Consensus statement

Clinical practice guidelines for systemic lupus erythematosus:
Recommendations for general clinical management

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OBJECTIVE

Systemic lupus erythematosus (SLE) is a complex rheumatic multisystemic disease of autoimmune origin with significant potential morbidity and mortality. It is one of the most common autoimmune diseases with an estimated prevalence of 20–150 cases per 100,000 inhabitants. The clinical spectrum of SLE is wide and variable both in clinical manifestations and severity. This prompted the Spanish Ministry of Health, Social Services and Equality to promote and fund the development of a clinical practice guideline (CPG) for the clinical care of SLE patients within the Programme of CPG in the National Health System which coordinates GuíaSalud. This CPG is intended as the reference tool in the Spanish National Health System in order to support the comprehensive clinical management of people with SLE by all health professionals involved, regardless of specialty and level of care, helping to standardize and improve the quality of clinical decisions in our context in order to improve the health outcomes of the people affected. The purpose of this document is to present and discuss the rationale of the recommendations on the general management of SLE, specifically, clinical follow-up, general therapeutic approach, healthy lifestyles, photoprotection, and training programs for patients. These recommendations are based on the best available scientific evidence, on discussion and the consensus of expert groups.

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Introduction

Systemic lupus erythematosus (SLE) is a complex, multisystemic, chronic and autoimmune disease and affects about half a million people in Europe. The prevalence in Spain has been estimated at around 9/10,000 inhabitants. Although the prognosis has improved in recent years, the quality of life of patients with SLE is lower than the general population and the risk of death is 2–3 times higher, with a significant socioeconomic impact.

The systemic nature of SLE requires a cooperative approach from various medical specialties. To this end, to help reduce differences in clinical practice and potential unwanted effects of care fragmentation and also improve the clinical management of people affected by SLE, the European League Against Rheumatism (EULAR) prepared in 2008 a set of 12 recommendations based on the scientific evidence available for the purpose of guiding the clinical decisions. Other 2 recommendation documents on SLE management were published in 2011 and 2013 respectively in Spain and Chile, with a limited degree of interdisciplinary participation and methodological transparency.

The Institute of Medicine of the USA described in 2011 a clinical practice guideline (CPG) as a set of recommendations to support clinical decisions and improve patient care. This CPG is based on the best scientific evidence from systematic reviews of the literature, where the benefits and risks of several alternatives have been considered. GuiaSalud is the agency of the Spanish National Health System (NHS) responsible for promoting the development, dissemination and use of CPGs and other tools and products based on scientific evidence [www.guiasalud.es].

The complexity involved in the clinical management of SLE along with the requirement of multidisciplinary approach, the recent development of new drugs with high economic impact, limited range of clinical questions previously addressed by the EULAR recommendations and the added need to update the scientific basis supporting these recommendations, justify the decision of the Ministry of Health to fund the development of a CPG on SLE (CPG-SLE). This activity was entrusted to the Assessment Service of the Canary Islands Health Service as part of the Spanish Network of Agencies for Health Technology Assessment and NHS assistance [BOE order SSI/1833/2013, 2 October].

The CPG-SLE addressed the assistance provided from primary care and specialized care to adults affected by SLE excluding the disease involving only the skin (cutaneous lupus) and patients with advanced renal failure. Sixty clinical questions were responded in 5 major sections: diagnosis, general management, management of specific clinical manifestations (renal, hematologic, mucocutaneous, neuropsychiatric and joint manifestations and antiphospholipid syndrome), sexual and reproductive health and, finally, comorbidity. This large number of questions have had to be split to enable their dissemination in general scientific journals in Spain. In this paper the report and discuss the recommendations suggested in response to clinical questions considered in the CPG on the general management of SLE patients.

The recommendations are based on scientific evidence available when drafting the guide or, if no evidence available, on the discussion and consensus of expert groups. These recommendations should be reviewed in the coming years when new relevant scientific knowledge is available.

Methods

This CPG was performed following the Methodology Manual on the Development of CPGs at the NHS and following the quality criteria provided in the AGRE II instrument. The methodology is detailed in the full document of the guideline.

The guideline development group (GDG) consisted of specialists in rheumatology, internal medicine, nephrology, hematology, dermatology, immunology, family and community medicine and clinical pharmacy, along with a nurse assigned to a hospital rheumatology department, a representative of patients, and CPG methodologists.

To ensure that this CPG gave answers to the most important health requirements perceived by SLE patients, from the initial design phase, 2 additional activities were conducted; a systematic review of the international literature and, subsequently, a survey to SLE patients in Spain.

Once the scope and objectives of the CPG-SLE has been defined, to specify its contents, there was a process of identifying and prioritizing the clinical questions to be included, which would be answered with the available scientific evidence, and the recommendations would be based on that. Table 1 shows the 17 questions for the general management of SLE patients finally included.

The literature searches were run until December 2013 in the following electronic databases: 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. To identify potential relevant clinical trials published subsequently, the entire working group was consulted until April 2014, deadline for the first draft of the guideline.

The studies considered were systematic reviews, meta-analyses, experimental, quasi-experimental studies and observational studies in adults (≥18 years) with SLE, published in English and Spanish. The clinical trials focusing on cutaneous lupus or in patients with advanced renal failure on dialysis, or kidney transplant recipients, were excluded. If the study intervention was addressed to a heterogeneous group of patients, the study was included if the results for target patients of CPG-SLE were reported separately or if they represented more than 80% of the target population. Qualitative studies, studies with fewer than 5 participants, conference proceedings and protocols were also excluded.
Levels of evidence and degrees of recommendation were established in accordance with the classification proposed by the Scottish Intercollegiate Guidelines Network (SIGN) (Table 2). To determine the strength of the recommendations, not only the level of evidence available was considered but also the balance between the desirable and undesirable consequences of carrying out the recommendation. When the GDG found important practical aspects considered necessary to emphasize but with no available scientific evidence, recommendations were formulated for good clinical practice (identified as √), agreed by consensus of a group of experts following a modified standard Delphi methodology.

In order to improve the quality of the guideline, after the GDG ordered an advanced draft, it was externally reviewed by a multidisciplinary group of experts in various clinical areas, methodology experts and a representative of the patients.

The selection of members of the GDG, panel of experts to reach a consensus on the recommendations of best practices, and external reviewers of the guideline, was carried out with the cooperation of the relevant scientific societies. All of them filled out and signed a form of potential conflicts of interest. No conflicts were reported limiting the participation of any of these people in the development of the CPG-SLE.

### Results

Below, we report the 49 recommendations of the CPG-SLE on the overall management of SLE patients, briefly discussing some fundamentals. The recommendations are organized under five different headings: clinical follow-up (Table 3); general therapeutic approach (Table 4), measures on lifestyle, photoprotection and training for patients (Table 5). The order of the recommendations does not respond to their significance or consistency but conforms to the logical sequence in a clinical and procedural hierarchy. The GDG selected 20 key recommendations, because of their most significant clinical relevance and special priority in implementation, which are identified in the relevant tables on gray background.

#### Recommendations and analysis of evidence

### Clinical follow-up

#### Clinical follow-up protocol and additional tests

1. **A comprehensive assessment is suggested (clinical and laboratory assessment) in confirming the diagnosis of SLE** (recommendation √).

No studies are available evaluating clinical follow-up protocols in SLE patients. Therefore, this is a recommendation of good clinical practice based on the recommendation of international professional organizations. GDG clinical experience and consensus of the expert group.

2. **The activity of SLE, organ damage, comorbidities (including vascular risk factors) and the possible toxicity of drug treatment should be monitored through: clinical interview, physical examination, blood pressure measurements and basic testing (blood count, renal biochemistry profile and urinalysis, complement and anti-dsDNA)** (recommendation √).
The lack of scientific evidence on monitoring SLE patients requires that this evidence be based on the opinion and consensus among experts, who recommend assessing at least once a year the standard factors of cardiovascular risk, the presence of vascular events, and physical activity. Among the additional tests, there is a consensus among experts to request a blood count during follow-up, a biochemical test with glucose, lipids, renal profile and urinalysis, complement and anti-dsDNA.

### Predictors of outbreak or increased disease activity

1. **Studies reporting that antinucleosoma or anti-C1q antibodies appear to predict SLE outbreaks better than levels of anti-dsDNA antibodies have no sufficient scientific validity,** placing these prognostic determinations as merely promising.

#### Overall therapeutic approach

**Therapeutic purposes.**

10. **The recommendation as a major therapeutic purpose is to monitor the perceived or verifiable clinical activity, preventing irreversible damage due to SLE or its therapies, trying to reduce the impact on quality of life and increase survival of patients** (evidence 2++/2+, recommendation B).

The risk of death in people with SLE is 3 times higher than the general population due to cardiovascular, infectious or kidney causes. The irreversible organ damage is the major predictor of mortality, especially if it happens in kidney or neuropsychiatric level. The lupus outbreaks and kidney and neurological condition, hypertension, antiphospholipid antibodies and antiphospholipid syndrome are associated with development of damage. Moreover, therapy with cyclophosphamide and azathioprine and especially with glucocorticoids increases the risk of damage. Serologically active patients in prolonged clinical remission report a favorable evolution and require no active

**Table 3**

<table>
<thead>
<tr>
<th>Recommendations for follow-up</th>
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<tbody>
<tr>
<td>1. A comprehensive assessment is suggested (clinical and laboratory assessment) in confirming the diagnosis of SLE</td>
<td>✓</td>
</tr>
<tr>
<td>2. The activity of SLE, organ damage, comorbidities (including vascular risk factors) and the possible toxicity of drug treatment should be monitored through: clinical interview, physical examination, blood pressure measurements and basic testing (blood count, renal biochemistry profile and urinalysis, complement and anti-dsDNA)</td>
<td>✓</td>
</tr>
<tr>
<td>3. In people with active SLE, monitoring interval is variable and must be adjusted to the clinical severity</td>
<td>✓</td>
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<tr>
<td>4. In the clinical and laboratory remission, monitoring is suggested every 6–12 months, depending on the time of course of disease and treatment intensity</td>
<td>✓</td>
</tr>
<tr>
<td>5. In patients clinically quiescent with maintained laboratory activity criteria, closer monitoring is suggested, every 3–4 months during the first years</td>
<td>C</td>
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<tr>
<td>6. Periodic determination of C3, C4 and anti-dsDNA is recommended as markers of active disease and risk of lupus nephritis</td>
<td>B</td>
</tr>
<tr>
<td>7. Levels of 25-OH vitamin D should be periodically measured when there are risk factors for osteoporotic fracture</td>
<td>D</td>
</tr>
<tr>
<td>Assessing the state of health of SLE patients</td>
<td>✓</td>
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<tr>
<td>8. The use of validated instruments is recommended to quantify the degree of activity, cumulative damage and quality of life</td>
<td>✓</td>
</tr>
<tr>
<td>Predictors of outbreak or increased disease activity</td>
<td>✓</td>
</tr>
<tr>
<td>9. Routine use of anti-C1q and antinucleosoma antibodies is not recommended as markers of lupus nephritis.</td>
<td>✓</td>
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SLE, systemic lupus erythematosus.

With gray background, key recommendation.
Table 4
Recommendations for general therapeutic approach.

<table>
<thead>
<tr>
<th>Therapeutic purposes</th>
<th>Degree</th>
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<tbody>
<tr>
<td>1. The recommendation as a major therapeutic purpose is to monitor the perceived or verifiable clinical activity, preventing irreversible damage due to SLE or its therapies, trying to reduce the impact on quality of life and increase survival of patients</td>
<td>B</td>
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<tr>
<th>Indications for treatment</th>
<th>Degree</th>
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<tbody>
<tr>
<td>11. The use of antimartials is recommended indefinitely (preferably hydroxychloroquine [HCQ] for best safety) as the baseline treatment of all SLE patients without contraindications for use</td>
<td>B</td>
</tr>
<tr>
<td>12. Combined mepredicine and HCQ is suggested in patients with refractory lupus activity, especially cutaneous, due to its potential synergistic effects</td>
<td>D</td>
</tr>
<tr>
<td>13. In patients with antimartial-induced retinal toxicity replacing HCQ or chloroquine with mepredicine is suggested</td>
<td>D</td>
</tr>
<tr>
<td>14. Monitoring the retinal toxicity is suggested in patients treated with HCQ or chloroquine</td>
<td>D</td>
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<tr>
<th>Biological purposes</th>
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<tbody>
<tr>
<td>15. Predniolone dose should not exceed 30 mg/day in patients with lupus nephritis. The dose should be individualized</td>
<td>B</td>
</tr>
<tr>
<td>16. Predniolone dose should not exceed 30 mg/day in the remaining SLE manifestations. However, the dosage should be assessed individually for each patient</td>
<td>√</td>
</tr>
<tr>
<td>17. In severe outbreaks, adjuvant therapy is recommended with pulses of methyl predniolone</td>
<td>B</td>
</tr>
<tr>
<td>18. Quick reduction of glucocorticoids (predniolone) to 5 mg/day is recommended within 6 months, with full withdrawal as soon as possible</td>
<td>C</td>
</tr>
<tr>
<td>19. If maintenance therapy is required, doses of predniolone should not exceed 5 mg/day</td>
<td>B</td>
</tr>
<tr>
<td>20. The use of pulses of methylpredniolone below 1000 mg has been suggested. However, a specific dose cannot be recommended</td>
<td>√</td>
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<table>
<thead>
<tr>
<th>Biological therapies</th>
<th>Degree</th>
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<tbody>
<tr>
<td>21. Intravenous cyclophosphamide is recommended as the first immunosuppressant drug in the treatment of severe non-renal manifestations</td>
<td>B</td>
</tr>
<tr>
<td>22. Methotrexate is recommended as the first immunosuppressant drug in the treatment of non-renal SLE with moderate activity, particularly on skin and joint manifestations</td>
<td>A</td>
</tr>
<tr>
<td>23. The use of immunosuppressants such as azathioprine, cyclosporine A, leflunomide or mycophenolate is recommended as alternatives to the treatment of non-renal SLE</td>
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<tr>
<th>Biological therapies</th>
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<tbody>
<tr>
<td>24. Belimumab is recommended in subjects with active SLE not caused by renal or neurological condition, not responding to standard treatment</td>
<td>A</td>
</tr>
<tr>
<td>25. Candidates for treatment with belimumab are subjects with active SLE and lack of response after at least 3 months of treatment, including anti-marial and predniolone and at least one immunosuppressant at suitable dose. Or, when requiring predniolone at 7.5 mg/day or higher to maintain remission despite the use of antimartials and, at least, one immunosuppressant. Or with the contraindication of immunosuppressants</td>
<td>B</td>
</tr>
<tr>
<td>26. Rituximab is recommended in patients with renal, neurological or severe hematoologic condition not responding to first-line immunosuppressive therapy</td>
<td>C</td>
</tr>
<tr>
<td>27. Today, there is no approved indication for the use of any other biological agents in SLE. However, when they have failed or the routine therapeutic measures cannot be used (including belimumab and rituximab), the following could be considered: infliximab (in refractory arthritis and nephritis), etanercept (arthritis and serositis), abatacept (especially in arthritis) and tocilizumab (deficient control of clinical activity)</td>
<td>√</td>
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<tr>
<th>Biological therapies</th>
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<tr>
<td>28. The use of intravenous immunoglobulins is justified in severe immune thrombocytopenia with life threatening risk for active bleeding or when surgery or bleeding-risk procedure is required</td>
<td>D</td>
</tr>
<tr>
<td>29. The risk of toxicity associated with immunoglobulin should be reduced, considering in each case the balance between risks and benefits, and also controlling the rate of infusion, avoiding compounds with high sucrose content and previously discarding immunoglobulin A deficiency. Ensuring hydration and considering thromboprophylaxis with heparin is recommended, to prevent the risk of thrombosis. In patients at risk of renal failure, associated, monitoring of renal function is suggested in the days following the infusion</td>
<td>D</td>
</tr>
<tr>
<td>30. The intravenous immunoglobulins may be used in people with high organ activity and involvement, highest in the presence of or suspected serious infection substantially limiting or contraindicating immunosuppressive therapy at 0.4 g/kg/day doses for 5 consecutive days. Lower doses (e.g. 0.5 g/kg one day) can also be effective, except with thrombocytopenia</td>
<td>√</td>
</tr>
<tr>
<td>31. Intravenous immunoglobulins are not recommended in maintenance treatment of any of the SLE manifestations since more effective and lower cost alternative therapies are available</td>
<td>√</td>
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<tr>
<th>Monitoring guidelines for the immunosuppressive and biological therapies</th>
<th>Degree</th>
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<tbody>
<tr>
<td>32. For monitoring hematological and liver toxicity of immunosuppressants, blood count and liver biochemistry is recommended at one to three month intervals</td>
<td>B</td>
</tr>
<tr>
<td>33. In patients treated with cyclophosphamide, active monitoring of bladder cancer is recommended by urinalysis to detect microscopic hematuria. This monitoring should not be discontinued after treatment discontinuation</td>
<td>B</td>
</tr>
<tr>
<td>34. Thiopurine methyltransferase enzyme activity or its polymorphisms should be determined before treatment with azathioprine</td>
<td>D</td>
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<tr>
<th>Indication of therapeutic apheresis</th>
<th>Degree</th>
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<tbody>
<tr>
<td>35. Apheresis is not recommended as first or second line therapy in general SLE or lupus nephritis</td>
<td>A</td>
</tr>
<tr>
<td>36. In severe cases refractory to other treatments, using plasmapheresis individually should be considered</td>
<td>C</td>
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<tr>
<th>Prevention of disease reactivation</th>
<th>Degree</th>
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<tbody>
<tr>
<td>37. Prolonged antimartial therapy is recommended, even during pregnancy, to prevent SLE reactivation</td>
<td>A</td>
</tr>
<tr>
<td>38. Due to the unfavorable balance between the beneficial effect reported and the potential toxicity associated with excess glucocorticoid therapy, preventive administration of predniolone is not recommended for patients with serological activity without associated clinical manifestations</td>
<td>A</td>
</tr>
<tr>
<td>39. Patients with serologically active and clinically quiescent lupus are not recommended to undergo immunosuppressive therapy to prevent outbreaks beyond their baseline treatment or remission maintenance therapy of lupus nephritis</td>
<td>B</td>
</tr>
<tr>
<td>40. Although vitamin D supplementation is not recommended with the sole aim of preventing activity outbreaks, the vitamin D deficiency should be corrected due to its adverse effects on bone mass and asthenia (only to normalize levels), not discarding a beneficial effect in controlling lupus activity</td>
<td>C</td>
</tr>
<tr>
<td>41. In addition to its harmful impact on overall health, smoking is not recommended for its potential effect on lupus activity, particularly at skin level</td>
<td>C</td>
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<tr>
<th>Treatment of associated asthma</th>
<th>Degree</th>
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<tbody>
<tr>
<td>Recommendation 40</td>
<td>√</td>
</tr>
<tr>
<td>42. Despite the effectiveness data arising from RCTs, the administration of belimumab is not recommended for the sole purpose of improving asthma</td>
<td>B</td>
</tr>
<tr>
<td>43. People with stable SLE should follow gradual home sessions of supervised aerobic exercise, due to its overall improvement effect on perceived health status by patients</td>
<td>B</td>
</tr>
<tr>
<td>44. Psychoeducational support is recommended to improve knowledge and understanding of the disease, restructure beliefs, and improve coping skills, self-management and social support</td>
<td>B</td>
</tr>
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</table>

RCT: randomized clinical trial; SLE: systemic lupus erythematosus.
With gray background, key recommendation.
drug treatment aimed at improving the analytical parameters. For these reasons, expert groups have also pointed out similar objectives in managing SLE. Other intermediate objectives are the complete clinical response, disease stabilization and discontinuation of immunosuppressive and steroidal therapy.

**Indications for treatment. Use of antimalarials**

11. The use of antimalarials (preferably hydroxychloroquine [HCQ] for best safety) is recommended as the baseline treatment of all SLE patients without contraindications for use (evidence 2++, recommendation B).

Antimalarial treatment increases survival in SLE patients. Specifically, their use reduces the risk of outbreaks, irreversible organ damage, severe infections, arterial and venous thrombosis and metabolic syndrome in SLE patients. They also have a low frequency and severity of adverse effects. Chloroquine toxicity is higher compared to HCQ, particularly in retina.

12. Combined mepracine and HCQ is suggested in patients with refractory lupus activity, especially cutaneous, due to the synergistic effects caused (evidence 3, recommendation D).

It has been reported that the addition of mepracine to baseline therapy (including HCQ) in subjects with active SLE decreases disease activity and prednisone dose.

13. In patients with antimalarial-induced retinal toxicity, replacing HCQ or chloroquine with mepracine is suggested (evidence 3, recommendation D).

The risk of HCQ-induced retinal toxicity appears to increase relevantly from cumulative dose of 1000 g. For mepracine, however, retinal toxicity has not been reported. This drug has not been marketed in Spain but it can be obtained through hospital pharmacies as a foreign medication.

14. Monitoring retinal toxicity is suggested in patients treated with HCQ or chloroquine. A baseline eye examination is recommended at least during the first year of treatment and annually after 5 years of treatment, although control should be started earlier in patients with macular disease from any other source or with additional risk factors (evidence 2++/2−/4, recommendation D).

Because of the risk of retinal toxicity associated with prolonged use of HCQ and, mainly, with chloroquine, periodic monitoring of the potential retinal involvement is recommended. The recommendation regarding the frequency of eye examinations arises from the most recent recommendations of the American College of Ophthalmology. Among these recommendations, the following techniques of screening should be included: at least a sensitive technique such as spectral domain optical coherence tomography, retinal autofluorescence or multifocal electroretinography with an automated visual field 10-2.

**Use of glucocorticoids**

15. Prednisone dose should not exceed 30 mg/day in patients with lupus nephritis. The dose should be individualized (evidence 1−/2+, recommendation B).

Treatment with average doses of prednisone (≤30 mg/day) obtain a similar response rate to high-dose treatment in patients with lupus nephritis, reducing the risk of adverse events. Long-term renal prognosis appears to be best in patients with lupus nephritis treated with average doses of prednisone (≤30 mg/day), pulses of methylprednisolone, HCQ and cyclophosphamide compared to patients treated with high doses of prednisone and cyclophosphamide. However the evidence supporting this statement is still low.

16. Prednisone dose should not exceed 30 mg/day in the remaining SLE manifestations. However, the dosage should be assessed individually for each patient (recommendation C).

This recommendation was carried out by consensus, from the evidence showing that glucocorticoid therapy increases the risk of infections regardless of the dosage and it is associated with irreversible damage, with no comparative data to support the higher effectiveness of high-dose compared to low-mid dosage.

17. In severe outbreaks, adjuvant therapy with methylprednisolone pulses is recommended (evidence 1+/1−, recommendation A).


18. Quick reduction of glucocorticoids (prednisone) to 5 mg/day is recommended within 6 months, with full withdrawal as soon as possible (evidence 2+/2++, recommendation C).

Glucocorticoid therapy is associated with irreversible damage and it increases the risk of infections depending on the dosage.

19. If maintenance treatment is required, doses of prednisone should not exceed 5 mg/day (evidence 2+/2++, recommendation B).

There are data supporting that prednisone doses below 5–6 mg/day do not cause an increased risk of clinically relevant irreversible damage, although the purpose is full suspension.

20. The use of pulses of methylprednisolone below 1000 mg has been suggested. However, a specific dose cannot be recommended (recommendation C).

Pulses of methylprednisolone do not cause serious adverse effects and irreversible damage when used at doses below 1000 mg/day. At higher doses they are associated with increased risk of serious infection. With this evidence, assessed as low (1−/2−/3−), it was only possible to formulate a recommendation of good practice.

Using nonbiological immunosuppressants

21. Intravenous cyclophosphamide is recommended as the first immunosuppressant drug in the treatment of severe non-renal manifestations (evidence 1+/1−, recommendation B).

Intravenous cyclophosphamide with prednisone or methylprednisolone is better than glucocorticoids alone in the short- and long-term neuropsychiatric SLE treatment and in reducing their relapses. Cyclophosphamide also improves functional class of
the New York Heart Association scale and reduces systolic pulmonary artery pressure in patients with SLA-associated pulmonary arterial hypertension.80 This recommendation is also supported by a systematic review of the evidence.81

22. Methotrexate is recommended as the first immunosuppressant drug in the treatment of non-renal SLE with moderate activity, particularly in skin and joint manifestations (evidence 1++, recommendation A).

In subjects with extrarenal lupus activity, despite standard treatment, the combination with methotrexate (7.5–20 mg/week) reduces the overall, joint and skin activity of the disease in the short/medium term (6/12 months) with a glucocorticoid sparing effect.82,83

23. The use of immunosuppressants such as azathioprine, cyclosporine A, leflunomide or mycophenolate is recommended as alternatives to the treatment of non-renal SLE (recommendation J).

The association of azathioprine with prednisone might reduce the relapse rate in people with serious SLE.84 In patients with renal and/or non-renal activity refractory to glucocorticoids or in glucocorticoid-dependent patients, the addition of cyclosporin A may reduce the activity and induce remission of the disease in the short term. Treatment with cyclosporine A is no less effective than azathioprine and both drugs have a similar glucocorticoid sparing effect in the medium term.84 The addition of cyclosporin A has also shown a glucocorticoid sparing effect in the long term.85 In patients with mild to moderate activity despite prednisone, leflunomide is more effective than placebo in reducing disease activity in the short term.86

Use of biological treatments

24. Belimumab is recommended in subjects with active SLE with no renal or neurological involvement not responding to standard treatment (evidence 1+/+1+, recommendation).

This recommendation is based on evidence from randomized clinical trials (RCTs) that prove that belimumab is effective in individuals with active SLE not responding to standard treatment.87,88 Belimumab has shown particular effectiveness in treating SLE musculoskeletal and cutaneous manifestations.89

25. Candidates for treatment with belimumab are subjects with active SLE and lack of response after at least 3 months of treatment, including anti-malarial and prednisone therapy and at least one immunosuppressant at suitable dose. Or, when requiring prednisone at 7.5 mg/day of higher to maintain remission despite the use of antimalarial and, at least, an immunosuppressant. Or with the contraindication of immunosuppressants (evidence 2++, B recommendation).

There is sufficient evidence to recommend, as candidates for treatment with belimumab, SLE patients not responding to a comprehensive therapy with antimalarials, prednisone and, at least, an immunosuppressant at suitable dose. However, the data are more limited over the time that must elapse to consider that the standard treatment has failed. The GDG recommends at least 3 months. Candidates can also be patients requiring prednisone (or equivalent glucocorticoid dose) at 7.5 mg/day doses or higher to maintain remission (given the risk of damage associated with doses maintained above this limit), despite being concomitantly receiving antimalarials and at least one immunosuppressant. Finally, candidates may also be SLE patients with a contraindication to use immunosuppressants.90

26. Rituximab is recommended in patients with renal, neurological or severe hematologic disorders not responding to first-line immunosuppressive therapy (evidence 2+, recommendation C).

Based on observational studies,91–94 rituximab appears to be effective in people with active SLE refractory to standard immunosuppressive therapy, including severe renal and neurological disorders, although in the 2 RCTs conducted to date (in active SLE without renal or CNS disorders and in lupus nephritis) the primary purposes have not been reached.95–97

27. Today, there is no approved indication for the use of other biological agents in SLE. However, when they have failed or the usual therapeutic measures cannot be used (including belimumab and rituximab), the following could be considered: infliximab (in refractory arthritis and nephritis), etanercept (arthritis and serositis), abatacept (especially in arthritis) and tocilizumab (deficient control of clinical activity) (recommendation J).

Infliximab has shown to have some effectiveness in lupus patients with refractory nephritis and arthritis, but with a narrow margin of safety.98 Etanercept was effective in patients with refractory arthritis and serositis without serious adverse effects in the short-term without worsening of renal activity.99 Abatacept might be effective in lupus arthritis.99 Tocilizumab has shown some benefits in the control of SLE clinical activity.100 All these studies evaluating these drugs individually, present a very high risk of bias (evidence 1−/2−/−3). Therefore, the GDG decided that this recommendation should be for good practice. This recommendation of good practice is in line with the proposals in the Consensus of the Spanish Society of Rheumatology on the use of biologic therapy in SLE.99

Use of immunoglobulins

28. The use of intravenous immunoglobulins is justified in severe immune thrombocytopenia with life threatening risk for active bleeding or when surgery or a bleeding-risk procedure is required (evidence 3, recommendation D).

Intravenous immunoglobulins can be effective in patients with SLE-associated severe thrombocytopenia, being potentially useful in situations of active bleeding by their rapid onset of action, although their effects are transient in most cases.101

29. The risk of toxicity associated with immunoglobulin should be reduced, considering in each case the balance between risks and benefits, and also controlling the rate of infusion, avoiding compounds with high sucrose content and previously discarding immunoglobulin A deficiency. Ensuring hydration and considering thromboprophylaxis with heparin is recommended, to prevent the risk of thrombosis. In patients at risk of renal failure associated, monitoring of renal function is suggested in the days following the infusion (evidence 4, recommendation D).

The risks inherent to the indication and administration of intravenous immunoglobulin can be reduced if the risk factors associated with potential adverse effects are considered and if preventive measures are used to improve the safety of intravenous administration.102

30. The intravenous immunoglobulins may be used in people with high organ activity and involvement, highest in the presence of or suspected serious infection substantially limiting or contraindicating immunosuppressive therapy at 0.4 g/kg/day doses for 5 consecutive days. Lower doses (e.g. 0.5 g/kg one day) can also be effective, except with thrombocytopenia (recommendation J).

The use of intravenous immunoglobulins is not associated with an increased risk of acute infection103,104 having shown an acceptable safety profile when used in patients with active SLE or blood disorders104–105 and they can be effective as maintenance treatment in lupus nephritis.106,107 This evidence, however, was assessed as high risk of bias (1−/2−/−3) which justified the recommendation was on good practice.

31. No intravenous immunoglobulin is recommended in the maintenance therapy of any of the SLE manifestations since more effective and lower cost alternative therapies are available (recommendation J).

Despite the evidence on the potential effectiveness of intravenous immunoglobulin in the maintenance therapy in lupus nephritis and because of its acceptable level of safety, the panel
of experts stresses they should not be used in the maintenance of any SLE manifestations, since best cost-effective ratio alternatives are available.106,107

Adverse effects and monitoring guidelines of biological and immunosuppressive therapies. 32. For monitoring hematological and liver toxicity of immunosuppressants, blood count and liver biochemistry is recommended at one to three month intervals (evidence 1++, recommendation B).

This recommendation is based on a systematic review of recommendations for monitoring the drugs commonly used in SLE108 that, according to its authors, is based on the opinion of expert groups.

33. In patients treated with cyclophosphamide, active monitoring of bladder cancer is recommended by urinalysis to detect microscopic hematuria. This monitoring should not cease after treatment discontinuation (evidence 1+, recommendation B).

A systematic review concluded that cyclophosphamide is associated with cumulative damage, development of cervical intraepithelial neoplasia, urothelial neoplasms and ovarian failure.108 In the treatment of lupus nephritis, mycophenolate mofetil has a better safety profile compared to oral or intravenous cyclophosphamide. In the absence of data, the GDG has not been positioned on specific screening recommendations for cervical cancer in women undergoing immunosuppressive therapy, other than those recommended in the general population.17,109

34. Determining the thiopurine methyltransferase enzyme activity or its polymorphisms is recommended before treatment with azathioprine (evidence 2+, recommendation D).

There is poor evidence that reducing the thiopurine methyltransferase enzyme activity is associated with an increased risk of serious adverse effects in homozygous patients treated with azathioprine.110

Indication of the therapeutic apheresis.

35. Apheresis as first or second line therapy is not recommended either in people with general SLE or with lupus nephritis (evidence 1++ to 2+, recommendation A).

Although treatment with extracorporeal immunoadsorption is a form of safe and effective apheresis for reducing proteinuria,111 C3, C4 levels112 and the circulating immune complexes,113 the available studies do not show that the addition of other plasmapheresis procedures to traditional therapies improve the course of mild SLE or lupus nephritis.114,115 In addition, other studies report a higher frequency of life-threatening infections in SLE patients treated with plasmapheresis (in addition to treatment with prednisone plus cyclophosphamide).116 However, these data are not consistent in the literature.117

36. In severe cases refractory to other treatments, using plasmapheresis individually should be considered (evidence 1+ to 2+, recommendation C).

Therapeutic apheresis may be an additional option in the treatment of severe SLE. The choice of treatment with plasmapheresis should be individualized depending on the patient’s conditions, the experience of the center and financial aspects.118,119 Synchronizing therapy with plasmapheresis might be useful in inducing remission in patients with proliferative lupus nephritis,111,120 and in decreasing SLE clinical activity.121−124

Prevention of disease reactivation.

37. Prolonged antimalarial treatment is recommended, even during pregnancy, to prevent SLE reactivation (evidence 1++ to 2++, recommendation A).

Antimalarials reduce the risk of no serious outbreaks and, possibly, the risk of serious outbreaks in SLE patients, including pregnant women.20,123,126 Low blood levels of HCQ are associated with a higher likelihood of having a lupus outbreak.127 In the GDG’s opinion, this recommendation, despite being strong, should be subject to a process of shared decision-making between the professional and the pregnant woman.

38. Due to the unfavorable balance between the beneficial effect observed and the potential toxicity associated with excess glucocorticoid therapy, preventive administration of prednisone is not recommended for patients with serologic activity without associated clinical manifestations (evidence 1++ to 2++, recommendation A).

Therapy with medium-dose prednisone prevents short-term outbreaks associated with significant increased anti-dsDNA antibodies, with a significant difference even in serious outbreaks.128,129 However, GDG does not recommend preventive use since it causes increased cumulative dose of prednisone with an unfavorable benefit/risk ratio.128,129

39. Patients with lupus and serologically active clinically quiescent are not recommended to undergo immunosuppressive therapy to prevent outbreaks beyond their baseline treatment or remission maintenance therapy of lupus nephritis (evidence 2++, B recommendation).

The clinical course of clinically quiescent and serologically active patients is usually benign. Therefore, preventive treatment with immunosuppressants is not recommended.57

40. Although vitamin D supplementation is not recommended with the sole aim of preventing activity outbreaks, vitamin D deficiency should be corrected due to its adverse effects on bone mass and asthenia (only to normalize levels), not discarding a beneficial effect in controlling lupus activity (evidence 2+, recommendation C).

While the levels of 25-OH vitamin D and lupus activity appear to be related,130 it has not been shown that supplementation with vitamin D3 in deficient patients results in a clinically relevant SLE activity reduction.36,131 Although some clinical observations suggest it, there is no consistent evidence on the effectiveness of vitamin D to improve asthenia.131,132

41. In addition to its harmful impact on overall health, smoking is not recommended for its potential effect on lupus activity, particularly at skin level (evidence 2+ to 2−, recommendation C).

While relation between smoking and SLE systemic activity is not well defined133,134 scientific evidence shows an association between smoking and increased activity and severity of lupus skin lesions.135 Moreover, tobacco use interferes with the therapeutic effect of antimalarials on cutaneous lupus.135,136

Treatment of systemic lupus erythematosus-associated asthenia. In this section, in addition to recommendation 40 on supplementation with vitamin D mentioned in the previous section to prevent reactivation of the disease, the following recommendations are added:

42. Despite the effectiveness data arising from RCTs, the administration of belimumab is not recommended for the sole purpose of improving asthenia (recommendation √).

The evidence available on using belimumab with standard treatment at 1 and 10 mg/kg doses versus placebo with standard treatment suggests that belimumab marginally reduces asthenia but with a high cost.88

43. People with stable SLE should follow gradual home sessions of supervised aerobic exercise, due to its overall improvement effect on perceived health status by patients (evidence 1+ to 2++, recommendation B).

Supervised aerobic exercise in people with stable SLE does not worsen disease activity and appears to improve health, vitality and physical capacity.137 To improve physical capacity in SLE patients, some degree of professional supervision is required in the design and implementation of physical exercise programs.138
44. Psychoeducational support is recommended to improve knowledge and understanding of the disease, restructure beliefs, and improve coping skills, self-management and social support (evidence 2++, B recommendation).

Psychoeducational interventions based on cognitive, personal or telephone treatment, can reduce asthenia and improve social support among patients receiving family support, also improving self-effectiveness in managing the disease. Interventions to improve SLE knowledge and understanding, beliefs, coping skills and social support as well as stress management programs and activities of expressive writing resulted in favorable health and appeared to reduce the asthenia levels in the short-medium term. 139

Lifestyle

This section, in addition to the 41st recommendation (on whether or not to quit smoking) and 43rd recommendation (for promoting supervised aerobic exercise) already included in a previous section, the following are added:

45. Overweight and physical inactivity is detrimental in all SLE patients (evidence 1+ to 3, recommendation C).

Low physical activity and sedentary lifestyle in people with SLE are associated with increased subclinical atherosclerosis and inflammatory and cardiovascular risk markers. 140,141 The evidence on the effect of exercise on anxiety, depression and pain is contradictory. No detrimental effect has been reported in these areas.

46. Diet should be poor in saturated fat and rich in omega-3 fatty acids in SLE patients (evidence 1+ to 3, recommendation C).

Consumption of omega-3 EPA and DHA has a positive effect on disease activity in the short term. 142–145 Currently, the effects on cardiovascular disease in SLE patients are unknown.

Photoprotection

47. Regular use of broad spectrum sunscreens with high sun protection factor is recommended, applied uniformly in all areas exposed in quantity of 2 mg/cm², 15–30 min before sun exposure and reapplied every 2 h and/or after immersion or sweating (evidence 1++ to 3 recommendation A).

Most people with SLE have some degree of photosensitivity. 146–148 Regular use of topical sunscreen is associated with reduced renal impairment, lower thrombocytopenia, fewer hospitalizations and fewer treatments with cyclophosphamide. Therefore, the use of sunscreen improves SLE prognosis, reducing the risk of kidney damage and the need for immunosuppressive therapy. 149 In addition to photosensitivity, after a brief period of exposure to sunlight, certain clinical manifestations such as fatigue, arthralgias, fever, etc. may occur. 148 Broad-spectrum sunscreens show high effectiveness in preventing skin lesions in SLE patients. 150

48. SLE patients, particularly those with cutaneous lupus or reporting a history of photosensitivity, should be systematically informed and trained on photoprotection measures, and the importance of use for best control of their disease and for preventing emergence of other symptoms (recommendation √).

Despite the lack of available scientific evidence on the effectiveness of specific educational programs on photoprotection, this recommendation of good practice was adopted by consensus in the group of experts, from the evidence on the deleterious effect of exacerbation of SLE symptoms after exposure to both sunlight and fluorescent light, particularly in those patients showing photosensitivity and/or SLE skin manifestations. 151

Training for patients

49. Educational programs should be structured and conducted from the department of nursing, aimed at SLE patients (evidence 1+/1−/2−, recommendation C).

Structured educational programs aimed at SLE patients are effective in reducing asthenia, depression and improving management and self-efficacy skills in these patients. 152,153 The psychological status of SLE patients, physical function and social support might improve significantly through interventions of telephone counseling focused on patients. 154,155 Psychoeducational group intervention might improve mental health outcomes in SLE patients. 156

Discussion

The 49 recommendations for the overall management of SLE included in the CPG-SLE, promoted by the Ministry of Health, Social Services and Equality through the Spanish Network of Agencies for Health Technology Assessment and benefits of NHS and GuiaSalud, address the most relevant aspects for the overall management and routine clinical management of SLE patients, including recommendations to standardize and improve the quality of clinical care and monitoring and general therapeutic approach; accompanied by educational recommendations to improve skills and training patients about their lifestyles. These recommendations are framed in 3 general principles.

In accordance with the first, the CPG-SLE has been intended as a reference tool to support comprehensive clinical management of SLE patients by all health professionals involved, regardless of their specialty and level of care in Spain, helping to standardize and improve the quality of clinical decisions in our environment with the purpose of improving health outcomes for the patients involved.

In accordance with the second general principle, the CPG-SLE is a tool that contributes to patient-focused care. For this reason, SLE patients have been represented at all stages of its development. The CPG-SLE promotes informed and shared decision-making between professionals and patients, particularly in recommendations subject to greater uncertainty, where the balance between benefits and risks is not clear enough, or when there are different alternatives of similar effectiveness and safety. To facilitate this process more effectively, the CPG-SLE includes a material for patients, summary document drafted in more general terms and simple language, available on the website of GuiaSalud (www.guiasalud.com). It will be distributed to all associations of SLE patients through FELUPUS.

Finally, the CPG-SLE is based on the principles of Evidence Based Medicine and on the expert consensus methodology. Based upon this principle, the CPG-SLE includes recommendations both on “what should be done” as on “what should not be done.” Thus, 8 recommendations, numbers 10, 28, 32, 36, 39, 40, 41 and 48 explicitly describe the clinical practices that should not take place based on the scientific knowledge available today. A significant number of the recommendations are based on a limited volume of moderate-quality studies published, reflecting the current knowledge on SLE and highlighting the need for more research and more scientific validity. Consequently, most recommendations are based on moderate levels of evidence, and a significant number of them were developed from expert judgment. Despite these limitations, the CPG-SLE is based on the most ambitious, inclusive and updated scientific knowledge instrument available internationally. 6–8

While the development of the CPG-SLE has been focused on effectiveness and safety criteria due to the limited availability of cost-benefit studies, economic issues have also been taken into account. Some recommendations have been assessed globally (proven benefits/potential risks/costs), taking into account both the needs of patients and the sustainability of the health system.
The concern of the GDG for all aspects related to safety or toxicity is collected in the 11 recommendations specifically focused on this aspect, which emphasize on both the episodic use of corticosteroids, such as maximum doses of prednisone at or below 30 mg/day (for nephritis or other SLE manifestations), and on the rapid reductions and maintenance doses below 5 mg/day. Similarly, recommendations for appropriate use of antimalarials, immunosuppressants and immunoglobulins include contents to improve patient safety.

The GDG indicated 20 of the 49 recommendations as key or priority. The CPG-SLE recommends the use of antimalarials indefinitely (preferably HCQ for best safety) as baseline treatment of all SLE patients (recommendation Nr. 15) and limits the recommendation of biological therapies to therapy with belimumab or rituximab, when no response to the standard strategy (recommendations 25–28).

The challenge CPG-SLE is facing now is implementation in the NHS. To this purpose, it must develop effective and cost-effective strategies for dissemination.\(^{157}\) This challenge is especially complex in the case of SLE because it is a multisystem disease that requires the intervention of a large group of health professionals and medical specialties. Recognition of the changing role of patients who take an increasingly active and participatory role in their interaction with health professionals,\(^ {158}\) allow the use of new implementation strategies. However, the PCGs have difficulties in obtaining a satisfactory degree of implementation.\(^ {159,160}\) To contribute to the implementation of the CPG-SLE, part of GDG is working on its transformation into a computerized tool to help decision-making, included in the electronic medical records.

Finally, the CPG-SLE should be reviewed and updated continuously within approximately 2–3 years.

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Conflict of interests

The authors declare no conflict of interest with the subject matter or materials discussed in this manuscript.

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Annex: Remaining members of the development group of the CPG-SLE

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References


