The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults: Executive Summary

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Scope and purpose of the guideline

Need for the guideline

SLE (or lupus) is a complex, multi-system autoimmune disease that affects nearly 1 in 1000 people in the UK [1]. Despite improvement in survival over the last 40 years, lupus patients still die on average 25 years earlier than the mean for women and men in the UK [2].

General recommendations for the management of lupus have not been published since 2008, although European

NICE has accredited the process used by the BSR to produce its guidance on the management of systemic lupus erythematosus in adults. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

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and USA guidelines for LN management were published in 2012 [3-5]. As the disease causes significant morbidity and mortality, and can be associated with the rapid accumulation of damage if not promptly diagnosed, regularly monitored and appropriately treated, an up-to-date guideline, consistent with current National Health Service (NHS) practice, is warranted to help improve the outcome of this disease.

**Objectives of the guideline**

To provide comprehensive recommendations, covering the diagnosis, assessment, monitoring and treatment of mild, moderate and severe active lupus disease based on a literature review (to June 2015) for non-renal lupus, supplemented as necessary by UK expert opinion and consensus agreement, and that do not imply a legal obligation. We also provide a summary of and our strength of agreement (SOA) with the EULAR and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for LN [4] in the full guideline [6].

**Target audience**

The guidelines have been developed by a multidisciplinary group established by the British Society for Rheumatology (BSR) and consisting of academic and NHS consultants in rheumatology and nephrology, rheumatology trainees, a general practitioner, a clinical nurse specialist, a patient representative and a lay member. The target audience for the guideline includes rheumatologists and other clinicians who care for lupus patients, such as nephrologists, immunologists, dermatologists, emergency medicine practitioners, general practitioners, trainees, clinical nurse specialists and other allied health professionals.

**Areas that the guideline does not cover**

This guideline does not cover the evidence for topical or systemic therapy for isolated cutaneous lupus, or paediatric lupus. Detailed dosing regimens are beyond the scope of this document. The management of the complications of lupus (including chronic fatigue, thrombosis, cardiovascular risk, osteoporosis, infection and cancer risk) are not discussed in detail and should be managed as for patients with similar risk factors according to relevant national and international guidelines.

**Key recommendations from the guideline**

The guideline was developed according to the BSR Protocol for Guidelines. The Scottish Intercollegiate Guidelines Network (SIGN) methodology [7] was used to determine the levels of evidence (LOEs) and grades of recommendations (GORs) for each statement, and these are shown in brackets below (LOE/GOR). For each recommendation, the strength of agreement (SOA) of the group was sought on a scale of 1 (no agreement) to 10 (complete agreement). The mean percentage agreement was calculated and is shown after each recommendation.

Treatment strategies are summarized in Table 1. The smallest effective dose of CS should be used. More detailed comments about the recommendations, the supporting evidence and cautions are provided in the full guideline, available at *Rheumatology* Online. NICE guidance for use of belimumab in active autoantibody-positive SLE in adults has been published (https://www.nice.org.uk/guidance/TA397). Reimbursement for rituximab is limited to the NHS England 2013 Interim Clinical Commissioning Policy statement for rituximab in adult SLE patients (https://www.england.nhs.uk/wp-content/uploads/2013/09/a13-psy.pdf).

**Clinical and serological features prompting consideration of diagnosis of SLE**

(i) SLE is a multisystem autoimmune disorder. The diagnosis requires a combination of clinical features and the presence of at least one relevant immunological abnormality. If there is a clinical suspicion of lupus, blood tests (including serological marker tests) should be checked (LOE 2++, GOR B, SOA 98%).

(ii) ANA are present in ~95% of SLE patients. If the test is negative, there is a low clinical probability of the patient having SLE. A positive ANA test occurs in ~5% of the adult population, and alone it has poor diagnostic value in the absence of clinical features of autoimmune rheumatic disease (2+/B, SOA 96%).

(iii) The presence of anti-dsDNA antibodies (2++/B), low complement levels (2+/C) or anti-Smith (Sm) antibodies (2+/C) are highly predictive of a diagnosis of SLE in patients with relevant clinical features. Anti-Ro/La and anti-RNP antibodies are less-specific markers of SLE (2+/C) as they are found in other autoimmune rheumatic disorders as well as SLE (2+/C) (SOA 95%).

(iv) aPLs should be tested in all lupus patients at baseline, especially in those with an adverse pregnancy history or arterial/venous thrombotic events (2+/B). Confirmatory tests for APS are positive LA, aCL (IgG, IgM) and/or anti-beta2 glycoprotein-1 (IgG, IgM) on two occasions at least 12 weeks apart (2+/B) (SOA 97%).

**Assessment of SLE patients**

(i) Clinical manifestations in SLE patients may be due to disease activity, damage, drug toxicity or the presence of co-morbidity. In the case of disease activity, it is important to ascertain whether this is due to active inflammation or thrombosis, as this will define treatment strategies (LOE 2++, GOR B, SOA 97%).

(ii) Clinical assessment of a lupus patient should include a thorough history and review of systems, full clinical examination and monitoring of vital signs, urinalysis, laboratory tests, assessment of health status and quality of life, and measurement of disease activity and damage using standardized
TABLE 1 SLE treatment strategies for examples of mild, moderate and severe non-renal lupus

<table>
<thead>
<tr>
<th>Item</th>
<th>Mild activity/flare BILAG C scores or single B score; SLEDAI &lt;6</th>
<th>Moderate activity/flare BILAG 2 or more systems with B scores, SLEDAI 6–12</th>
<th>Severe activity/flare (non-renal) BILAG 1 or more A scores; SLEDAI &gt;12</th>
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<tbody>
<tr>
<td>Typical manifestations attributed to lupus</td>
<td>Fatigue, malar rash, diffuse alopecia, mouth ulcers, arthralgia, myalgia, platelets 50–149 × 10⁹/l</td>
<td>Fever, lupus-related rash up to 2/9 body surface area, cutaneous vasculitis, alopecia with scalp inflammation, arthritis, pleurisy, pericarditis, hepatitis, platelets 25–49 × 10⁹/l</td>
<td>Rash involving &gt;2/9 body surface area, myositis, severe pleurisy and/or pericarditis with effusion, ascites, enteritis, myelopathy, psychosis, acute confusion, optic neuritis, platelets &lt;25 × 10⁹/l</td>
</tr>
<tr>
<td>Initial typical drugs and target doses if no contraindications</td>
<td>CSs: topical preferred or oral prednisolone ≤20 mg daily for 1–2 weeks or I.m. or IA methyl-prednisolon 80–120 mg and HCQ ≤6.5 mg/kg/day and/or MTX 7.5–15 mg/week and/or NSAIDs (for days to few weeks only)</td>
<td>Prednisolone ≤0.5 mg/day or i.v. methyl-prednisolone ≤250 mg × 1–3 or i.m. methyl-prednisolone 80–120 mg and AZA 1.5–2.0 mg/kg/day or MTX (10–25 mg/week) or MMF (2–3 g/day) or ciclosporin ≤2.0 mg/kg/day and HCQ ≤6.5 mg/kg/day</td>
<td>Prednisolone ≤0.5 mg/day and/or i.v. methyl-prednisolone 500 mg × 1–3 and prednisolone ≤0.75–1 mg/kg/day and AZA 2–3 mg/kg/day and MMF 2–3 g/day or CYC i.v. or ciclosporin ≤2.5 mg/kg/day and HCQ ≤6.5 mg/kg/day</td>
</tr>
<tr>
<td>Aiming for typical maintenance drugs/doses providing no contraindications</td>
<td>Prednisolone ≤7.5 mg/day and HCQ 200 mg/day and/or MTX 10 mg/week</td>
<td>Prednisolone ≤7.5 mg/day and AZA 50–100 mg/day and/or MTX 10 mg/week and/or MMF 1 g/day or ciclosporin 50–100 mg/day and HCQ 200 mg/day;</td>
<td>Prednisolone ≤7.5 mg/day and MMF 1.0–1.5 g/day or AZA 50–100 mg/day and ciclosporin 50–100 mg/day and HCQ 200 mg/day;</td>
</tr>
</tbody>
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*The lowest effective dose of prednisolone or other CSs should be used at all times.

SLE assessment tools (2 ++/B). Imaging (4/D), renal (2 ++/B) and other biopsies (4/D) should be performed where indicated (SOA 100%).

(iii) Disease activity is categorized into mild, moderate and severe, with the occurrence of flares (2+C). Mild disease activity is clinically stable with no life-threatening organ involvement, mainly manifestations as arthritis, mucocutaneous lesions and mild pleuritis. Patients with moderate disease activity have more serious manifestations, and severe disease activity is defined as organ- or life-threatening (4/D) (SOA 93%).

Monitoring of SLE

(i) Patients with lupus should be monitored on a regular basis for disease manifestations, drug toxicity and co-morbidities (LOE 2 ++, GOR B, SOA 99%).

(ii) Those with active disease should be reviewed at least every 1–3 months (2+, C/D), with blood pressure (1+/A), urinalysis (1+/A), renal function (1+/A), anti-dsDNA antibodies (2 ++/B), complement levels (2+/C), CRP (2+/C), full blood count (3/C), and liver function tests (4/D) forming part of the assessment, and further tests as necessary (4/D). Patients with stable low disease activity or in remission can be monitored less frequently, for example, 6–12 monthly (4/D) (SOA 99%).

(iii) The presence of aPLs is associated with thrombotic events, damage, and adverse outcomes in pregnancy (2 ++/B). If previously negative, they should be re-evaluated prior to pregnancy or surgery, or in the presence of a new severe manifestation or vascular event (4/D) (SOA 98%).

(iv) Anti-Ro and anti-La antibodies are associated with neonatal lupus (including congenital heart block) and should be checked prior to pregnancy (1+/A) (SOA 100%).

(v) Patients with lupus are at increased risk of co-morbidities, such as atherosclerotic disease, osteoporosis, avascular necrosis, malignancy and infection (2+/C). Management of modifiable risk factors, including hypertension, dyslipidaemia, diabetes, high BMI and smoking, should be reviewed at baseline and at least annually (4/D) (SOA 98%).

(vi) Immunosuppressive therapy may lead to toxicities. Close monitoring of drugs by regular laboratory tests and clinical assessment should be performed in accordance with drug monitoring guidelines (4/D) (SOA 98%).
Management of mild SLE

(i) Treatments to be considered for the management of mild non-organ-threatening disease include the disease-modifying drugs HCQ (1+/A) and MTX (1+/A), and short courses of NSAIDs (3/D) for symptomatic control. These drugs allow for the avoidance of or dose reduction of CSs (SOA 94%).

(ii) Prednisolone treatment at a low dose of ≤7.5 mg/day may be required for maintenance therapy (2+/C). Topical preparations may be used for cutaneous manifestations, and IA injections for arthritis (4/D) (SOA 93%).

(iii) High-Sun Protection Factor (SPF) UV-A and UV-B sunscreen are important in the management and prevention of UV radiation-induced skin lesions (2+/B). Patients must also be advised about sun avoidance and the use of protective clothing (4/D) (SOA 97%).

Management of moderate SLE

(i) The management of moderate SLE involves higher doses of prednisolone (up to 0.5 mg/kg/day) (2+/C), or the use of i.m. (4/D) or i.v. doses of methylprednisolone (2+/C). Immunosuppressive agents are often required to control active disease and are steroid-sparing agents (2+/C). They can also reduce the risk of long-term damage accrual (4/D) (SOA 98%).

(ii) MTX (1+/A), AZA (2+/C), MMF (2++/B), ciclosporin (2+/C) and other calcineurin inhibitors (3/D) should be considered in cases of arthritis, cutaneous disease, serositis, vasculitis or cytopenias if HCQ is insufficient (SOA 97%).

(iii) For refractory cases, belimumab (1+/B) or rituximab (2+/C) may be considered (SOA 98%).

Management of severe SLE

(i) Patients who present with severe SLE, including renal and neuropsychiatric manifestations, need thorough investigation to exclude other aetiologies, including infection (4/D). Treatment depends on the underlying aetiology (inflammatory and/or thrombotic), and patients should be treated accordingly with immunosuppression and/or anticoagulation, respectively (4/D) (SOA 98%).

(ii) Immunosuppressive regimens for severe active SLE involve i.v. methylprednisolone (2+/C) or high-dose oral prednisolone (up to 1 mg/kg/day) (4/D) to induce remission, either on their own or more often as part of a treatment protocol with another immunosuppressive drug (4/D) (SOA 98%).

(iii) MMF or CYC are used for most cases of LN and for refractory severe non-renal disease (2+/B) (SOA 98%).

(iv) Biologic therapies belimumab (1+/B) or rituximab (2+/C) may be considered, on a case-by-case basis, where patients have failed to respond to other immunosuppressive drugs, due to inefficacy or intolerance (SOA 98%).

(v) IVIG (2-/D) and plasmapheresis (3/D) may be considered in patients with refractory cytopenias, thrombotic thrombocytopenic purpura (1+/B), rapidly deteriorating acute confusional state and the catastrophic variant of APS (SOA 93%).

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References