The British Society for Rheumatology guidelines for the management of systemic lupus erythematosus in adults

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Executive summary

Scope and purpose of the guideline

Need for the guideline

Systemic lupus erythematosus (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 and USA guidelines for lupus nephritis 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 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 with the EULAR/ERA-EDTA recommendations for lupus nephritis(4) in the full guideline.

Target audience

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

The areas that the guideline does not cover

This guideline does not cover the evidence for topical or systemic therapy for isolated cutaneous lupus, nor paediatric lupus. Detailed dosing regimens are beyond the scope of this document. The management of 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. SIGN methodology(6) was used to determine levels of evidence (LOE) and grades of recommendations (GOR) 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 corticosteroid 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-psa.pdf).

Clinical and serological features prompting consideration of diagnosis of SLE

I. SLE is a multi-system 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 markers should be checked. (LOE 2++, GOR B, SOA 98%)

II. ANA are present in about 95% of SLE patients. If the test is negative, there is a low clinical probability of the patient having SLE. A positive ANA occurs in approximately 5% of the adult population and alone 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-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. Antiphospholipid antibodies 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 antiphospholipid syndrome are positive lupus anticoagulant , anti-cardiolipin antibodies (IgG, IgM) and/or anti-beta-2 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 standardised 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 categorised 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 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 comorbidities. (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), and 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 eg 6 to 12 monthly (4/D). (SOA 99%)

III. The presence of antiphospholipid antibodies is associated with thrombotic events, damage and adverse pregnancy outcomes (2++/B). If previously negative, they should be re-

evaluated prior to pregnancy or surgery and in the presence of a new severe manifestation or vascular event (4/D). (SOA 96%)

IV. Anti-Ro and 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 body mass index 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 disease modifying drugs hydroxychloroquine (1++/A) and methotrexate (1+/A), and short courses of non-steroidal anti-inflammatory drugs (3/D) for symptomatic control. These drugs allow for the avoidance of or dose reduction of corticosteroids. (SOA 94%)

II. Prednisolone treatment at a low dose of up to 7.5mg/day may be required for maintenance therapy (2+/C). Topical preparations may be used for cutaneous manifestations and intra-articular injections for arthritis (4/D). (SOA 93%)

III. High factor 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 intramuscular (4/D) or intravenous doses of methylprednisolone (2+/C). Immunosuppressive agents are required often 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. Methotrexate (1+/A), azathioprine (2+/C), mycophenolate mofetil (2++/B), ciclosporin (2+/C) and other calcineurin inhibitors (4/D) should be considered in cases of arthritis, cutaneous disease, serositis, vasculitis or cytopaenias if hydroxychloroquine 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 IV 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. Mycophenolate mofetil or cyclophosphamide are used for most cases of lupus nephritis 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 other immunosuppressive drugs due to inefficacy or intolerance. (SOA 98%)

Intravenous immunoglobulin (2-/D) and plasmapheresis (3/D) may be considered in patients with refractory cytopaenias, thrombotic thrombocytopaenic purpura (1+/B), rapidly deteriorating acute confusional state and the catastrophic variant of antiphospholipid syndrome. (SOA 93%)

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Table 1. SLE treatment strategies for examples of mild, moderate and severe non-renal lupus

	Mild activity/flare BILAG C scores or single B score; SLEDAI <6	**Moderate activity/flare** BILAG 2 or more systems with B scores, SLEDAI 6-12;	**Severe activity/flare (non-renal)** BILAG 1 or more A scores; SLEDAI >12
Typical manifestations attributed to lupus	Fatigue, malar rash, diffuse alopecia, mouth ulcers, arthralgia, myalgia, platelets 50-149 x 10^9/l	Fever, lupus related rash up to 2/9 body surface area, cutaneous vasculitis, alopecia with scalp inflammation, arthritis, pleurisy, pericarditis, hepatitis, platelets 25-49 x 10^9/l	Rash involving >2/9 body surface area, myositis, severe pleurisy and/or pericarditis with effusion, ascites, enteritis, myelopathy, psychosis, acute confusion, optic neuritis, platelets <25 x 10^9/l
Initial typical drugs and target doses if no contra-indications	*Corticosteroids topical preferred **or** oral prednisolone ≤20mg daily for 1-2 weeks **or** IM or intra-articular methyl-prednisolone 80-120mg **and** Hydroxychloroquine ≤6.5mg/kg/day **and/or** methotrexate 7.5-15mg/week **and/or** NSAIDs (for days to few weeks only)	*Prednisolone ≤0.5 mg/day **or** IV methyl-prednisolone ≤250mg x 1-3 **or** IM methyl-prednisolone 80-120mg **and** AZA 1.5-2.0 mg/kg/day **or** methotrexate (10-25 mg/week) **or** MMF (2-3 g/day) **or** ciclosporin ≤2.0mg/kg/day **and** hydroxychloroquine ≤6.5mg/kg/day	*Prednisolone ≤0.5 mg/day **and/or** IV methyl-prednisolone 500mg x 1-3 **or** prednisolone <0.75-1mg/kg/day **and** AZA 2-3 mg/kg/day **or** MMF 2-3 g/day **or** cyclophosphamide i.v. **or** ciclosporin ≤2.5mg/kg/day **and** hydroxychloroquine ≤6.5mg/kg/day

Aiming for typical maintenance drugs/doses providing no contra-indications	*Prednisolone ≤ 7.5 mg/day **and** Hydroxychloroquine 200 mg/day **and/or** methotrexate 10 mg/week **Aim to reduce and stop drugs except hydroxychloroquine eventually when in stable remission**.	*Prednisolone ≤ 7.5 mg/day **and** AZA 50-100 mg/day **or** methotrexate 10 mg/week **or** MMF 1g/day **or** ciclosporin 50-100mg/day **and** hydroxychloroquine 200 mg/day. **Aim to reduce and stop drugs except hydroxychloroquine eventually when in stable remission**.	*Prednisolone ≤7.5 mg/day **and** MMF 1.0-1.5 g/day **or** AZA 50-100 mg/day **or** ciclosporin 50-100mg/day **and** hydroxychloroquine 200 mg/day **Aim to reduce and stop drugs except hydroxychloroquine eventually when in stable remission.**

*the lowest effective dose of prednisolone or other corticosteroids should be used at all times.