Systemic lupus erythematosus can affect any part of the body and its presentation is highly variable. SLE management should therefore be individualised depending on symptoms, organ involvement and disease severity.

The goals of therapy for patients with SLE are to:

- Control symptoms, such as joint pain and fatigue
- Prevent flares or treat them when they occur
- Minimise damage to organs
- Avoid long-term complications from the medicines used

This article describes the options available for prevention and treatment of SLE flares and organ damage. Recent advances in the management of lupus are also discussed.

Avoiding triggers

Triggers that can precipitate SLE flares should be identified where possible and targeted to prevent future flares. Patients should be counselled on avoiding common triggers, such as ultraviolet (UV) light, smoking and stress.

About two thirds of patients with SLE experience rashes or worsening of lupus symptoms when exposed to UV light. Sun avoidance or appropriate use of sun block should therefore be recommended.

Increased endogenous oestrogen production has been linked with SLE flares, particularly during pregnancy (see Box 1, p201). However, the use of low-dose oral contraceptives has not been shown to increase flares in mild SLE. For many women with SLE, the benefits of contraception in avoiding unintended pregnancy are likely to outweigh the risks. Oestrogen-based contraception should be used with caution in women with antiphospholipid antibodies because of their underlying increased risk of thrombosis.

Pharmacological management

Most SLE therapies fall outside product licences and should be introduced under the supervision of specialist clinicians. Patients experiencing muscle or joint pain, fatigue, rashes and other non-severe symptoms may only require conservative treatment. Regular use of simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and antimalarials can help to manage mild symptoms.

Patients with internal organ involvement, or who do not respond to antimalarials or NSAIDs, will often require more potent therapies, such as corticosteroids and other immunomodulatory drugs, to suppress the disease activity. Such treatment falls into two main categories:

- Induction — ie, medicines used during a flare to induce remission by controlling immunological activity
- Maintenance — ie, medicines used to consolidate remission and reduce the risk of future flares

Biologic medicines offer new treatment options for patients with SLE, although their precise role in treatment is yet to be established (see Box 2, p203).

NSAIDs

NSAIDs are commonly prescribed for people with SLE to treat arthralgias or polyarthritis. They also have a role in the symptomatic control of fever and serositis (the inflammation of the tissue lining the lungs, heart and abdomen). The choice of NSAID should be based on cost and patient preference, and the lowest effective dose should be used for the duration of a flare. NSAIDs can cause gastritis and concomitant use of acid-suppressing medicines should be considered. Baseline and routine monitoring of renal function is advised to detect any renal dysfunction with NSAID use.
ongoing use. Low-dose corticosteroids (up to 10mg of prednisolone daily, or equivalent) are recommended for mild SLE flares, particularly for patients who are not responding to NSAIDs and antimalarials. High-dose corticosteroids (≥30mg of prednisolone daily, or equivalent) are used for SLE with organ involvement. Pulse therapy with intravenous methylprednisolone, 500mg to 1g daily for three consecutive days, is reserved for more severe flares, eg, involving lupus nephritis or cerebritis.

Corticosteroids may also play a role in preventing severe SLE flares for patients with increasing levels of anti-double-stranded DNA antibodies and decreasing C3 levels — so called “serological flare”. A small study showed that a four-week course of prednisolone (reducing dose) reduces the occurrence of severe flares for patients with evidence of a serological flare.11 For patients who require corticosteroids long term, electrolytes, glucose, lipids and weight should be monitored routinely to identify metabolic complications. Preventive treatment for osteoporosis and gastritis should be considered with long-term corticosteroid use.

Immunomodulators
For patients who cannot tolerate or do not respond to corticosteroids, or who are unable to reduce their doses of corticosteroids, adjunctive immunosuppressant therapy is recommended. Azathioprine, methotrexate, leflunomide, mycophenolate and cyclophosphamide are all used off-label for this indication. Most clinical trials of immunosuppressants have been undertaken in patients with lupus nephritis and there is a paucity of data around effective immunosuppressive treatment for other SLE complications.

Azathioprine Azathioprine is an antiproliferative drug that suppresses cell-mediated and humoral immune responses, particularly lymphocyte proliferation, through the inhibition of purine synthesis. It has been studied extensively for maintenance therapy of lupus nephritis, and as a corticosteroid-sparing medicine in SLE. Azathioprine maintenance therapy for lupus nephritis is associated with remission rates equivalent to those for

Box 1: Management of SLE in pregnancy
Pregnant women with SLE have an increased risk of disease flares, miscarriage, thrombosis, pre-eclampsia and pre-term delivery. Further complicating the management of such patients is the fact that many SLE treatments have the potential to be teratogenic. Therefore, women with SLE should have discussions around pregnancy with a specialist clinician, ideally before they conceive.

Where possible, cyclophosphamide, methotrexate and mycophenolate should be discontinued (and disease should be clinically stable on an alternative therapy that is safe in pregnancy) six to 12 months before conception. Antimalarials, corticosteroids and azathioprine can be continued throughout pregnancy. Antithrombotic therapy is often indicated for SLE patients who are pregnant, especially if they also have antiphospholipid syndrome. A Cochrane review concluded that use of heparin and aspirin may reduce the number of miscarriages by 54% in patients with antiphospholipid antibodies.1

Antimalarials
Antimalarials are used widely to prevent and treat SLE flares, and are particularly useful for cutaneous symptoms and for arthralgias controlled poorly with NSAIDs. The antimalarials have immunosuppressive and anti-inflammatory properties but their exact mechanism of action in SLE is not fully understood. Their benefit in lupus nephritis is not proven.

Antimalarials may block absorption of UV light, thereby improving cutaneous symptoms. The antimalarials are also believed to have some disease-modifying properties and there is evidence that they can prevent further flares, severe organ damage and thrombosis with long-term use. Relief from arthritic pain and remission of skin lesions can occur one to six months after starting antimalarials, so long-term use is often required.

Hydroxychloroquine is the most commonly used antimalarial for SLE because it is less likely to cause retinal damage than chloroquine. Patients who continue taking hydroxychloroquine after a flare has resolved are less likely to experience future mild flares than those who stop taking the drug. It is therefore common for patients to remain on long-term hydroxychloroquine therapy even in disease remission.

Hydroxychloroquine is also a treatment option for patients with antiphospholipid syndrome (see Box 3, p204). Patients who start taking antimalarials should be advised to have their eyes tested annually by an optometrist because of concerns with drug-induced retinopathy. Hydroxychloroquine has several clinically significant drug interactions; for example, it can increase plasma concentrations of digoxin. Concomitant use of amiodarone and hydroxychloroquine should be avoided because of an increased risk of ventricular arrhythmias. Hydroxychloroquine can lower the seizure threshold.

Corticosteroids
Although patients with SLE respond quickly to corticosteroid treatment, long-term side effects limit their use. Preventive treatment for osteoporosis and gastritis should be considered with long-term corticosteroid use. Preterm treatment for osteoporosis and gastritis should be considered with long-term corticosteroid use.

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Leflunomide Leflunomide may be useful for SLE patients with articular involvement who are intolerant of, or do not achieve an adequate response with, methotrexate. An initial loading dose of 100mg daily for three days, followed by 20mg daily thereafter, has been used in small case studies. Rare cases of hepatotoxicity with leflunomide have been reported, with some fatal cases. Therefore, liver function tests, platelet counts and leucocyte counts should be monitored every two weeks after starting treatment, or if the dose is altered.

Cyclophosphamide Cyclophosphamide is an alkylating medicine that depletes B and T cells and reduces production of the pathogenic autoantibodies in SLE. It is used in combination with high-dose corticosteroids to treat complications of severe SLE, including lupus nephritis, optic neuritis and pulmonary hypertension.

Intravenous administration of cyclophosphamide has largely replaced oral therapy because it has equivalent clinical efficacy but is associated with a lower cumulative exposure to cyclophosphamide and less frequent cytopenias. In addition, intravenous treatment avoids problems of non-adherence and means that medicines to protect against the bladder-related adverse effects of cyclophosphamide can be administered easily (see below).

There are two cyclophosphamide regimens used commonly for lupus nephritis. The US National Institutes of Health (NIH) regimen — monthly intravenous cyclophosphamide pulses (500mg/m² to 1g/m² depending on renal function and disease severity) plus methylprednisolone pulses (three doses, each 500mg–1g) for six months — was associated with improvement in GFR compared with pulse methylprednisolone alone. In practice, maintenance oral prednisolone can be used instead of pulses of intravenous methylprednisolone.

The Euro-Lupus group compared the gold-standard NIH regimen with a less intensive protocol — intravenous cyclophosphamide 500mg every two weeks, for six doses. Similar renal and extra-renal outcomes were seen with this dosing schedule, but with less toxicity. However, participants in this trial had less severe renal disease at baseline (lower mean creatinine) compared with those in the NIH trial, so this less intensive dose is not used for patients with severe renal dysfunction in practice.

According to a Cochrane review, the combination of cyclophosphamide plus corticosteroids reduces the risk of a doubling in serum creatinine compared with corticosteroids alone (risk ratio 0.59, 95% confidence interval 0.40–0.88), but does not improve mortality (RR 0.98, 0.53–1.82). Cyclophosphamide treatment can cause myelotoxicity and severe infections. Strict monitoring for infection and leucopenia is essential, particularly 10–14 days after a dose when white blood cell counts will be at their lowest. Profound lymphopenia commonly occurs and subsequent dose reduction may be required if lymphocytes fail to recover. Prophylaxis against pneumocystis pneumonia (using co-trimoxazole) is recommended for patients undergoing cyclophosphamide therapy; prophylaxis against tuberculosis and viral infections should also be considered for high-risk patients.

Another possible adverse effect of cyclophosphamide is haemorrhagic cystitis. Administration of mesna, before oral cyclophosphamide (see below). Additionally, azathioprine has a lower immunosuppressive burden than cyclophosphamide and, until recently, it has been the drug of choice for maintenance therapy, following induction with cyclophosphamide. (New evidence supporting the use of mycophenolate, see below, is expected to change this practice.)

Before starting azathioprine treatment a patient's thiopurine methyltransferase (TPMT) enzyme activity should be measured, since underactivity of this enzyme will result in slower metabolism of azathioprine and an increased risk of bone marrow suppression.

Dose reduction or discontinuation of azathioprine may be required if patients experience adverse effects such as bone marrow suppression, nausea or diarrhoea. Azathioprine can also cause hypersensitivity reactions, in which case the medicine should be stopped immediately.

Cyclophosphamide can be administered easily (see below). Concurrent treatment with xanthine oxidase inhibitors which case the medicine should be stopped immediately.

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Intravenous cyclophosphamide can be used, with corticosteroids, to treat SLE

Methotrexate In two placebo-controlled trials, once-weekly methotrexate (5–20mg) was shown to be effective for control of cutaneous and articular manifestations of SLE, and enabling corticosteroid dose reduction. Adverse effects were greater in the treatment group than in the placebo group, but most patients with adverse events did not require treatment discontinuation. Because the drug accumulates in renal impairment, methotrexate should be used with caution for patients with a glomerular filtration rate (GFR) <30mL/min and doses should not exceed 12.5mg, once weekly (50% of maximum licensed dose). Methotrexate is not recommended in end-stage renal disease.

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discussions with patients around sperm banking.\textsuperscript{20} Cyclophosphamide treatment and clinicians should have positive results in women receiving chemotherapy for the treatment of malignancies.\textsuperscript{21} Ovarian failure affects 38–52\% of women receiving cyclophosphamide treatment. Starting a gonadotrophin-releasing hormone analogue around two weeks before cyclophosphamide may provide gonadal protection by suppressing ovarian function (this has demonstrated positive results in women receiving chemotherapy for the treatment of malignancies).\textsuperscript{21} Male hypogonadism is expected with cyclophosphamide treatment and clinicians should have discussions with patients around sperm banking.\textsuperscript{20}

**Box 2: Role of biologic medicines in the treatment of SLE**

Recent advances in the understanding of SLE immunopathology have led to the development of therapies that target specific inflammation pathways, particularly those involving B cells.

**Rituximab** Rituximab binds to CD20, a surface antigen on developing B cells, and causes cell lysis and a rapid decline in the number of peripheral B cells after 1–4 weeks. This effect can last for 4–9 months. The “lupus nephritis assessment with rituximab” (LUNAR) study compared the use of rituximab with placebo (added to background treatment with mycophenolate and corticosteroids) for 144 patients with lupus nephritis. Response rates did not differ between the two groups (57\% versus 46\%, respectively; \( P=0.55\)).\textsuperscript{3}

Likewise, the EXPLORER study failed to demonstrate that rituximab was better than placebo for patients with moderate-to-severe extra-renal SLE (when added to background immunosuppression).\textsuperscript{1}

Neither study showed significant benefits over placebo; however, the studies had substantial limitations, including poor trial design and inadequate follow-up periods.

Nevertheless, encouraging serological results in the above studies and case reports suggest that a role for rituximab in SLE may still be found. Currently, rituximab should be reserved for patients with disease that does not respond to mycophenolate or intravenous cyclophosphamide.

**Belimumab** Belimumab inhibits B-lymphocyte stimulator (BLyS), a cytokine essential for B cell growth and maturation; decreases in BLyS levels are associated with improvements in SLE. Belimumab is the first medicine to be licensed for SLE for over 30 years. Its indication is add-on therapy for adults with active, autoantibody-positive SLE and a high degree of disease activity despite standard therapy.

The BLISS-52 and BLISS-76 studies\textsuperscript{5,6} compared belimumab 1mg/kg, belimumab 10mg/kg and placebo in patients with serologically positive SLE and active disease, despite standard therapy. Belimumab was given every two weeks for the first three doses, and then every four weeks thereafter. Patients previously treated with rituximab or cyclophosphamide were excluded, as were patients with severe lupus nephritis or lupus-related neurological problems.

The primary endpoint for both studies was a composite measure of response (the SLE responder index). In both studies, belimumab achieved a better response rate than placebo at 52 weeks — 57.5\% versus 43.6\%, respectively, in BLISS-52 (\( P=0.0006\)) and 43.3\% versus 35.5\%, respectively, in BLISS-76 (\( P=0.021\)).

In BLISS-76 the response rate at week 76 was not better for belimumab than for placebo. A possible explanation for this is the fact the study was powered to evaluate response at 52 weeks.

These studies also showed that belimumab exhibited a corticosteroid-sparing effect, compared with placebo. Belimumab was well tolerated in both studies, with rates of adverse events, infections and discontinuations similar to those with placebo.

The recommended dose of belimumab is 10mg/kg every two weeks for three doses and then every four weeks thereafter. The dose is administered by intravenous infusion over one hour; patients should receive premedication with an antihistamine, with or without paracetamol, because of the risk of hypersensitivity reactions (the incidence of which is 0.9\%).

Belimumab is not recommended for patients with severe active lupus nephritis or lupus affecting the central nervous system. No dose adjustments are recommended for patients with renal impairment, although caution is required when treating patients with severe renal impairment because of a lack of experience in such patients.

The National Institute for Health and Clinical Excellence published a final appraisal determination for belimumab earlier this year, in which it did not recommend use of the medicine within its licensed indication; this decision is being appealed. Likewise, the Scottish Medicines Consortium does not recommend use of the drug in Scotland, primarily due to its high cost.

Cyclophosphamide is cytotoxic so pregnancy should be avoided during therapy.

Other common adverse effects of cyclophosphamide include reversible alopecia and nausea.

**Mycophenolate** Recent research has provided evidence that mycophenolate, an anti-proliferative drug, is effective for induction and maintenance treatment of lupus nephritis.

The Aspreva lupus management study (ALMS) compared oral mycophenolate mofetil with intravenous cyclophosphamide (NIH regimen) for induction treatment of severe lupus nephritis; non-renal outcomes were a secondary endpoint.\textsuperscript{22} Mycophenolate, up to 3g a day, was associated with equivalent response rates to intravenous cyclophosphamide (56.2\% versus 52\%, respectively, at 24 weeks; \( P=0.58\)). As such, mycophenolate is considered an alternative to intravenous
cyclophosphamide for first-line induction treatment of severe lupus nephritis. No robust data are available to support the use of mycophenolate for neuropsychiatric SLE and therefore pulses of intravenous cyclophosphamide remain the treatment of choice for induction treatment of severe SLE that affects the central nervous system.

The MAINTAIN nephritis study, which included patients with lupus nephritis from across Europe, failed to show that mycophenolate was better than azathioprine for maintenance treatment — the rate of renal relapse was 19% for patients taking mycophenolate compared with 25% for those taking azathioprine (P = 0.001). In this study, all patients were randomised after receiving 12 weeks of induction with low-intensity cyclophosphamide (regardless of whether or not cyclophosphamide induced remission). Unlike ALMS, the MAINTAIN nephritis study was open-label, included a predominantly Caucasian population and had fewer participants; these factors could have contributed to the non-significant result.

Mycophenolate can cause gastrointestinal side effects, such as diarrhoea and nausea, which, in some cases, can be overcome by dividing the dose across the day. Nevertheless, dose reduction is often necessary, particularly for patients with low body weight.

Multi-target therapy shows promise for induction treatment of lupus nephritis. A single randomised trial, including 40 patients, compared standard therapy (intravenous cyclophosphamide) with mycophenolate plus corticosteroids and tacrolimus. Rates of remission were better with triple therapy than standard care (65% versus 32%, respectively; P = 0.005). Treatment discontinuation rates and severe adverse events were also less common among patients taking mycophenolate.

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