

Drug treatment of systemic lupus erythematosus

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This article, which is the second part of our special feature, discusses the various drug regimens used in managing systemic lupus erythematosus. Case studies have been used to highlight salient points

Systemic lupus erythematosus (SLE), or lupus, is an autoimmune disease which can affect practically any organ or tissue in the body.

SLE arises from a malfunction of the immune system such that cells and proteins of that system start to attack and damage tissues of the body itself. The evidence in support of this is conclusive. Biopsy samples

taken from tissues such as skin or kidney which have been inflamed in active SLE show an accumulation of cells of the immune system (notably lymphocytes) and deposition of substances such as antibodies and complement. These deposits are not found in healthy tissues and are characteristic of an active immune reaction. SLE is also characterised by the presence of autoantibodies in the bloodstream. Most antibodies produced by the immune system recognise foreign substances such as bacteria and viruses. Autoantibodies, however, recognise substances which are components of the

body itself. In patients with SLE, a wide variety of different autoantibodies have been reported, but the most common are those directed against constituents of the cell nuclei.¹ A number of different reports have confirmed that over 90 per cent of patients with SLE test positive for these antinuclear antibodies. The most important of the antinuclear antibodies are probably antibodies to double-stranded DNA (anti-dsDNA).² Anti-dsDNA antibodies are present in 50 to 75 per cent of patients with SLE and the levels of these antibodies tend to rise when the disease becomes more active. Experiments in

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laboratory mice have shown that some anti-dsDNA antibodies can cause kidney damage in those animals very similar to the damage found in SLE itself.³

Although there is evidence that SLE is an autoimmune disease and that autoantibodies play a role in causing tissue damage, it is not yet possible to identify the exact defects in the immune system which give rise to the disease. For this reason, there is no curative treatment. Drugs such as corticosteroids and cyclophosphamide can be used to suppress the immune system in active SLE, but these drugs have potentially serious side effects and it is not necessary to use them in all manifestations of the disease.

Drug treatment of SLE is therefore challenging for three main reasons:

1. There are many possible manifestations of the disease. Some are more severe, though not necessarily more symptomatic, than others. It is important to use the correct regime of drugs for each form of SLE
2. The underlying cause is unknown. Treatment of severe forms of SLE therefore relies upon the use of broad spectrum immunosuppressive drugs which may have a number of side effects in addition to the desired effect of disease suppression
3. Patients tend to be young and often female. Since the disease can be suppressed but not cured by drugs, these patients may be faced with the prospect of taking potent drugs for long periods. This may raise social and psychological difficulties which must be recognised and discussed by doctors and pharmacists. In particular, the question of pregnancy will be considered later in this article

DRUG TREATMENT

The drugs used to treat lupus can conveniently be considered in two groups. Drugs such as the non-steroidal anti-inflammatory drugs (NSAIDs) and hydroxychloroquine are used in mild SLE and have little or no immunosuppressive activity. Drugs such as corticosteroids and

cyclophosphamide suppress the immune system and are used in more severe manifestations of SLE, but give rise to greater concerns about toxicity.

Many patients with SLE remain well for long periods without requiring any drugs. General measures to maintain this state of health in such patients include the avoidance of strong sunlight. Photosensitivity of the skin is a common feature of SLE and, in some cases, exposure to sunlight can stimulate a more generalised flare of the illness, including symptoms such as joint pain and severe fatigue. Patients with SLE are advised to avoid going out in strong sunlight. If they have to, they should apply sunblock (sun protection factor 15 or higher) and wear clothes which cover their arms and legs if possible. This particularly applies to white patients.

This article will first consider the drugs commonly used in the management of SLE and then the clinical scenarios in which they are employed.

NSAIDs and paracetamol The most common symptoms of SLE are fatigue and pain in the joints and muscles. It has been estimated that joint pain occurs in 85 to 90 per cent of patients with the condition,¹ although it rarely leads to joint swelling or deformity (in contrast with rheumatoid arthritis where both swelling and deformity are common).

Joint and muscle pain may be persistent and troublesome even when the disease is otherwise quiescent, with no involvement of major organs such as the kidney. Under these circumstances, immunosuppressive drugs are not necessary and NSAIDs or paracetamol may be sufficient to relieve the symptoms.

Paracetamol should be the drug of first choice, since it is very safe.

If this does not relieve the pain, NSAIDs such as ibuprofen or diclofenac are most commonly used. Long-term use of NSAIDs is associated with a risk of severe side effects, notably irritation of the gastrointestinal mucosa, which may lead to ulceration or bleeding. For patients who cannot tolerate their symptoms without taking NSAIDs regularly, gastro-protective drugs such as ranitidine or lansoprazole may be prescribed simultaneously. An alternative is to give the NSAID in combination with misoprostol, a prostaglandin analogue which protects the gastric mucosa. A number of these combined preparations are available. Arthrotec (diclofenac with misoprostol) is probably the most commonly prescribed. However, misoprostol is contraindicated in pregnancy and often avoided in women of childbearing age.

Hydroxychloroquine Hydroxychloroquine is an antimalarial agent which is useful in some autoimmune conditions, notably rheumatoid arthritis and SLE. Its main use in

SLE is in those who suffer greatly from joint pain and fatigue despite symptomatic treatment, but whose lupus is not active enough to warrant the prescription of corticosteroids. The dose of hydroxychloroquine is either 200mg or 400mg daily. Some of those who initially require the higher dose to bring their symptoms under control may later find that they can reduce it to 200mg per day, or even 200mg on alternate days, without experiencing any adverse consequences.

Hydroxychloroquine is also useful in the treatment of cutaneous lupus, where a rash, which may be photosensitive, is the predominant symptom. Mepacrine is an alternative antimalarial sometimes used in cutaneous lupus.

Hydroxychloroquine is a relatively safe drug with few side effects. It may cause a rash in some patients. The most serious side effect is retinal toxicity, which is very rarely severe enough to cause reduced visual acuity (this occurs in about 1 in 1,800 patients) and usually resolves on discontinuing the drug. A recent review⁴ found no conclusive evidence that regular monitoring of the eyes by an ophthalmologist was necessary but, in some units, patients taking regular hydroxychloroquine are asked to attend for such checks every six to 12 months.

Chloroquine is not generally used in SLE because it has a greater potential for ocular toxicity than hydroxychloroquine.

Corticosteroids Corticosteroids have been used in the treatment of SLE for almost 50 years. They have proved to be effective in many different manifestations of the disease and can be life-saving in severe forms of lupus, such as renal or cerebral lupus. The potential for serious side effects, however, is well known, particularly when corticosteroids are continued at high doses for long periods.

Some patients can usually manage without corticosteroids (often controlling symptoms of disease with NSAIDs and/or hydroxychloroquine), but have occasional flares of activity. Flares may be diagnosed on the basis of an increase in symptoms, a rise in the blood level of anti-dsDNA antibodies or erythrocyte sedimentation rate, a fall in the blood level of complement, or a combination of a number of these features. A flare of this kind may respond to a single intramuscular dose of a corticosteroid preparation such as methylprednisolone or prednisolone acetate. Single doses of this kind are unlikely to have long term adverse effects.

In other cases, an acute flare of disease may require a short course of oral corticosteroids. Acute pleurisy or pericarditis might be examples, particularly if the pain does not respond to analgesics or NSAIDs. For prednisolone, a starting dose of 20mg to 30mg per day would be appropriate, with a reduction by 5mg every one to two weeks until a

dose of 5mg per day is reached. Further reduction would need to be judged on an individual basis since, in some patients, the symptoms may return if corticosteroids are withdrawn completely.

Higher doses of oral corticosteroids (often 60mg prednisolone per day or more) are used in renal lupus, cerebral lupus and also where lupus is associated with profound haemolytic anaemia or thrombocytopenia. Particularly in renal and cerebral SLE, pulses of intravenous methylprednisolone (750mg to 1,000mg) may also be given in an attempt to rapidly bring disease activity under control.

Due to the high starting dose of oral prednisolone needed, gradual reduction of this dose in such patients may take many months. For this reason, these patients are exposed to high doses of corticosteroids for long periods and are particularly likely to develop side effects.

Managing adverse effects Hirsutism and weight gain are often very distressing, to the extent that patients with SLE may be reluctant to continue taking corticosteroids, or to restart them in response to a worsening of their disease. Furthermore, patients often find it difficult to lose this weight again, even after prednisolone has been discontinued.

High dose corticosteroids may precipitate or exacerbate diabetes mellitus or hypertension, so it is wise to monitor blood pressure and check urine samples for glucose in patients taking these drugs. In patients who already have either of these conditions, a change in drug therapy may be required. For example, a non-insulin dependent diabetic may require insulin during the period when he or she is being treated with high dose corticosteroids.

Since the purpose of giving corticosteroids is to suppress the immune system, these patients are increasingly prone to infection, which is one of the major causes of death in patients with SLE. While prophylactic antibiotics are not generally thought to be indicated, swift and appropriate prescription of antibiotics in response to clinical evidence of developing infection is important.

Live vaccines should be avoided in patients who are taking either corticosteroids or other immunosuppressive drugs for SLE.

Osteoporosis is a major side effect of corticosteroids. This is particularly true in postmenopausal women. Although it was previously believed that daily doses of prednisolone below 7.5mg carry little risk of enhancing bone loss, a more recent study in primary care suggested that even doses of 5mg or less might have some adverse effect on the bones, with increased risk of fracture.⁵ In any patient who is likely to be taking 7.5mg prednisolone or more for at least six months, the possibility of bone loss should

be considered.

In most of these patients, a preparation of calcium and vitamin D (eg, Calcichew D3 Forte, two tablets per day) should be prescribed.

In some of these patients, the addition of a bisphosphonate such as alendronate, etidronate or risedronate is also indicated. This is particularly true for those patients in whom bone density is shown to be low even at the onset of treatment with prednisolone. Bone density can be measured using a dual energy X-ray absorptiometry (DEXA) scanner, now available in most large hospitals.

It is important to advise patients of other ways to prevent the development of osteoporosis, for example, to stop smoking and to take weight-bearing exercise (such as walking) regularly. The use of hormone replacement therapy is controversial in SLE. Although it can clearly reduce the rate of bone loss and the incidence of fractures in postmenopausal women (with or without SLE), HRT can cause an exacerbation of SLE in some patients.

In summary, although corticosteroids are helpful in some patients with SLE and essential in others, the plethora of side effects make it important to use them at the lowest dose and for the shortest period possible. The use of immunosuppressant drugs, such as azathioprine and cyclophosphamide, in combination with corticosteroids, is one way of reducing the dose of corticosteroid necessary to control the disease.

Cyclophosphamide Cyclophosphamide is an alkylating agent which is used in combination with corticosteroids to treat the most severe forms of SLE such as renal or cerebral disease. It can be given either orally at a dose of 2mg to 4mg per kg per day, or intravenously (750mg to 1,000mg pulses) at monthly intervals. Some groups advocate the intravenous route on the grounds of improved compliance and reduced risk of gonadal dysfunction. The latter claim has not been proved beyond doubt.

The best evidence supporting the use of cyclophosphamide in SLE relates to kidney disease, where a number of studies have shown that maintenance of renal function is better in patients treated with both corticosteroids and cyclophosphamide than in those given corticosteroids alone.⁶ A number of regimes have been used and there is no clear consensus that any one of these is better than the others. One of the most common regimes is that described in studies by the US National Institutes of Health (NIH).⁷

In the NIH regime, the patient is started on oral prednisolone at a dose of between 30 and 80mg per day depending on disease severity. This dose is reduced, the rate of reduction depending on the original starting dose and on how well the patient responds. A typical regime would be to cut the daily dose of prednisolone by 5mg every two to

four weeks until a dose of 15mg per day is reached, and then reduce the dose by 2.5mg every two to four weeks until a dose of 10mg per day is reached. After this, the dose would be reduced more slowly as dictated by the clinical response.

Intravenous boluses of 750mg to 1,000mg cyclophosphamide are given at monthly intervals for six months, then every three months for up to two years. Cyclophosphamide pulses should be accompanied by adequate intravenous hydration. The use of mesna (mercaptoethane sulfonate) reduces bladder toxicity.

The use of cyclophosphamide may be associated with alopecia, nausea, bladder toxicity and gonadal dysfunction in patients of both sexes. In women, this may lead to prolonged amenorrhoea and infertility. The risk of such gonadal problems is greater in those above the age of 25⁸ and is of great concern in SLE, a disease which presents most commonly in women of childbearing age.

The cumulative dose of cyclophosphamide administered is related to the likelihood of developing adverse effects. This highlights the need to use this drug for as short a period as is necessary to achieve and maintain control of the disease. It should be stressed, however, that severe lupus nephritis carries a high risk of dialysis dependence or even death if treated inadequately, so that the risk of adverse effects may be a secondary consideration in comparison.

Cyclophosphamide may also cause bone marrow suppression. During a programme of cyclophosphamide pulses, the white blood cell count falls to a nadir 10 days after each pulse and should be measured at that time in order to be able to determine if the next pulse can be safely given. Nausea and vomiting during pulses may be so severe that anti-emetics such as metoclopramide or

granisetron are necessary.

Both cyclophosphamide and azathioprine can increase the risk of developing malignancy (particularly bladder tumours in the case of cyclophosphamide). As with corticosteroids, treatment with either of these immunosuppressive drugs makes patients more prone to infection.

Azathioprine Azathioprine is a weaker immunosuppressive agent than cyclophosphamide with less severe side effects. It is used in SLE at a dose of 2mg to 3mg per kg per day, usually in combination with corticosteroids. It is most commonly used in one of two scenarios:

1. To replace cyclophosphamide where a severe manifestation of SLE has been brought under control, for example, after a programme of intravenous pulses of cyclophosphamide has been used to induce remission in renal SLE. Some patients with milder forms of renal SLE can be treated with prednisolone and azathioprine from the outset and never require cyclophosphamide at all
2. To enable the dose of corticosteroids to be reduced in a patient whose SLE seems to flare every time such a reduction is made. For example, a patient whose disease normally flares every time the dose of prednisolone is reduced below 10mg daily may respond to a combination of 7.5mg prednisolone and 100mg azathioprine daily

Important side effects of azathioprine include bone marrow suppression and liver dysfunction. Regular blood tests for full blood count and liver function are recommended. These should be carried out every one to two weeks initially, and subsequently every one to three months. The risk of bone marrow suppression in patients taking azathioprine is increased by the concurrent administration of some other drugs, notably allopurinol or captopril.

Anticoagulants and aspirin About 20 to 30 per cent of patients with SLE have antiphospholipid antibodies (APL) in their bloodstream. In some of these patients, autoantibodies can interfere with the clotting mechanism of blood. This leads to an increased likelihood of arterial or venous thromboses, low platelet count, miscarriages and a skin rash called livedo reticularis. The presence of clinical features such as these in a patient with antiphospholipid antibodies constitutes the antiphospholipid antibody syndrome (APS). Patients with high levels of APL in their blood are usually asked to take aspirin (75mg to 150mg per day) as a means of protection against thromboses. Patients who have high levels of APL and have already suffered from recurrent thromboses or miscarriages may have to take warfarin

Case 1

Anna is a 25-year-old woman who was diagnosed with SLE five years ago. The disease has been mild, and the predominant symptoms are joint pain and tiredness. She has previously taken ibuprofen for the pain. Over the past few months, these symptoms have become worse and her fatigue is now so bad that she finds it difficult to work. Over the past two weeks she has suffered widespread joint pain. Her blood tests show raised erythrocyte sedimentation rate (ESR) and slightly raised anti-dsDNA antibodies. There is no evidence of renal or cerebral involvement.

Management Anna's lupus is clearly becoming more active and NSAIDs alone are not controlling her symptoms. She could be given an intramuscular dose of prednisolone acetate (75mg to 100mg) to treat her acute flare of joint pain. Hydroxychloroquine 400mg per day could be added to help reduce her fatigue and pain in the longer term. In some units, she might be referred to an ophthalmologist to monitor her eyes for hydroxychloroquine toxicity.

Case 2

Brenda is a 35-year-old Caucasian woman whose SLE primarily affects her skin. She has a widespread rash, which she finds unsightly, and is also suffering from loss of her hair in clumps. She feels otherwise well and her ESR, anti-dsDNA and complement levels are normal.

Management Brenda has cutaneous lupus and no other organs are involved at this stage. She should certainly avoid strong sunlight. Topical corticosteroids and oral hydroxychloroquine or mepacrine are often sufficient to treat the rash. In severe cases, a course of oral prednisolone may be required.

Case 3

Catherine is a 50-year-old woman who has suffered from SLE for 20 years and usually manages fairly well on hydroxychloroquine 200mg daily. She has a two-week history of left-sided chest pain on breathing in. This pain has not improved with NSAIDs or simple analgesia. Examination and a chest x-ray suggests that she has acute pleurisy. Her ESR and anti-dsDNA are also raised, suggesting active SLE.

Management This form of flare is commonly treated with a short course of oral prednisolone. The starting dose might be 20mg to 30mg per day with a reduction of 5mg every one to two weeks as judged by the response. One would aim to discontinue the corticosteroids as soon as practicable without causing a recurrence of her symptoms.

Case 4

Diane is a 32-year-old woman who presents to her local hospital with proteinuria, oedema of the ankles, high blood pressure and raised urea and creatinine levels. Her ESR and anti-dsDNA levels are very high and her complement level is low. A biopsy of her kidney confirms that she has severe lupus nephritis.

Management Diane is seriously ill and at high risk of requiring dialysis. It is important to treat her SLE aggressively to avoid irreversible kidney failure. She should be given high dose oral prednisolone and oral or intravenous cyclophosphamide. If the intravenous route is chosen, pulses should be given every month for at least six months, after which pulses every three months would be adequate. Her blood pressure should be controlled: ACE inhibitors are often used to achieve this. If her disease remains active despite the use of cyclophosphamide, or the drug proves intolerable, mycophenolate mofetil would be an alternative.

Over the next few months, the dose of prednisolone could be reduced gradually. Cyclophosphamide pulses could be stopped between one and three years after presentation (depending on progress) and azathioprine might be introduced instead.

It would be very important to consider possible adverse effects. Each pulse of cyclophosphamide should be given with hydration, mesna and adequate anti-emetics. Diane is at high risk of developing persistent amenorrhoea and infertility due to the cyclophosphamide, and this should be discussed with her. She should be given calcium and vitamin D and possibly a bisphosphonate to protect her against osteoporosis.

indefinitely.

Mycophenolate mofetil This relatively new immunosuppressive agent is sometimes used in severe cases of SLE which have proved refractory to other methods of treatment. For example, it has been used in patients with renal SLE, especially where cyclophosphamide has proved ineffective or intolerable. In a recent study of 42 patients with nephrotic syndrome due to lupus nephritis, the combination of mycophenolate mofetil and prednisolone was found to be as effective as prednisolone with oral cyclophosphamide in inducing remission.⁹ In the study, the starting dose of mycophenolate mofetil was 1g twice a day and this was halved after six months. Mycophenolate mofetil was stopped at 12 months and replaced with azathioprine. Also, cyclophosphamide was replaced by azathioprine at six months in the comparator group of patients in the study.

Mycophenolate mofetil suppresses the proliferation of lymphocytes and the formation of antibodies. In contrast, cyclophosphamide and azathioprine are more broadly acting immunosuppressants which are not selective for lymphocytes. Mycophenolate mofetil may cause gastrointestinal disturbance but has fewer major side effects than cyclophosphamide. It does not cause bladder toxicity or gonadal dysfunction and may well become more widely used in the future, if equivalence of efficacy with cyclophosphamide is confirmed in larger studies with longer periods of follow-up.

OTHER DRUGS

In renal SLE, it is very important to maintain control of blood pressure, both in the acute phase of the illness and after remission has been obtained. Such patients are always likely to maintain some degree of proteinuria and the protein leak can be minimised by keeping the blood pressure low. ACE inhibitors, such as ramipril, are particularly useful in this condition. Diuretics, such as frusemide, and alpha adrenergic antagonists, such as doxazosin, are also used.

Severe cerebral SLE may present with convulsions. Treatment with anticonvulsants will usually be necessary in addition to the use of corticosteroids, and possibly azathioprine or cyclophosphamide, to suppress the abnormal immune response. It can be difficult to decide when to discontinue anticonvulsants after the flare of SLE has been controlled, and the advice of a neurologist is often sought.

In severe thrombocytopenia, the platelet level may sometimes rise in response to infusions of intravenous immunoglobulin. Where neither high dose corticosteroids nor immunoglobulins can achieve this effect, the patient may require splenectomy.

SLE AND PREGNANCY

Since many patients with SLE are women of childbearing age, the question of drug therapy during pregnancy is frequently raised. In general, most patients with SLE should be able to conceive and to undergo full term pregnancy without complications. However, close follow-up by rheumatologists and obstetricians is advisable. Patients who have APS are at increased risk of miscarriage, probably due to placental insufficiency. These women are treated with low dose aspirin and subcutaneous heparin (5,000 units twice a day would be appropriate). Treatment may be started as soon as the pregnancy is confirmed and continued until delivery.¹⁰ Warfarin must be stopped during pregnancy because it is teratogenic.

Cyclophosphamide and mycophenolate mofetil are contraindicated in pregnancy. Hydroxychloroquine appears to be safe, but data relating to human pregnancy are scarce and the manufacturer advises against its use in pregnant women with rheumatic diseases. Azathioprine is not usually recommended in pregnancy since there have been some reports of adverse effects on the foetus in mothers taking this drug.

Prednisolone is usually continued during pregnancy and the dose may be increased if there is a flare of SLE. Although there is some risk that high doses of systemic corticosteroids could cause suppression of the foetal adrenal gland, it would be considered a greater risk to allow active SLE to be treated inadequately in a pregnant woman.

PRESCRIBING IN SLE

In prescribing drug therapy for a patient with SLE, a physician will usually be confronted with the following questions:

- Is immunosuppressive treatment required, or are NSAIDs and/or hydroxychloroquine controlling the disease adequately?
- If the patient is already taking corticosteroids, is the dose appropriate? If the disease is becoming more active, an increase in dosage may be needed whereas if disease activity has been low for some time, a gradual reduction may be possible to reduce side effects.
- Does the patient require another immunosuppressive drug in addition to corticosteroids?
- How can adverse effects be reduced?

These issues are illustrated by the case scenarios in the Panel.

SUMMARY

SLE is an autoimmune disease which can affect practically any organ or tissue in the body. Some patients have mild disease and their symptoms can be controlled with

paracetamol, NSAIDs and/or hydroxychloroquine. Corticosteroids are the mainstay of drug therapy in more severe cases and may be given by oral, intravenous or intramuscular routes. Combinations of corticosteroids with immunosuppressants, such as cyclophosphamide, azathioprine or mycophenolate mofetil, are required for the most severe forms of SLE, such as kidney disease.

It is important to recognise and to discuss with patients the possible adverse effects of drugs given to treat SLE. In some cases, the use of other agents (such as mesna) may help to reduce these adverse effects.

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