LR + < 2 or 0.5 < LR - < 1 = insignificant capacity.

**Masking:** Condition imposed on an individual or group of individuals with the purpose of them not knowing or learning anything about the observation, such as the treatment allocation.

**Mean (standardised) difference:** Difference between two means divided by an estimation of the internal standard deviation of the study. When an outcome (such as pain) is measured differently in the different studies (using different scales), it may not be possible to directly compare or combine the results of the studies of a systematic review. If the effects are expressed as a standardised value, the results may be combined as they do not have units then. Standardised mean differences are sometimes called d-index.

**Medline/PubMed:** Predominantly clinical database produced by the National Library of Medici¬ne that includes quotes from biomedical articles taken from the Medline database and additional, free access, scientific journals.

**Meta-analysis:** Statistical technique that permits integrating the results from different studies (diagnostic test studies, clinical trials, cohort studies, etc.) in one single estimator, giving greater weight to the results of larger studies. Sometimes it allows establishing the efficacy of a treatment when the individual clinical trials have few patients, or the results are contradictory. The results of the published studies can be used directly, or individual data can be used. This technique can also be applied with observational studies. It is also used to refer to systematic reviews that use meta-analyses.

**Methodological quality (synonym:** see Validity). Extent to which the design and development of a clinical trial have avoided probable systematic errors (bias). The variation in the quality of the studies may explain the variation of the results of the clinical trials included in a systematic review. The more rigorously designed clinical trials (with better quality) probably provide results that are closer to the "truth".

**Morbidity:** Proportion of people who fall sick in a place during a certain time interval, related to the total population of that place.

**Negative Predictive Value:** Referring to diagnostic tests, likelihood of a person with a negative result not suffering from the disease. It is calculated by means of the ratio between the number of individuals with a negative test and who do not have the disease (d) and the sum of all those who have a negative test (c + d).

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**Observational study (synonym:** non-experimental study): Study in which nature is allowed to take its course. The changes or differences in a characteristic (e.g., if the population did or did not receive the intervention of interest) are studied in connection with the changes or differences in other(s) (e.g. if they passed away or not), without the intervention of the researcher.

They represent a greater risk of selection bias than the experimental studies (randomised controlled clinical trials).

**Osteopenia:** See Bone mineral density.

**Osteoporosis:** Skeletal disease characterised by impairment of bone resistance, predisposing a person to a greater risk of fracture according to the consensus definition of the NIH of the United States. See Bone mineral density.

*P* **Value:** Probability (whose value varies between zero and one) of the results observed in a study or more extreme results than those observed being able to occur by chance. In a meta-analysis, the *P* value for the global effect assesses the global statistical significance of the difference between the treatment and control groups, whilst the *P* value for heterogeneity studies objectifies the statistical significance of the differences between the effects observed in each study.

**Physical exercise:** Recreational physical activity, which is carried out at leisure times or during free time, that is, outside work or working activity. It is a hobby that obtains pleasurable, communicative, creative and social experience for our bodily practices. Physical exercise entails carrying out planned and specifically designed body movements to be in good physical conditions and enjoy good health. The term, physical exercise, includes gymnastics, dancing, sport and physical education.

**Pivotal Trial:** Study that is considered essential to manage to register a drug for an indication. These are generally clinical trials in phase III that show the efficacy of the drug compared with a placebo or control. Some authorities accept the registration of a drug if its efficacy has been proven in two controlled clinical trials with a large number of patients.

**Placebo:** Substance or intervention administered to a patient which, lacking any therapeutic action per se, produces a curative effect on the patient if he/she receives it, convinced that that substance or intervention really possesses that action. It is used in clinical trials in order to devise real pharmacological effects of the expectations associated with the treatment or of the disease fluctuations.

**Plasmapheresis:** Extracorporeal blood purification technique, designed to eliminate high molecular weight substances from the plasma. Large amounts of plasma (usually between 5 and 2 L) are extracted from the patient and replaced with newly frozen or stored plasma.

**Positive Predictive Value:** In diagnostic tests, likelihood of a person with a positive result really suffering from the disease. It is calculated by means of the ratio between the number of individuals with a positive test correctly diagnosed as having the disease (a) and the sum of all those who have a positive test (a + b).

**Precision:** Extent to which a measurement is carried out without random error, and also degree of concordance between measured and real values. Synonym of repeatability, reliability and trustworthiness. This refers to whether an instrument is measuring something in a reproducible manner. The lack of precision is due to a random error, and essentially attributable to the sample variation, which depends on the sample size and on the statistical characteristics of the estimator.

**Prevalence:** Proportion of individuals of a population who present a disease or a characteristic at any time, or during a certain period of time. It tells us the likelihood of an individual from a certain population having a disease at a time or during a certain period of time.

**Primary osteoporosis:** Osteoporosis explained by the involutive changes of ageing, as well as by hormone changes of menopause.

**Prospective study:** In the assessments of the effects of the health interventions, a study in which the people are divided into two groups that are or are not exposed to the intervention or

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interventions of interest before the outcome has occurred. Controlled clinical trials are always prospective studies, and case and control studies never are. Concurrent cohort studies are prospective studies, whilst the historical cohort studies are not (see, also cohort study), despite the fact that, in epidemiology, a prospective study is sometimes used as a synonym for cohort studies. (see retrospective study).

**Phase III studies:** Trial aimed at assessing the efficacy and safety of the experimental treatment in a more representative sample of patients from the general population to whom the drug will be addressed. These studies are preferably controlled, randomised and masked. In general, the control group is a drug of known efficacy (standard) in that disease and the use of placebo is less frequent.

**Quasi–experimental trial:** A trial that uses a quasi-random method to allocate patients to different health-care alternatives. There is a greater risk of selection bias in quasi-random trials where the allocation is not adequately masked, compared with controlled clinical trials with adequate allocation concealment.

**Randomisation:** Procedure whereby the selection of the sample or assignment to one treatment or another, or to placebo, is done by random mechanisms.

**Randomised clinical trial:** A clinical trial in which the individuals are randomly allocated to two groups: One (experimental group) receives the treatment that is being tested and the other (comparison or control group) receives standard treatment (or sometimes a placebo). The two groups are monitored to observe any difference in the results. Thus the efficacy of the treatment is assessed.

**Relative risk (RR) (also risk ratio):** Epidemiological association measurement obtained from cohort studies resulting from dividing the incidence of disease of the exposed population by the incidence on the non-exposed population, indicating the likelihood of developing a disease in the exposed group compared with the non-exposed group. The risk ratio is determined in the intervention group divided by the risk in the control group. The risk (proportion, probability or rate of events) is the ratio of the number of people with a characteristic in a group divided by the total number of members in the group.

**RR = 1 indicates that there is no difference between the groups that are compared. For undesirable results, a relative risk of less than 1 indicates that the intervention was efficient as it reduced the risk of that event.**

**Relative risk reduction:** Epidemiological measurement obtained in intervention studies, resulting from subtracting the incidence of the disease in the control group from the incidence of the disease in the group with the new intervention, and dividing it by the incidence of the disease in the control group. It expresses the risk reduction respect to the control group.

**Retrospective cohort study:** Type of cohort study in which two groups are compared with respect to exposure in the past to a specific factor, and to the presence of the disease in the present. A good registration system is necessary to be able to carry out this type of study.

**Retrospective study:** Study in which the events or outcomes have occurred to the participants before the study began. Case and control studies are always retrospective, whilst cohort studies sometimes are and control clinical trials are never (see prospective study).

**Risk factor:** This is any circumstance (characteristic or lifestyle of a person, or of his or her environment), that increases the likelihood of a person getting a disease.

**Scottish Intercollegiate Guidelines Network (SIGN):** Scottish multidisciplinary agency that prepares evidence-based clinical practice guidelines as well as methodological documents on their design. Its objectives are to improve the quality of healthcare for Scottish patients in order to reduce variability in normal clinical practice and in the results, based on the development and dissemination of national CPGs that contain recommendations for effective practice based on current evidence.

**Secondary osteoporosis:** Osteoporosis caused or exacerbated by other pathologies or drugs.

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It is not always possible to talk about an isolated cause, but rather we are more likely to find a group of causes involved. The causes are multiple: genetic diseases, endocrine, gastrointestinal, haematological, rheumatologic, nutritional, pharmacological, etc. The administration of glucocorticoids is the most frequent cause of secondary osteoporosis, representing 25% of the cases of osteoporosis, and it is caused by these agents regardless of the disease treated, and of the sex and age of the patient.

**Sensitivity:** Proportion of really sick individuals that have been classified as such by using a diagnostic test, with which a highly sensitive test would give few false negative results. It is calculated by means of a ratio between correctly diagnosed patients and the total of patients with the disease (a / a + c).

**Simple blind (synonym:** simple masking): Method where the researcher knows about the treatment or intervention that the participant receives, but not so the participant.

**See blinding, double blind, triple blind.**

**Specificity:** Referring to diagnostic tests, likelihood that a test is negative when the disease is really absent. That is, the proportion of real negatives (a highly specific test gives few false positive results).

**Statistical significance:** Estimation of the likelihood of an effect, as broad as or broader than the effect observed in a study, having occurred by chance. It defines the risk of making a mistake, assumed by the researcher on rejecting null hypothesis, when really this is true (likelihood of committing type I error). Normally it is expressed as the *P* value. Thus, for example a *P* value of 0.049 for a bias difference of 10% means that there is less than 1 out of 20 probabilities (0.05) that such a large or larger effect or association like this has occurred by chance, and therefore, it could be said that the results are statistically significant at the level of *P*= 0.05.

**The cut-off point for statistical significance usually lies at 0.05, but sometimes at 0.01 or 0.10. These cut-off points are arbitrary and have no specific importance. Although this is often done, it is not appropriate to interpret the results of a study in a different way depending on the *P* value; if this *P* value is, for example 0.055 or 0.045 (which are very similar but not opposing values). By convention, a risk of under 5% (*P*<0.05) is normally accepted.**

**Statistically significant:** In a study, it is said that the differences are statistically significant if the likelihood of the differences in effect found when two groups are compared is less than a previously defined significance level; that is, that it is not very likely that the differences observed between compared treatments or groups are due to chance. Normally a significance level of 5% is used, and it is usually presented as $p < 0.05$. However, it should be taken into account that a difference between treatments may be statistically significant, but this does not always mean that the difference found is "clinically significant" or relevant.

**Stratification:** Technique to control the effect of the confusion variables on the data analysis. It consists in assessing the association in homogeneous categories of the confusion variable.

**Study case (synonyms:** anecdote, history of a case, information of an individual case): Non-controlled observational study that includes an intervention and an outcome in an individual person.

**Sun exposure:** Exposure to radiation from the sun. The sun is extremely important for people's health. Depending on the characteristics of the person and the exposure time to its radiations, it is going to produce a series of repercussions on the organism that may be positive or negative. A positive aspect is the role that the sun plays in preventing certain avitaminosis (lack or decrease of vitamins). More specifically, sun radiations favour the production of the vitamin D necessary to metabolise calcium and avoid rickets (a disease characterised by bone deformation, which mainly affects boys). Regarding negative aspects on the skin, inadequate sun exposure produces disorders that may be expressed in the short or long term.

**Systematic review (SR):** This is a review whereby the evidence about a topic has been systematically identified, assessed and summed up in agreement with predetermined criteria. It is a method used to analyse a clearly formulated question, and which uses an explicit system to

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identify, select and critically assess the relevant research, as well as to obtain and analyse the data of the studies included in the review. Statistical methods (meta-analyses) may or may not be used to analyse and sum up the results of the studies included. See also Cochrane review.

**Validity (synonym:** internal validity). Extent to which a result (or a measure or a study) probably comes near the truth and is free from bias (systematic errors). Validity has some other meanings. It is normally accompanied by a word or a sentence that qualifies it; for example, in the context of making a measurement, expressions such as construction validity, content validity and criterion validity are used. The expression, internal validity, is sometimes used to distinguish this type of validity (the degree to which the observed effects are true for the people of the study) from the external validity or generability (the degree to which the observed effects in a study really reflect what is expected to be found in a broader target population than the people included in the study).

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# Appendix 14. Abbreviations, initials and acronyms

| | |
|---|---|
| **25(OH) D:** | 25-hydroxivitamin D |
| **ACEI:** | Angiotensin Converting Enzyme Inhibitors |
| **ACKD:** | Advanced chronic kidney disease |
| **aCL:** | Anticardiolipin antibodies |
| **ACR:** | *American College of Rheumatology* |
| **AGREE II:** | *Appraisal of Guidelines for Research & Evaluation II* |
| **AMI:** | Acute Myocardial Infarction |
| **ANA:** | Antinuclear antibodies |
| **ANAM:** | *Automated Neuropsychological Assessment Metrics* |
| **ANCA:** | *Anti-neutrophil cytoplasmic antibodies* |
| **APL:** | Antiphospholipid antibodies |
| **aPS:** | Anti-phosphatidylserine |
| **APS:** | Antiphospholipid syndrome |
| **ARA:** | Angiotensin Receptor Antagonists |
| **ARI:** | Acute renal insufficiency |
| **ASA:** | Acetylsalicylic acid |
| **AZA:** | Azathioprine |
| **BDI-II:** | *Beck Depression Inventory-II* |
| **BILAG:** | *British Isles Lupus Assessment Group* |
| **BILD:** | *Brief Index of Lupus Damage* |
| **BMD:** | Bone mineral density |
| **BMI:** | Body mass index |
| **CCT:** | Controlled clinical trial |
| **CKD:** | Chronic kidney disease |
| **CI:** | Confidence Interval |
| **CLASI:** | *Cutaneous Lupus Erythematosus Disease Activity and Severity Index* |
| **CLE:** | Cutaneous lupus erythematosus |
| **CNS:** | Central Nervous System |
| **CPG:** | Clinical Practice Guideline |
| **CPM:** | Cyclophosphamide |
| **CR:** | Complete response |
| **CRP:** | C reactive protein |
| **CsA:** | Cyclosporine A |
| **CVD:** | Cardiovascular disease |

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| | |
|---|---|
| **CQ:** | Cloroquine |
| **CVA:** | Cerebrovascular accident |
| **DAS:** | *Disease Activity Score* |
| **DHA:** | *Docosahexaenoic acid* |
| **DHEA:** | Dehydroepiandrosterone |
| **DLE:** | Discoid lupus erythematosus |
| **DI:** | *Damage Index* |
| **DNA:** | Desoxyribionucleic acid |
| **DsDNA:** | Double stranded desoxyribionucleic acid |
| **ECLAM:** | *European Consensus Lupus Activity Measurement* |
| **EEG:** | Electroencephalogram |
| **ELISA:** | *Enzyme-linked immunosorbent assay* |
| **ELNT:** | *Eurolupus Nephritis Trial* |
| **ENA:** | *Extractable nuclear antigens* |
| **EPA:** | *Eicosapentaenoic acid* |
| **ESR:** | Erythrocyte sedimentation rate |
| **EULAR:** | *European League Against Rheumatism* |
| **EUSCLE:** | *European Society of Cutaneous Lupus Erythematosus* |
| **FDA:** | *Food and Drug Administration* |
| **FELUPUS:** | Spanish Lupus Federation |
| **FSS:** | *Fatigue Severity Scale* |
| **FUNCIS:** | Canary Island Foundation of Research and Health |
| **GEAS:** | Group of systemic autoimmune diseases |
| **GLADEL:** | Latin American Study Group of Lupus Erythematosus |
| **GP:** | Glucoprotein |
| **HBV:** | Hepatitis B virus |
| **HCQ:** | Hydroxychloroquine |
| **HCV:** | Hepatitis C virus |
| **HDL:** | *High density lipoprotein* |
| **HIV:** | Human immunodeficiency virus |
| **HPV:** | Human papilloma virus |
| **HR:** | *Hazard ratio* |
| **HRQoL:** | Health-related quality of life |
| **HRT:** | Hormone replacement therapy |
| **IB:** | Immunoblotting |
| **ICD:** | Counterimmunoelectrophoresis |
| **IIF:** | Indirect immunofluorescence |
| **Ig:** | Immunoglobulin |

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|---|---|
| **INR:** | *International Normalised Ratio* |
| **IR:** | *Infrared radiation* |
| **ISN/RPS:** | *International Society of Nephrology/Renal Pathology Society* |
| **ITP:** | Idiopathic thrombocytopenic purpura |
| **IUD:** | Intrauterine device |
| **LA:** | Lupus anticoagulant |
| **LAI:** | *Lupus Activity Index* |
| **LDIQ:** | *Lupus Damage Index Questionnaire* |
| **LDL:** | *Low density lipoprotein* |
| **LEF:** | Leflunomide |
| **LMWH:** | Low Molecular Weight Heparin |
| **LN:** | Lupus nephritis |
| **MA:** | Meta-analysis |
| **MAT:** | Thrombotic microangiopathy |
| **MMF:** | Mycophenolate mofetil |
| **MIA:** | microsphere-based immunoassays |
| **MPred:** | Methylprednisolone |
| **MRI:** | Magnetic Resonance imaging |
| **MTX:** | Methotrexate |
| **n:** | Sample size |
| **nRCT:** | Non-randomised clinical trial |
| **NICE:** | *National Institute for Health and Care Excellence* |
| **NIH:** | *National Institutes of Health* |
| **NLR:** | Negative likelihood ratio |
| **NP-SLE** | **Neuropsychiatric systemic lupus erythematosus** |
| **NSAID:** | Non-Steroid Anti-inflammatory Drugs |
| **NYHA:** | *New York Heart Association* |
| **OR:** | *Odds ratio* |
| **PET:** | *Positron emission tomography* |
| **PGA:** | *Physician Global Assessment* |
| **PR:** | Partial response |
| **PLR:** | Positive likelihood ratio |
| **PT:** | Prothrombin |
| **QFT-G:** | *QuantiFERON Gold test* |
| **RA:** | Rheumatoid arthritis |
| **RCT:** | Randomised clinical trial |
| **RIA:** | Radioimmunoassay |
| **RIFLE:** | *Responder Index for Lupus Erythematosus* |

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| | |
|---|---|
| **RNA:** | Ribonucleic acid |
| **RNP:** | Ribonucleoproteins |
| **RR:** | Relative risk |
| **RTX:** | Rituximab |
| **SAD:** | Systemic autoimmune disease |
| **SAID:** | Systemic autoimmune disease |
| **SELENA:** | *Safety of Estrogens in Lupus Erythematosus National Assessment* |
| **SEMI:** | Spanish Society of Internal Medicine |
| **SEN:** | Spanish Neurology Society |
| **SER:** | Spanish Rheumatology Society |
| **SF-36:** | *36-item Short-Form Health Survey* |
| **SIGN:** | *Scottish intercollegiate guidelines network* |
| **SIR:** | *Standardised Incidence Ratio* |
| **SLAM:** | *Systemic Lupus Activity Measure* |
| **SLAM-R:** | Reviewed SLAM |
| **SLE:** | Systemic lupus erythematosus |
| **SLAQ:** | *Systemic Lupus Activity Questionnaire* |
| **SLE:** | *Systemic Lupus Erythematosus* |
| **SLEDAI:** | *Systemic Lupus Erythematosus Disease Activity Index* |
| **SLEDAI-2K:** | *Systemic Lupus Erythematosus Disease Activity Index 2000* |
| **SLICC:** | *Systemic Lupus International Collaborating Clinics* |
| **SMR:** | Standardised mortality ratio |
| **snRNP:** | Small nuclear ribonucleoprotein polypeptide |
| **SNS:** | Spanish National Health System |
| **SPECT:** | *Single positron emission computed tomography* |
| **SPF:** | Sun protection factor: |
| **SR:** | Systematic review |
| **SRI:** | *SLE Responder Index* |
| **TNF:** | *Tumour necrosis factor* |
| **TST:** | *Tuberculin skin test* |
| **TWEAK:** | TNF-*like weak inducer of apoptosis* |
| **UV:** | Ultraviolet |
| **UVA:** | Ultraviolet A |
| **UVB:** | Ultraviolet B: |
| **WHO:** | World Health Organisation |

**MEASUREMENT UNITS**

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|---|---|
| **cm:** | centimetre |

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|---|---|
| **dl:** | decilitre |
| **g:** | gram |
| **h:** | hour |
| **IU:** | International Units |
| **kg:** | kilogram |
| **l:** | litre |
| **mg:** | milligram |
| **ml:** | millilitre |
| **µg:** | µgram |

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