Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease characterised by the involvement of almost any organ or system and the production of numerous autoantibodies.

There is no definitive diagnostic test for SLE, and the diagnosis rests on the clinician’s judgment. This is invariably influenced by one of two sets of classification criteria. The better established set, the revised criteria of the American College of Rheumatology (ACR) is shown in Table 1. Four of these criteria need to be present (though not simultaneously).

The Systemic Lupus International Collaborating Clinics (SLICC) group divides lupus features into clinical and serological. Again four criteria must be present, with at least one each from these two groups of features. A key difference is that the SLICC criteria also recognise that histologically confirmed lupus nephritis may be a dominant feature and allow, in this situation, for only three criteria to be present.

### Patient groups most susceptible

The precise aetiopathology of SLE remains unknown. A multifactorial complex of genetic, hormonal and environmental factors is clearly involved. More than 40 SLE-associated loci predisposing to disease susceptibility have been identified. The genes involved participate in different immunologic pathways including immune complex handling, B cell signalling, regulation of apoptosis, antigen processing and presentation. Much has been learnt during the last decade regarding epigenetic alterations. For instance, inhibiting DNA methylation in CD4+ T lymphocytes induces autoreactivity and these autoreactive cells promote B cell activation and consequent autoantibody production. Furthermore, it is noteworthy that CD4+ T cells present H4 and H3 histone deacetylation associated with altered gene expression in SLE patients.

The interaction of hormonal and environmental factors modifies this genetic susceptibility and the clinical expression of the disease. Approximately 90 per cent of SLE patients are women. Multiple stud-
ies have shown that oestrogens effect in immune function. Finally, some environmental factors notably UV light but also chemical agents, drugs and infections, may trigger the start of the disease or disease flares.

A key immunological dysfunction is the failure of phagocytes to remove efficiently apoptotic material from dying cells. This leads to immune system aberrations beginning with the unusual exposure of nuclear antigens to antigen presenting cells and subsequent triggering of B and T cells. The disease is thus the consequence of the failure of “waste-disposal”. The end result of this process is the production of pathogenic autoantibodies, some of which determine the clinical manifestations of SLE.

**Signs and symptoms**
The course of SLE is often characterised by exacerbations (or flares) and remissions of disease activity. In assessing SLE patients, the occurrence of new signs or symptoms must be carefully evaluated. Most patients initially develop non-specific constitutional symptoms (eg fatigue, weight loss and fever). The diversity and approximate prevalence of lupus features is shown in Table 2.

**Mucocutaneous disease**
The skin lesions can be divided into lupus specific and lupus non-specific lesions. The former includes acute, subacute or chronic lesions. A typical lesion of acute cutaneous lupus is the bilateral malar erythema (butterfly rash) with sparing of the nasolabial fold area. It is usually transient, photosensitive and resolves without scarring. Subacute cutaneous lupus may have a papulosquamous presentation or an annular aspect, often sparing the midfacial skin, while the sides of the face, neck, upper chest, upper back, shoulders, and extensor surfaces of the arms are commonly involved.

The most common form of chronic cutaneous lupus is discoid lupus erythematosus (DLE). The discoid lesions are erythematous plaques covered by adherent scale that extends into dilated hair follicles. Generalised DLE is the term used when lesions are present both above and below the neck.

Non-specific cutaneous lesions are morphologically varied. The most common are photosensitivity, vasculitis, alopecia and Raynaud’s phenomenon.

**Musculoskeletal manifestations**
Clinical symptoms range from arthralgia and morning stiffness, to obvious arthritis. A non-deforming, non-erosive and symmetrical arthritis is the most characteristic articular manifestation of SLE. Sometimes, especially if it involves proximal interphalangeal and metacarpophalangeal joints in association with joint hypermobility, the consequence may be deformities which mimic those of rheumatoid arthritis. These non-erosive, reducible joint subluxations are called Jaccoud’s arthropathy. This situation occurs in about 5 per cent of SLE patients. In another 3–5 per cent a true erosive arthritis occurs. The condition is sometimes referred to as “Rhupus”.

**Renal manifestations**
Renal involvement is the most important factor influencing prognosis in SLE. Lupus affects all renal compartments

<table>
<thead>
<tr>
<th>Feature</th>
<th>Prevalence %</th>
<th>Feature</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td><strong>Dermatological</strong></td>
<td></td>
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<tr>
<td>Arthralgia/arthritis</td>
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<td>Butterfly rash</td>
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<td>Myalgia</td>
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<td>Maculopapular eruption</td>
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<td>Tenosynovitis</td>
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<td>Discoid lupus</td>
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<td>Myositis</td>
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<td>Relapsing nodular non-suppurative panniculitis</td>
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<tr>
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<td></td>
<td><strong>Cerebral</strong></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>60</td>
<td>Migraine</td>
<td>40</td>
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<tr>
<td>Reduced 24-hour creatinine clearance</td>
<td>35</td>
<td>Seizures</td>
<td>20</td>
</tr>
<tr>
<td>Casts</td>
<td>30</td>
<td>Depression</td>
<td>15</td>
</tr>
<tr>
<td>Serum albumin &lt;35g/L</td>
<td>30</td>
<td>Hemiplegia</td>
<td>10</td>
</tr>
<tr>
<td>Serum creatinine &gt;125µmol/L</td>
<td>30</td>
<td>Cranial nerve lesions</td>
<td>10</td>
</tr>
<tr>
<td>Haematuria</td>
<td>10</td>
<td>Psychosis</td>
<td>5</td>
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<tr>
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<td></td>
<td><strong>Cerebellar signs</strong></td>
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<td>Pulmonary function abnormalities</td>
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<td><strong>Meningitis</strong></td>
<td>1</td>
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<tr>
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<td>Anaemia of chronic disease</td>
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<td>Leukopenia</td>
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<tr>
<td>Pericarditis</td>
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<td>Anaemia (iron deficiency)</td>
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<td>Thrombocytopenia</td>
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<td>Lupus pneumonitis</td>
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<td>Autoimmune haemolytic anemia</td>
<td>15</td>
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<tr>
<td>Interstitial fibrosis</td>
<td>5</td>
<td>Circulating anticoagulants</td>
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<tr>
<td>Myocardial infarction</td>
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<td><strong>Gastrointestinal</strong></td>
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<td>Anorexia</td>
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<tr>
<td>(nonspecific)</td>
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<td>Abdominal pain</td>
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<tr>
<td>Alopecia</td>
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<td>Hepatomegaly</td>
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<tr>
<td>Vasculitic skin lesions</td>
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<td>Nausea</td>
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<tr>
<td>Purpuric lesions</td>
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<td>Splenomegaly</td>
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<td>Livedo reticularis</td>
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<td>Vomiting</td>
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</tr>
<tr>
<td><strong>Diarrhoea</strong></td>
<td></td>
<td>Diarrhoea</td>
<td>10</td>
</tr>
<tr>
<td><strong>Ascites</strong></td>
<td></td>
<td>Ascites</td>
<td>10</td>
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</tbody>
</table>

*Table 2. Approximate prevalence of SLE clinical manifestations*
glomeruli, tubules, interstitium and blood vessels). The best classification of lupus nephritis is the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification. This classification divides lupus nephritis into six main subtypes of which the most worrying are type III (focal proliferative disease), type IV (diffuse proliferative disease) and type V (membranous disease).

Urinalysis, looking for both protein and blood, is important in the assessment and monitoring of renal disease activity. Urine sediment should be analysed to look for hyaline, granular, leukocytes, and/or erythrocyte casts and dysmorphic erythrocytes. A 24-hour collection to measure proteins is less often used than previously as it is often incomplete and patients do not like carrying the required bottles when they have to travel long distances to hospital. In preference, the urine protein/creatinine ratio based on a simple sample given on arrival at the clinic is now widely used. Renal biopsy, done under ultrasound, is important, providing evidence for prognosis and the rationale for treatment. Hypertension in SLE patients is often a feature of renal disease and must be well controlled, to help ensure a good outcome.

Cardiac manifestations
The heart is affected in about 30 per cent of patients with SLE. Any part of the heart can be affected, notably the pericardium, myocardium, the conduction system, valves, and coronary arteries. A high incidence of acute cardiovascular events is increasingly recognised as a cause of mortality. Female SLE patients between the ages of 35 and 44 years, are 50 times more likely to have a myocardial infarction. This coronary disease is not fully explained by traditional risk factors.

It is associated, however, with several non-traditional SLE-related risk factors including disease duration, disease activity and severity, autoantibody positivity and exposure to drugs such as corticosteroids.

Pulmonary manifestations
Pulmonary manifestations of SLE include pleuritis, interstitial lung disease, shrinking lung syndrome, pulmonary hypertension, alveolar hemorrhage and thromboembolic disease. Pleuritis is the most common pulmonary problem. The effusion is usually bilateral and scanty, but can be massive.

Neuropsychiatric manifestations
The prevalence of the most common SLE neuropsychiatric manifestations is shown in Table 2. Several pathogenic mechanisms have been suggested including cerebral vasculitis, the consequence of thrombosis linked to antiphospholipid antibodies, antibodies which bind directly to antigens in the CNS and antibodies that cross-react with targets both within and outside the nervous system. As an example of the last of these four mechanisms, some antibodies to DNA actually recognise a peptide and the amino-acid sequence is also present on N-methyl-D-aspartate receptors in the amygdala and...
hippocampus. However, for an antibody mechanism to be viable there must also be a deficiency of the blood-brain barrier to allow them access to the CNS.

**First- and second-line treatment options**

Treatment of SLE aims at ensuring long-term survival, preventing organ damage, and optimising health-related quality-of-life, by controlling disease activity and minimising comorbidities and drug toxicity.9

Management of SLE treatment depends on disease severity and the particular manifestations. The main indications for use of anti-inflammatory and conventional immunosuppressive drugs in SLE are shown in Figure 1.

**Mild disease**

The European League Against Rheumatism (EULAR) recommends that antimalarials and/or glucocorticoids are of benefit in the treatment of SLE without major organ manifestations. In addition, photo-protection is likely to help in patients with skin manifestations and should be encouraged.10

Hydroxychloroquine has a central role for long-term treatment in all SLE patients. The LUMINA trial has offered evidence of a decrease in flares and prolonged life in patients treated with hydroxychloroquine.11

The mechanism of action of antimalarials in SLE is not completely elucidated. Hydroxychloroquine seems to induce the modulation of the innate immune response, increasing the lysosomal pH in macrophages and other antigen-presenting cells, thus interfering with endosomal toll-like receptor activation and with “antigen processing” required to stimulate CD4+ T cells.12

In addition to their immunomodulatory and anti-inflammatory effects, antimalarials have a broad spectrum of beneficial effects. They have shown favorable metabolic properties on both glucose control and lipid levels and reduce the thrombotic complications.13

Hydroxychloroquine typically is well tolerated at the recommended dose (≤6.5mg/kg daily), and serious side-effects are rare. The most common side-effects are gastrointestinal disorders and skin rashes. In very rare cases, hydroxychloroquine may cause retinal toxicity, with visual changes or loss of vision. The risk of toxicity increases in those aged 60 years or older taking high doses for many years, or in those with renal disease or a pre-existing maculopathy, which might be a contraindication to its use. Baseline examination within first year of use and annual screening after every five years of treatment (or sooner if there are risk factors) is recommended.14 The goal is to recognise early signs of paracentral tissue damage to avoid serious visual loss. Screening by an ophthalmologist should include dilated fundus examination and automated visual field testing.

**Moderate disease**

In patients with moderate SLE or in patients not able to reduce steroids below 10mg daily, immunosuppressive agents such as azathioprine, mycophenolate mofetil and methotrexate should be considered. A high cumulative dose of steroids is associated with side-effects such as cataracts, hypertension, osteoporosis, diabetes, infections and atherosclerosis.

Azathioprine (2mg/kg daily) is used for inducing disease remission in SLE patients with mucocutaneous, serositis or haematological manifestations. It is also used as maintenance therapy, after cyclophosphamide, in severe SLE manifestations.15 Azathioprine is a synthetic purine analogue. It is rapidly metabolised in the liver and red blood cells to 6-mercaptopurine (6-MP), which blocks the intracellular purine synthesis, resulting in a reduction of B and T cells activity. As a result of its main action on the cells during active proliferation, the most common side-effect of azathioprine is bone marrow suppression.

Individuals who are homozygous or heterozygous for thiopurine S-methyltransferase (TPMT) polymorphisms may have increased risk of severe myelotoxicity when receiving azathioprine. There is no general consensus as to whether determining TPMT activity is cost-effective. Some authors16 suggest that TPMT activity levels should be tested before azathioprine is prescribed. Others believe that starting a thiopurine drug at a low dose and simply checking the blood count after a week could identify individuals who have very low or absent enzymatic activity (≤1 per cent). However, more cost-effectiveness studies are necessary.

Other common side-effects of azathioprine include nausea, vomiting, diarrhoea and abnormal liver enzymes.

If allopurinol is being co-prescribed, the dose of azathioprine should be reduced by 50−75 per cent. Allopurinol increases the blood levels of azathioprine by blocking the xanthine oxidase enzyme which metabolises 6-mercaptopurine to inactive metabolites.

Methotrexate is an antifolate drug that induces the inhibition of enzymes involved in purine synthesis. It is used as a steroid sparer or in non-responsive patients with arthritis and skin disease.

Mycophenolate mofetil is metabolised in the liver to the active mycophenolic acid, which inhibits inosine monophosphate dehydrogenase, the enzyme that controls the de novo pathway of purine synthesis, resulting in a reduction of B and T lymphocyte proliferation. It is used in cases of moderate to severe SLE, for inducing disease remission or as maintenance therapy after cyclophosphamide.

**Severe disease**

More prolonged steroid use and intensive immunosuppressive therapy is generally reserved for patients with involvement of vital organs.

Cyclophosphamide is an alkylating agent that interferes with the DNA integrity causing cell death in highly proliferative tissues (bone marrow, gastrointestinal tract, and reproductive system). It is often used in patients with severe renal involvement. Long-term efficacy in SLE nephritis has been demonstrated only for cyclophosphamide-based regimens,17,18 but this drug may cause infertility and bone marrow suppression. However, in short- and medium-term trials, mycophenolate mofetil has demonstrated at least similar efficacy compared with pulse cyclophosphamide and has a more favorable toxicity profile.19 In addition, mycophenolate mofetil seems to be more effective in African or Hispanic populations and in patients with...
membranous glomerulonephritis.

Recently, the Euro-Lupus Nephritis trial reported that a shorter treatment protocol of six pulses of 500mg cyclophosphamide is as effective and possibly safer than the standard high-dose regimen in induction therapy of lupus nephritis.20

For maintenance treatment, mycophenolate mofetil has been shown to be superior to azathioprine in maintaining a renal response to treatment and in preventing relapse in patients with lupus nephritis who had a response to induction therapy.21 Maintenance therapy aims for the lowest glucocorticoid dosage needed to control disease.

If a SLE patient does not respond to conventional immunosuppressive drugs, some biological drugs are available. Belimumab, which blocks a B cell activating factor known as BLYS, is the first biological agent to be approved by the Food and Drug Administration (FDA) in 50 years for patients with antibody-positive SLE who have active disease despite treatment with conventional drugs. In addition, off-label use of rituximab, which blocks the CD20 molecule present on many B cells, has also been recommended when conventional therapies have proved ineffective. Many open-label studies strongly support its clinical efficacy in inducing remission in SLE patients.22 Despite results from non-randomised studies, the two double-blind trials that have assessed the efficacy of rituximab in patients with active SLE (EXPLORER and LUNAR trials) failed to reach their primary endpoints.23,24 However, the concomitant use of high doses of glucocorticoids and immunosuppressive therapies used in both studies made it difficult to show any benefit for rituximab. Furthermore, the recently published EULAR and the ACR recommendations on induction therapy in lupus nephritis support the off-label use of rituximab as second-line regimen in SLE patients who are refractory to conventional immunosuppressive treatment.25,26

There is also increasing interest in the notion that rituximab followed by mycophenolate or azathioprine could be used at the time of lupus diagnosis, replacing oral steroids (which cause many side-effects) altogether. A major clinical trial, RITUXILUP, is underway to test this hypothesis. Finally, blockade of other different pathways, such as T cell co-stimulation, IL-6 and INF-alpha, have been shown to have efficacy in SLE patients.27

The GP’s role in management
SLE is a chronic and often relapsing/remitting condition. Close links between primary and secondary care are essential in managing these patients. The GP has a pivotal role in excluding other possible causes in patients presenting with non-specific features. A GP should be conscious of the clinical features that suggest SLE, interpret laboratory tests in the light of the clinical context and refer to a specialist for prompt evaluation, as appropriate.

In long-term management the GP has a role in monitoring the toxicity and efficacy of immunosuppressive drugs, improving adherence to medication and in managing infections and vaccinations. In particular, live viral vaccines should be avoided in those on 10mg daily prednisolone or more, or taking an immunosuppressive. Live attenuated vaccinations (eg herpes zoster) should be undertaken before starting a DMARD or a biological agent. Killed vaccines (eg pneumococcal, influenza, hepatitis B) should be given based on age and risk. If the patient starts a biological drug, the vaccination schedule should be discussed with the consultant rheumatologist.

With regard to the management of comorbidities and the assessment of cardiovascular risk, the GP may also help in the promotion of lifestyle changes, in the identification of additional atherosclerosis risk factors, and in measuring and maintaining normal blood pressure, especially in those patients on long-term higher dose steroids and those with renal organ damage.

SLE impacts many aspects of patients’ health, so the GP and the specialist must co-operate to optimise the life-long management of these patients.

References

Declaration of interests
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