

REVIEW

Management of systemic lupus erythematosus (SLE)

S. J. MORTON and R. J. POWELL

Clinical Immunology Unit, University Hospital, Queens Medical Centre, Nottingham, UK

An occasional series of articles on “Updates in Clinical Immunology” based on presentations at previous meetings of the British Society for Allergy and Clinical Immunology.

Introduction

The diagnosis of SLE depends upon the recognition of specific symptoms and the identification of autoantibodies such as antinuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA) and extractable nuclear antigens (ENAs). It is important to be aware of the fact that patients who are ANA-negative and Ro-negative rarely have systemic LE and that antibodies to dsDNA are not diagnostic of lupus, occurring in only approximately 50% of cases and being present in other rheumatic conditions, including drug-induced LE [1]. Also, the frequently quoted ‘ARA criteria’ [2] can be used to categorize patients for research purposes, but should not be relied upon to make a diagnosis.

There is no universally applicable test to determine lupus activity but erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complement levels including complement conversion products (C3dg), anti-dsDNA, and urine neopterin all have their proponents. Various eponymous clinical scoring systems exist, such as BILAG, SLAM and SLEDAI, but they all fall short, on some account, of being an ideal clinical activity marker. Therefore combinations of two or more of the scores are often used.

Treatment

General measures

Information about the nature of SLE should be provided for all patients and supplemented with leaflets and access to local lupus support groups. Specific reference needs to be made to the issue of photosensitivity and the various precautionary measures that should be taken, e.g. avoidance of exposure to sunlight (and fluorescent lighting) for long

periods, use of high factor sun blocks (SPF 25–50) and of sensible light clothing to cover exposed areas. The need to take drugs with potentially toxic side-effects, and the risk of drug interactions can be addressed when the need arises. We do not discourage women from taking oral contraceptives [3] or hormone replacement therapy [4], and women wishing to have a family can be told that despite the increased risk of fetal loss they can usually achieve a reasonable family size.

Drugs (see Fig. 1)

Corticosteroids Steroids remain the mainstay of treatment for disease flares (reviewed in *Dubois’ Lupus Erythematosus* [5]), but with the advent of new immunosuppressive agents maintenance therapy with oral prednisolone is now less commonly required. In patients with mild/moderate disease including rashes, synovitis and pleuro/pericarditis, it is our practice to use short courses, e.g. 2–3 weeks of oral prednisolone (30–40 mg). More severe disease flares causing systemic vasculitis, lupus cerebritis, nephritis and severe thrombocytopenia or haemolytic anaemia may warrant treatment with intravenous methylprednisolone; often three pulses of 1 g each are given on 3 consecutive/alternate days. A reducing course of oral prednisolone is usually given following this. Prior to administering high doses of steroids, it is necessary to exclude as far as possible underlying infection and urine neopterin levels ($> 1000 \mu\text{mol/mol}$ creatinine) can be useful in suggesting ‘covert’ infections with cytomegalovirus (CMV), leishmaniasis, etc. [6].

Despite vigorous attempts to minimize the use of steroids, some patients with repeated flares will inevitably receive large cumulative doses. It is these people who remain at risk of developing long-term side-effects including hyperlipidaemia and atherosclerosis, culminating in ischaemic heart disease, now one of the most important causes of mortality in SLE [7].

Correspondence: Dr Richard Powell, Clinical Immunology Unit, University Hospital, Queens Medical Centre, Nottingham NG7 2UH, UK.

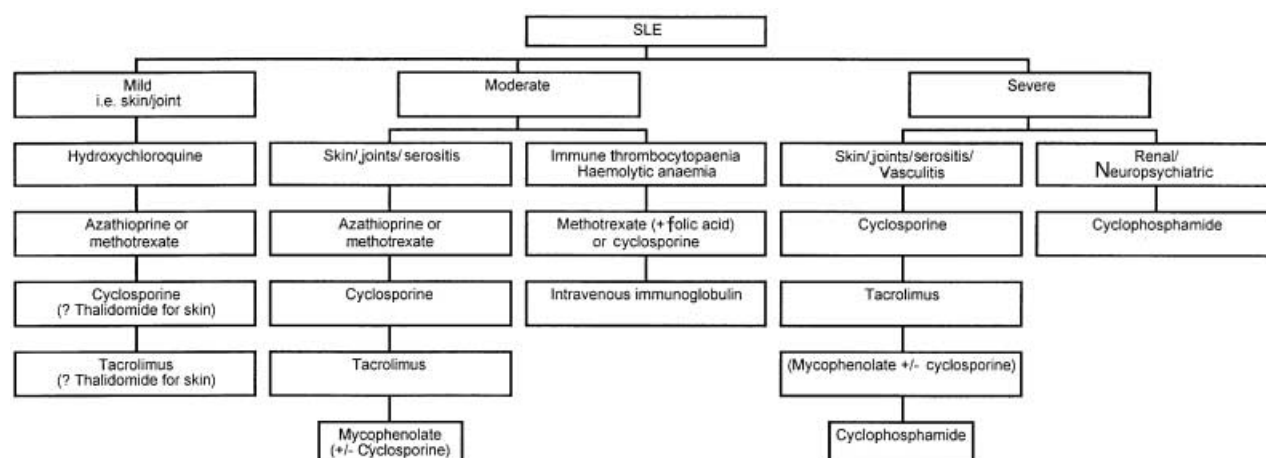


Fig. 1. Flow chart of suggested drug treatment of SLE. Corticosteroids have not been represented in this chart, but are used for acute flares of disease when necessary.

Hydroxychloroquine The antimalarial, hydroxychloroquine, is an effective treatment for cutaneous and joint manifestations as well as serositis and mild systemic symptoms [8]. It has steroid sparing properties and has been shown to reduce the risk of flares of mild and severe disease. In addition, a recent editorial by Petri [9] highlighted the potential for hydroxychloroquine to reduce the risk of atherosclerosis through its cholesterol lowering effects, and of thrombosis through anti-platelet effects. These are both valuable properties given the widespread use of steroids for SLE, and with the knowledge that thrombosis, sometimes associated with the presence of anti-phospholipid antibodies, contributes in part to the pathogenesis of SLE.

Hydroxychloroquine is generally well tolerated and bone marrow toxicity is very rare. However, there is a small risk of retinopathy (a pigmentary maculopathy) with long-term use [10]. In our experience higher doses, e.g. 400–600 mg/day of hydroxychloroquine, are rarely more effective than 200 mg for treatment of mild lupus and at the lower doses ocular toxicity is uncommon. The Royal College of Ophthalmologists guidelines [11] state that patients treated with the drug should have a baseline ophthalmic assessment and that they should be provided with an Amsler chart to monitor their own vision on a regular basis. Only those patients who have received hydroxychloroquine for longer than 6 years require formal ophthalmic reviews.

Thalidomide Thalidomide can be valuable for the treatment of discoid lupus [12], subacute cutaneous lupus [13] and lupus profundus [14], and it acts by inhibiting tumour necrosis factor- α [15]. There is a consensus that it should be considered only after treatment with hydroxychloroquine and steroids has failed to control cutaneous disease. All female patients need to be warned of its

teratogenic effects and adequate contraception must be used for the duration of, and for 3 months after treatment [16]. In view of its potential to cause an axonal polyneuropathy [17], nerve conduction studies (sensory nerve action potential amplitudes) need to be carried out twice prior to treatment and then at regular intervals during treatment (either every 6 months or after cumulative doses of 10 g) [16]. The optimal dosage and duration of treatment is not known but good results have been achieved with short-term use, e.g. up to 2 months at doses of 100–200 mg at night to avoid sedation during the day.

Methotrexate Methotrexate is a cytotoxic drug of the folate antagonist group, which when used in the context of SLE has beneficial immunosuppressant effects, even when prescribed with folic acid. The effects of methotrexate on cytokine profiles in mouse models of SLE have been documented [18] but there have as yet been relatively few trials of methotrexate in humans [19–22]. It seems to be effective for treatment of skin, joint and muscle manifestations; however, its use in the presence of renal or CNS lupus has not been studied.

Side-effects can be a problem and they include nausea, mucositis, hepatotoxicity, pulmonary fibrosis, and bone marrow suppression [23]. The latter effect is reduced through the concurrent use of folic acid, which in turn helps to reduce the confounding effect of marrow suppression in the presence of lupus-associated cytopenias.

The dose required to treat lupus varies widely between individuals and has to be adjusted according to clinical response but usually lies between 7.5 mg and 25 mg per week. The slow onset of action of methotrexate can be a disadvantage, necessitating the use of steroids for longer periods when initiating treatment, and by the same proviso

longer trials of treatment before considering patients as 'methotrexate failures'.

Azathioprine Azathioprine, like Mycophenolate Mofetil (see below), inhibits purine synthesis and it reduces flare rates when used for lupus [24], including renal manifestations [25]. There is a lack of evidence, however, that it is capable of inducing disease remission during an acute flare [26]. Unfortunately it can take up to 3 months to produce a clinically beneficial effect, but unlike the situation with methotrexate, it is possible to use the neutrophil count as a guide to optimal dosage. We routinely aim to keep the neutrophil count as close to $2 \times 10^9/L$ as possible, counts of between 1.5 and $2 \times 10^9/L$ would prompt a reduction in dose, and complete withdrawal of azathioprine would be considered with neutrophil counts of $< 1.5 \times 10^9/L$. The dose required to achieve the desired degree of immunosuppression can range from 75 to 250 mg daily.

It is generally well tolerated but hypersensitivity reactions can occur [27], often characterized by a rash which is worst in the evenings. It is also said that up to 1 in 300 of the normal population have an inherited deficiency of the enzyme thiopurine methyltransferase [28], which is required for normal metabolism of the drug, and it is in these people that the potentially life-threatening pancytopenias occur. As blood counts can fall as soon as 1 week after commencing azathioprine, it has been suggested that a FBC should be carried out 7 days after treatment is commenced [29].

Cyclosporin Cyclosporin is a newer immunomodulatory drug and although it is not yet licensed for use in SLE there have been a small number of open studies which have demonstrated that it is effective in renal lupus [30–33] and for various non-renal manifestations [34,36]. There are two major advantages of cyclosporin over other drugs. One is the fact that it does not cause bone marrow suppression which means that concurrent cytopenias can be attributed to active disease without there being a confounding variable. The second important benefit is its rapid onset of action, often within 72 h, which may in some circumstances eliminate the need to use steroids for acute flares. In the routine clinical setting, the efficacy of cyclosporin appears to be greater for the manifestations of thrombocytopenia and arthritis, than for myalgia and fatigue [36].

A dose of between 2 and 5 mg/kg per day is usually adequate, and we aim to maintain trough, i.e. predose, blood levels at 100–200 ng/mL. A useful clinical marker of attainment of therapeutic doses is the development of a burning sensation in the hands and feet. Cyclosporin has a number of potentially serious side-effects including nephrotoxicity, hypertension and neurological abnormalities. This necessitates at least monthly checks of blood

pressure and of U & Es and serum creatinine. Withdrawal of cyclosporin needs to be considered if the serum creatinine rises by 30% above pretreatment levels [37], whilst hypertension can usually be controlled with an ACE inhibitor or a calcium channel blocker such as amlodipine (nifedipine interacts with cyclosporin). Other less serious, but nevertheless problematic side-effects include general malaise, headaches, hypertrichosis, gingival hypertrophy, angioedema and hyperkalaemia. The potential for anti-malarials, so often prescribed for foreign holidays, to interact adversely with cyclosporin should also be born in mind. Overall, many patients withdrew from cyclosporin therapy in the first 6 months due to lack of efficacy or side-effects [36].

We are using cyclosporin, followed if indicated by tacrolimus (see below), before resorting to Cyclophosphamide.

Tacrolimus Tacrolimus is an immunosuppressive, macrolide antibiotic, which appears to have a similar mode of action to cyclosporin. In an animal model of SLE the drug showed a potential to prolong life span, to reduce proteinuria and to prevent progression to nephropathy [38]. There has so far been only one publication highlighting its place in the treatment of severe and poorly controlled human lupus [39].

It is highly potent (compared with cyclosporin) and only small doses, e.g. 0.10–0.15 mg/kg per day seem to be required. As with cyclosporin we monitor trough blood levels of the drug and aim to keep these between 1 and 10 µg/L. Because the renal side-effect profile is similar to cyclosporin, regular monitoring of blood pressure and renal function is needed. Unfortunately, it is expensive (approx. £300.00/week) and we currently limit its use to patients who have relapsed/failed on cyclosporin. However, a number of specific side-effect profile benefits are emerging for tacrolimus; it lacks the peripheral adrenergic action of cyclosporin, and may also be less likely to induce hypertension and gingival hypertrophy.

Cyclophosphamide Cyclophosphamide is an alkylating agent and is currently regarded as the most effective form of treatment for renal and neuropsychiatric lupus, but it can also be used to good effect for other manifestations that are refractory to the above drugs (reviewed in [40]). The combination of Cyclophosphamide and corticosteroid has been shown to be more effective than Cyclophosphamide alone (for renal lupus in particular), and it is our practice to give 1 g of i.v. methylprednisolone with each of the first four pulses of i.v. Cyclophosphamide. The optimal length of treatment and dosage interval are not yet known but most studies have been based on the use of monthly i.v. Cyclophosphamide for approximately 6 months. In Nottingham we achieve high rates of remission with a regime

of weekly doses for a month, fortnightly doses for 2 months and monthly doses for a final 3 months. We would normally commence treatment with a pulse of 1 g but future doses are dictated by the degree of predose neutropenia, as shown below: if neutrophil count = $2.0 \times 10^9/L$, Cyclophosphamide usually given but possibly at a reduced dose; if neutrophil count = $1.5\text{--}2.0 \times 10^9/L$, treatment may be deferred for a week and future doses reduced/interval between doses increased; if neutrophil count $< 1.5 \times 10^9/L$, Cyclophosphamide is deferred until the neutrophil count is $> 1.5 \times 10^9/L$ and future doses reduced/interval between doses increased.

To reduce the risk of haemorrhagic cystitis, mesna is administered with every Cyclophosphamide infusion and high fluid intake is encouraged. We also routinely prescribe a prophylactic anti-emetic such as ondansetron. Throughout the treatment period cotrimoxazole is given (960 mg 3 $\times$ /week) as prophylaxis against *Pneumocystis pneumoniae* infection (previously a significant problem with our intensive regime). Transitional cell carcinoma of the bladder is a worrisome long-term complication and the risk is increased following administration of Cyclophosphamide via the oral route [41]. Therefore in patients < 60 years we tend to give it in pulses intravenously; however, when venous access is a problem oral pulse therapy is an alternative. Premature ovarian failure occurs in up to 40% of all females treated with Cyclophosphamide and the level of risk correlates with older age, lower predose neutrophil count and greater cumulative dose [37]. All females therefore have to be counselled appropriately and if there is time consideration given to storage of embryos (ova can not be stored) prior to treatment. Fertility can also be jeopardized in males, therefore sperm storage needs to be offered to these patients.

Chlorambucil Chlorambucil is an alkylating agent with similar efficacy to azathioprine, but greater toxicity. It does not cause haemorrhagic cystitis (cf. Cyclophosphamide) but it has the potential to cause more prolonged cytopenias [42] and there have been reports of irreversible aplastic anaemia. In addition, treatment with it increases the risk of malignancy (haematological and cutaneous) by a similar magnitude to Cyclophosphamide [43]. We limit its use to cases in which all other alternatives have been tried and 2–8 mg/day are given with regular and vigilant monitoring of full blood counts, e.g. monthly.

Mycophenolate Mofetil Mycophenolic acid, the chief metabolite of Mycophenolate Mofetil, is an inhibitor of purine synthesis and it is currently licensed for use as prophylaxis against renal allograft rejection, when given in combination with cyclosporin and corticosteroids. There are a number of documented cases of psoriasis [44],

autoimmune haemolytic anaemia [45], pemphigus vulgaris [46], pemphigoid [47] and systemic vasculitis [48], which have responded well to the drug.

There is now an emerging literature of evidence (eight case series) of a useful role in refractory severe lupus nephritis [49].

In our experience of non-renal disease, there is a small number of SLE patients who fail to respond to or relapse on cyclosporin and tacrolimus who will improve with Mycophenolate Mofetil. There is a theoretical possibility that combined therapy with cyclosporin may be better than Mycophenolate alone [50], but this has not yet been formally assessed in the context of SLE.

It has a number of side-effects, the most common of which are gastrointestinal, but hypertension can occur and there is a significant risk of contracting infections with CMV, herpes simplex, aspergillus and candida [51]. Unfortunately, because it does not cause a dose-related neutropenia (unlike azathioprine, Chlorambucil and Cyclophosphamide), it is difficult to assess whether adequate immunosuppression has been achieved other than by monitoring the patient clinically. Whilst it does induce lymphopenia, it can be difficult to distinguish disease-induced lymphopenia from drug effect. It is usually given at a dose of 1–1.5 g twice daily, independent of the patient's weight.

Cladribine In view of the potential major side-effects of Cyclophosphamide, therapeutic strategies which specifically target lymphocytes are appealing. The purine nucleoside analogue cladribine (2-chloro-2-deoxyadenosine) is a selective lymphocyte-depleting agent, which, in early reports, appears to be a promising agent in severe lupus nephritis [52,53]. It is administered as a continuous central intravenous infusion over 7 days. Our limited experience suggests that cladribine may be effective for other manifestations of SLE (cutaneous vasculitis) but that it does not appear to have a consistent effect in lupus nephritis. Further studies are required to establish the position of cladribine in SLE, particularly in view of the emerging efficacy of Mycophenolate.

Plasmapheresis This technique involves selective extraction of plasma from whole blood [54]. The rationale behind its use in SLE is that circulating immune complexes and immune reactants such as free antibody and complement components can be removed. There is some doubt as to whether the benefit observed is derived from this process alone or whether some is due to the immunoglobulin-containing fresh frozen plasma that used to be infused at the end of the process to restore plasma volume.

There are a limited number of situations where the benefits of plasmapheresis are clear cut: (i) thrombotic

thrombocytopenia, (ii) cryoglobulinaemia, and (iii) hyper-viscosity syndrome [54]. With the advent of the newer and more effective immunosuppressants cyclosporin and tacrolimus, the need for this unproven form of therapy is likely to diminish.

Intravenous Gamma Globulin (IVIG) The evidence supporting the use of IVIG is limited. Beneficial effects have been observed in autoimmune thrombocytopenia and in a single open-label study of 12 patients with moderately severe disease an improvement in activity scores and anti-dsDNA antibody titres was noted [55]. In one other report of two cases with severe disease, prolonged treatment, i.e. 20 months, resulted in induction of remission [56].

If used, it is usually given at a dose of 0.4 kg/day for 5 consecutive days on a monthly basis. An advantage of this form of treatment is that opportunistic infection is unlikely to occur, but there is a small risk of transmission of infective particles such as the hepatitis viruses and new variant CJD. IVIG can cause acute renal failure and pre-existing renal impairment should be regarded as a relative contraindication [57]. Expense, the inherent risk of virus transmission and the lack of evidence of efficacy from controlled trials mean that we rarely use this treatment modality.

Experimental modalities

Extracorporeal photochemotherapy This form of treatment (reviewed by Holbrook & Powell [58]) involves the oral administration of methoxypsoralen to the patient, followed 2 h later by removal of blood at room temperature. The blood is then exposed to ultraviolet A and reinfused. It seems to have an immunomodulatory role through the operation of several different mechanisms including psoralen-mediated damage to intracellular DNA, inactivation of intracellular enzymes and modification of leucocyte membrane DNA fragments.

The technique has been applied to the treatment of cutaneous T cell lymphoma, rheumatoid arthritis, psoriasis, and progressive systemic sclerosis, and there have been two reports of its use in SLE. In one of the lupus reports improvements in cutaneous and articular manifestations occurred in 7/8 cases and it was well tolerated, but cases with neuropsychiatric and cardiopulmonary lupus were excluded as were those with a serum creatinine of >190 mmol/L. It has not been widely used because of expense, limited availability and lack of trials comparing it with other treatment.

Haematopoietic stem cell transplantation Bone marrow-derived stem cells ($CD34^+$) are harvested from the patient, usually from the peripheral blood following colony-stimulating factor treatment, then reinfused after the

administration of immunoablative chemotherapy [59]. In this way clones of pathogenic leucocytes can be eliminated without completely destroying the patient's ability to regenerate bone marrow. There have been three reports of patients with haematological malignancy who also had SLE [59–61], and in two of these autologous stem cell transplantation resulted in complete remission of both diseases [59,60]. So far there have been only two reported cases [62,63] where SLE has been the sole indication, i.e. with no additional haematological malignancy: in both cases clinical and serological remission was induced, but follow up was short.

We have no experience of the technique, but those that do reserve it for patients with life-threatening lupus who have responded poorly to aggressive immunosuppressive therapy. A precondition must be that they have adequate function of major organs to reduce the risks of morbidity/mortality related to the procedure [64].

SLE and the anti-phospholipid antibody syndrome (APLS)

The anti-phospholipid antibody syndrome can be diagnosed when one or more of a well-recognized group of clinical scenarios occurs in association with either a positive lupus anticoagulant (LA) test and/or a positive anti-cardiolipin assay (IgG or IgM in a moderate/high titre). The clinical criteria are arterial and venous thromboses, recurrent fetal loss and thrombocytopenia [65].

There are primary and secondary forms of the syndrome, and the association with lupus represents one of the latter. In a Nottingham-based epidemiological study of SLE, 13% of lupus patients had positive LA tests, 25% had IgG APL antibodies and 30% had IgM APL antibodies (personal communications). The proportion of these patients who had the clinical APLS was not ascertained, but in another study by Hughes 35% of lupus patients had APLS [66]. This estimate seems rather high and may be due to the inclusion of a selected group of patients attending specialist clinics. Indeed, distinguishing primary APLS, with accompanying arthralgia and thrombocytopenia, from SLE with APLS, is problematical.

From a management point of view, patients with positive tests (borderline/low titres excluded) should be advised to take low-dose aspirin [67,68] and anyone with a history of thrombosis or fetal loss should be fully anti-coagulated with warfarin (INR target range = 3–4.5) [65]. Pregnancy represents a special problem, as warfarin is teratogenic, so conversion to heparin is required.

The recent development of a test which identifies antibodies directed against the plasma protein β_2 -glycoprotein 1, a cofactor for binding to phospholipid, promises to increase diagnostic specificity for the syndrome, which up

to now has been plagued by the confounding effect of infections, which also increase APL antibody titres [69].

Management of lupus during pregnancy and lactation

Pregnancy represents a risk to both mother (due to increased flare rate) and fetus (fetal loss occurring in 20% of all lupus pregnancies [70]). Some of the strategies aimed at reducing these risks are discussed below (see [71]).

1. Every woman wishing to have a family should be advised not to conceive either during or within a few months of a lupus flare.

2. If pregnancy is planned then the treating physician should take steps to avoid treatment with Cyclophosphamide, methotrexate and Chlorambucil, as these are teratogenic.

3. During pregnancy flares should be treated with prednisolone and if disease-modifying drugs are required hydroxychloroquine, cyclosporin and azathioprine are the safer alternatives.

4. Patients with anti-cardiolipin antibodies should be given low-dose aspirin (see below), and those with anti-Ro antibody should be monitored closely for the development of congenital heart block in the fetus.

5. It is our practice to prescribe low-dose aspirin to all pregnant lupus women to reduce the risk of fetal loss, preeclampsia and intrauterine growth retardation. Others, however, prefer to use it only for people with particularly high risks of the above conditions, e.g. prior history. High-dose aspirin and NSAIDs can be harmful during the later stages of pregnancy.

Summary points

1. Diagnosis dependent on clinical history and serological investigations; an ANA⁺/Ro⁺ patient is very unlikely to have lupus.

2. FBC, ESR, complement levels, urinary neopterin, CRP and urinalysis are all useful in the assessment of disease activity.

3. Distinguishing between fibromyalgia and SLE is often difficult, but a patient's response to steroids can serve as a useful guide.

4. The step ladder of treatment has expanded to include cyclosporin, tacrolimus and Mycophenolate, reducing our reliance on cyclophosphamide.

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