Management Strategies For Systemic Lupus Erythematosus

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Introduction

The management of systemic lupus erythematosus (SLE) is a challenging task. All interventions to-date are palliative rather than curative as the pathogenesis of the disease remains enigmatic. Treatment-related side effects can be as problematic as the disease itself. The following is a review of the practical management of the disease based on our experience. (HK Pract 1996; 18: 475-480)

摘要

目前處理系統性紅斑狼瘡症仍然是一項富挑戰性的任務，主要由於系統性紅斑狼瘡症病理成因不明，所有現行的治療方法，均屬姑息性。此外，治療過程中所引發的副作用亦與病變本身一樣，問題多多。以下是根據過往經驗對實際可行治療方法作回顧。

To treat conservatively or aggressively?

It is essential to decide the strategy of therapy for each individual SLE patient as once committed, treatment has to be maintained for a long period of time. In general, non-life-threatening manifestations are treated conservatively while life-threatening major organ involvement requires aggressive immuno-suppressive therapy. Clinical subsets (e.g. the antiphospholipid syndrome in which immunosuppression is not beneficial) have to be recognised. (Table 1).

Table 1: Indications for conservative/aggressive treatment of systemic lupus erythematosus (SLE)

Indications for conservative treatment of SLE
Musculoskeletal symptoms
Cutaneous lupus
Systemic upset
Serositis
Indications for aggressive treatment of SLE
Lupus nephritis
Cerebral lupus
Transverse myelitis
Peripheral neuropathy
Pneumonitis, pulmonary haemorrhage
Severe and refractory serositis
Severe haemolysis or thrombocytopenia
Myocarditis

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Conservative management

Musculoskeletal manifestations

Arthralgia, arthritis and myalgia are common presenting symptoms of SLE. They are usually mild but can sometimes be very disabling. Non-steroidal anti-inflammatory drugs (NSAID) usually provide rapid relief of symptoms. However, the use of NSAID in SLE requires special cautions. Through their inhibitory effects on renal prostaglandins, all NSAIDs (including sulindac) reduce glomerular filtration rate and renal blood flow, especially in patients who have clinical and subclinical nephritis, or are taking diuretics. Salt and fluid retention may elevate blood pressure and cause peripheral oedema. Gastrointestinal toxicity with bleeding can develop at any time during therapy. Headache, dizziness, and aseptic meningitis (particularly with ibuprofen) may occur and confuse with central nervous system manifestation of the disease. Finally, SLE patients are more prone to NSAID-induced hepatotoxicity, which is usually manifested as elevation of liver transaminases. Therefore, it is mandatory to monitor patients closely for renal, gastrointestinal and hepatic side-effects after commencement of therapy.

When musculoskeletal symptoms are not well controlled with NSAIDs, a trial of antimalarials is indicated. Hydroxychloroquine is preferred because of its lower incidence of retinal toxicity and other side-effects. The starting dose is 300 mg to 400 mg/day and should be tapered to a maintenance of 200 mg/day once a response is achieved because retinal damage is related to the cumulative dose. In unmonitored patients, the incidence of antimalarial retinopathy is 3-4%.[1] Properly monitored, Spalton *et al*[2] have shown that irreversible retinopathy is unlikely to occur when hydroxychloroquine, at a daily recommended dose of less than 6.5 mg/kg, in the absence of renal dysfunction, is used for less than 10 years. Most rheumatologists recommend referring patients to the ophthalmologist for baseline eye examination before the start of the drug and regular follow up, particularly when treatment has been continued for more than 3 years. In our Unit, a drug holiday, viz treatment for 5 days per week, is introduced when the patient has been stable on hydroxychloroquine for 2 years. In general, the drug is seldom used continuously for longer than 5 years. Besides retinopathy, other uncommon side-effects of antimalarials include corneal deposits, gastrointestinal disturbance, rash, peripheral neuropathy, proximal myopathy, cardiomyopathy and skin pigmentation.

For occasional patients whose symptoms are resistant to antimalarials, low dose prednisone (less than 15 mg/day) and even immunosuppressives may be considered if quality of life is seriously impaired. These, however, should be discontinued as soon as the symptoms are controlled. It is also noteworthy that local causes such as avascular necrosis may give rise to persistent pain in one or two joints and should be seriously excluded before more aggressive treatment is considered.

Cutaneous lupus

Around 70% of all SLE patients are photosensitive with flares of lupus activity. Patients should avoid exposure to sunlight by wearing protective clothings and applying sunscreens. Acute lupus dermatitis usually responds to topical steroids. Fluorinated high-potency preparations such as betamethasone and fluocinonide are very effective but are more likely to cause atrophy, striae, acne and folliculitis. They should not be used for more than 2 weeks (especially on face lesions), after which less potent preparations such as hydrocortisone should be substituted.

Antimalarials are also useful in the treatment of cutaneous lupus (acute, subacute, chronic/discoid) because of their sun-blocking, anti-inflammatory and immunosuppressive effect. Sixty to 90% of patients have excellent response to antimalarials.[3] For hydroxychloroquine, improvement often requires 3 to 6 months. The dosage should be tapered once when there is a response.

For patients who are resistant to antimalarial therapy, more aggressive treatment including systemic glucocorticoids, dapsone, etretinate, or cytotoxic drugs such as azathioprine may be required. The use of dapsone in cutaneous lupus should be very cautious because of its significant haematological toxicities. We recently reported 2 cases of severe dapsone syndrome after low dose treatment (50 mg/day).[4] One died as a result of fulminant toxic hepatitis and hypoalbuminaemia. The mechanism of this syndrome is unclear and is believed to be an extreme idiosyncratic reaction to the drug.

Systemic complaints

Systemic upset such as fever, fatigue and weight loss is common and may be difficult to treat. NSAIDs, salicylates, antimalarials and low dose glucocorticoids are the main stay of management although occasionally a higher dose of steroid is required.

Serositis

Lupus serositis causes episodes of chest and abdominal pain. They usually respond to NSAIDs (especially indomethacin), antimalarial or low dose steroid (less than 15 mg/day). Significant effusion in the pericardial or pleural cavities occurs infrequently and requires drainage because it compromises the function of the heart and lung. More aggressive immunosuppressive therapy may be needed in refractory cases.

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Aggressive treatment of SLE

Patients with life-threatening complications of SLE or involvement of major organ(s) should be aggressively treated. This usually begins with high dose steroid, followed by cytotoxic agents. Manifestations of SLE that require high dose glucocorticoids are listed in (**Table 2**). Some lupus manifestations are not steroid sensitive (e.g. pure membranous glomerulonephritis, thrombosis) and intense immunosuppression is not justified. Infection may mimic disease flare and should be vigorously eliminated before the institution of immunosuppression. When in doubt, antibiotic coverage should be given at the same time. Serological evidence of increased disease activity includes raised titre of anti-DNA antibody and depressed serum complement levels. In general, serum C-reactive protein (CRP) level remains normal or low except when there is significant synovitis, serositis, active vasculitis or coexisting infection. Raised serum CRP should alert the physician of infective complications.

Corticosteroids

Daily oral short-acting glucocorticoids (prednisone, prednisolone, methylprednisolone) is the standard regimen for steroid therapy in SLE. The starting dose for prednisolone is usually between 0.5 to 1.5 mg/kg/day. In general, a higher initial dose may be required for control of central nervous system disease and severe renal and haematological involvement. The rapidity of response to steroid varies among individuals and disease manifestations. Organic brain syndrome may improve within days while cytopenia usually takes 5 – 15 days to recover. Serology markers may only respond 1-3 weeks after treatment. A complete response is usually expected after 4 to 10 weeks. If the desired effect is not obtained within the appropriate time frame despite a good compliance, a review of the diagnosis, change of steroid dose, additional cytotoxic therapy or other modalities should be considered.

Table 2 : Manifestations of systemic lupus erythematosus (SLE) which are responsive/resistant to steroid treatment

Manifestations of SLE which are usually responsive to high dose corticosteroids
Vasculitis
Polyserositis
Myocarditis
Pneumonitis
Proliferative glomerulonephritis
Haemolysis, thrombocytopenia
Cerebritis
Transverse myelitis
Peripheral neuropathy
Manifestations of SLE which are often steroid-resistant
Thrombosis, antiphospholipid syndrome
Pure membranous glomerulonephritis, scarred end-stage disease
Mild behavioural/cognitive disturbances

Daily high-dose intravenous methylprednisolone (15mg/kg) for 3 to 5 doses, followed by daily oral prednisolone (40 – 60 mg) maintenance, which is rapidly tapered, is increasingly popular in the treatment of SLE. Uncontrolled trials suggest that more than 75% of patients with severe nephritis, central nervous system disease, pneumonitis, polyserositis, vasculitis and thrombocytopenia improve within a few days.[5] The overall side effects are probably not increased when compared with the oral high-dose regimen but acute psychosis, seizure, rapid increase in blood pressure, gastrointestinal bleeding, arrhythmia and sudden death have been reported.[6]

Cytotoxic agents

Azathioprine (a purine antagonist) and cyclophosphamide (an alkylating agent) are the two commonest cytotoxic agents used in the treatment of SLE. Both drugs inhibit B-cells. Cyclophosphamide has an additional suppressive effect on the T-cells and is more effective, but also more toxic. Previous studies have shown that either of the drugs together with corticosteroid is more superior than corticosteroid alone in the control of the disease in the long run.[7]

Azathioprine

Azathioprine (1 – 3 mg/kg/day) is used in lupus nephritis and as a steroid sparing agent in many of the less serious manifestations of the disease. Although uncommon, an idiosyncratic reaction causing marrow aplasia or agranulocytosis may occur during the first few weeks of therapy. Adverse effects of chronic azathioprine therapy include increased rate of opportunistic infection (especially herpes zoster), marrow suppression (dose-related), hepatic damage and malignancy.[8]

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Cyclophosphamide

Cyclophosphamide is more toxic than azathioprine and is reserved for treatment of more severe and life-threatening complications of SLE such as proliferative/crescentic glomerulonephritis, lupus cerebritis, severe thrombocytopenia, pneumonitis and pulmonary haemorrhage. Two regimens are currently available. Intravenous monthly pulse cyclophosphamide (0.5 – 1 gm/m^2 surface area) has the disadvantages of the need for in-patient treatment, venous access and a higher incidence of nausea and vomiting. Daily oral cyclophosphamide (1 – 2 mg/kg/day) is convenient and probably more effective. However, the risk of bladder toxicity such as haemorrhagic cystitis is higher. We generally adopt the oral regimen for our lupus patients and it appears that Chinese lupus patients tolerate this well and there are extremely few cases of cystitis noted.

Long term toxicities of cyclophosphamide are significant and it is generally agreed that the drug should not be used for more than 2 years. Opportunistic infections may be life-threatening; bone marrow suppression, increased malignancies and infertility are of major concern. Premature ovarian failure contributes to osteoporosis and accelerates atherosclerotic disease in women taking corticosteroids. In our Unit, cyclophosphamide treatment is usually maintained for 6 months after a remission is achieved. The treatment is then switched to maintenance azathioprine. This sequential therapy regimen has been shown to be useful for patients with lupus nephritis.[9]

Monitoring of adverse effects during immunosuppressive therapy

Osteoporosis, accelerated atherosclerosis, avascular necrosis, secondary diabetes, hypertension, psychiatric disturbances, and increased opportunistic infection are well known long term side effects of corticosteroids.[10] It is therefore important to reduce the steroid dose once the disease is controlled. There are many ways of doing this and the alternate-day tapering regimen is most popular as this is associated with significantly less suppression of the hypothalamic-pituitary axis, as well as less nitrogen and potassium wasting, hypertension, Cushingnoid changes and infection.[11]

For patients taking long term steroids, electrolytes, blood counts, sugar level, blood pressure, intraocular pressure and the lens should be regularly checked and monitored. Signs of infection and osteroporosis should also be looked out for. Patients should be advised to have adequate calcium intake (1000 – 1500 mg/day) and Vitamin D can be considered if 24 hour calcium excretion is less than 120 mg. Regular complete blood counts and liver function tests are mandatory in patients taking cytotoxics. Microscopic haematuria should be screened for patients taking cyclophosphamide. Finally, patients should be warned of the possibility of infertility and increased malignancies before the start of cyclophosphamide.

Special situations

Pregnancy

Patients with SLE should not be deprived of the opportunity to conceive. Exacerbation occurs in around 50% of patients during pregnancy and in the post-partum period. The risk is higher when disease is active within 6 months before conception.[12] Relapse of the disease may lead to irreversible organ damage while aggressive treatment may lead to fetal death. It is therefore important to give patients adequate pre-pregnancy counselling and contraceptive advice. In general, pregnancy is only recommended when the disease has been stable for a comfortable period of time (e.g. 1 – 2 years) and should be closely monitored, with the collaboration of an experienced obstetrician. All drugs used in SLE, with the exception of corticosteroids, are potentially teratogenic/embryotoxic and should be avoided, especially in the first trimester of pregnancy.

Antiphospholipid syndrome (APS) and recurrent abortion

APS is characterised by recurrent vascular thrombosis, pregnancy wastage, and thrombocytopenia associated with a persistently positive lupus anticoagulant or anti-cardiolipin antibodies.[13] It can exist alone as a primary form or associated with SLE. Daily low-dose aspirin or long-term anticoagulation is the treatment of choice. Immunosuppression is not justified as the anti-cardiolipin antibodies are notorious for its steroid resistance. For those patients who experience recurrent fetal loss, low-dose aspirin, aspirin plus prednisone, or subcutaneous heparin treatment throughout the pregnancy improves fetal survival.

Cytopenias

Severe cytopenia definitely contributes to mortality in SLE. High dose glucocorticoids (prednisone 1 – 1.5 mg/kg or intravenous pulse therapy) is often needed. For severe thrombocytopenia, intravenous gammaglobulin (0.4 gm/kg/day for 5 days or 1 gm/kg/day for 2 days) can lead to a rapid increase in platelet count and is reserved for emergency treatment for life-threatening bleeding or preparation for emergency surgery. Cytotoxic agents including azathioprine, cyclophosphamide and vinca alkaloids may be tried in steroid-resistant cases. Danazol, an anabolic steroid, may be useful in some cases of lupus thrombocytopenia. However, it is less effective in the younger patients and the side effects of hirsutism, menopausal symptoms, deepening of voice, hepatitis and weight gain maynot be acceptable.

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Table 3 : Experimental therapies for systemic lupus erythematosus

Experimental therapies for SLE
Plasmapheresis, leukopheresis, cryophersis
Cyclosporin A
Intravenous immunoglobulins (IVIG)
Manipulation of sex hormone levels (androgens, luteinizing hormone blocking agents)
Newer immunosuppressives (FK506, rapamycin, mycophenolic acid)
Interventions of T-B cell interactions (monoclonal antibody against CD4, CD3, or IL2 receptor, total lymphoid irradiation)

Drug-induced lupus

Many drugs are capable of inducing a lupus-like syndrome, characterised by fever, rash, arthritis, serositis, a positive ANA and anti-DNA-histone antibodies. Chlorpromazine, hydralazine, procainamide, isoniazid, α-methyl-dopa are notorious for this. However, it should not be confused with the many other drugs which may exacerbate an existing lupus. Sulphonamides, anticonvulsants and oestrogen-containing contraceptive pills have been attributed to exacerbate lupus activity from earlier studies and should therefore be avoided in SLE patients.

Pure membranous glomerulonephritis

Lupus membranous glomerulonephritis (WHO class V) is well known for its resistance to steroid or cytotoxic therapy, using daily protein excretion as a measure of response. Renal failure occurs less frequently and later than with proliferative glomerulonephritis. We usually treat our patients with moderate to high dose steroid together with azathioprine. If no response is obtained after 6 – 12 weeks, immunosuppression will be gradually withdrawn, provided that it is not due to other causes like renal vein thrombosis and change of histology into a more serious or mixed form.

Experimental therapies

Table 3 lists the currently available experimental therapies for SLE. It is out of our scope here to mention all of them in details. One drug that is noteworthy, mentioned here, is cyclosporin A (3 – 5 mg/kg/day) which, when added to glucocorticoid therapy, has been shown to improve renal and extrarenal manifestations of SLE.[14] Undesirable effects include tremor, hirsutism, hypertension, hyperlipidaemia and nephrotoxicity. However, it is expensive and should only be considered in patients with steroid-resistant disease or marrow suppression when cytotoxic agents cannot be use.

Conclusion

SLE is a complex disease with diverse manifestations and wide individual variability in the presentation and severity. The goal of management is not just to induce remission in the short term, but also to minimise toxicities of long term therapy. Expert care from experienced rheumatologists is needed. The use of various drugs like antimalarials, corticosteroids and cytotoxic agents should be fully justified and carefully monitored. ■

References

1. Bernstein DHN. Ophthalmologic considerations and testing in patients receiving long-term antimalarial therapy. *Am J Med* 1983; 75: 25.
2. Spalton DJ, Verdon Roe GM, Hughes GRV. Hydroxychloroquine, dosage parameters and retinopathy. *Lupus* 1993; 2: 155-158.
3. Callen JP. Treatment of cutaneous lesions in patients with lupus erythematosus. *Dermatol Clin* 1990; 8: 355-365.
4. Mok CC, Lau CS. Severe dapsone syndrome in cutaneous lupus. *J Rheumatoid* 1996; 23(4): 766-768.
5. Isenberg DA, Morrow WJW, Sanith ML. Methylprednisolone pulse therapy in the treatment of systemic lupus erythematosis. *Ann Rheum Dis* 1982; 41: 347.
6. Hahn BH. Management of systemic lupus erythematosus. In: Textbook of Rheumatology. Eds: Kellar WN, Harris ED, Ruddy S, Sledge CB (Eds). *Saundars WB;* 4th edition 1993; pp 1043-1055.
7. Balow JE, Austin HA, Tsokos GC *et al.* NIH Conference. Lupus nephritis. *Am Intern Med* 1987; 106: 79.
8. Mok CC, Kwong YL, Lau CS. Secondary acute myeloid leukaemia with 7q- complicating azathioprine treatment for rheumatoid arthritis. *Ann Rheum Dis* 1995; 54: 155-156.
9. Chan TM, Li FK, Wong RW, Wong KL, Chan KW, Cheng IK. Nephron. Sequential therapy for diffuse proliferative and membranous lupus nephritis: cyclophosphamide and prednisolone followed by azathioprine and prednisolone. 1995; 71(3): 321-327.
10. Mok CC, Lau CS, Poon SP. Primary nocardial meningitis in systemic lupus erythematosus. *Br J Rheumatol* 1995; 34(2): 178-181.
11. Fauci AS. Alternate-day corticosteroid therapy. *Am J Med* 1978; 64: 729.
12. Kitridou RC, Mintz G. The mother in systemic lupus erythematosus. In: Dubois' Lupus Erythematosus. Eds: Wallace DJ, Hahn BH. Lea and Febiger, *Philadelphia* 1992; pp 487-507.
13. Lau CS. Antiphospholipid syndrome. *Vasc Med Rev* 1994; 5(1): 33-45.
14. Tokuda M, Kurata N, Mizoguchi A, *et al.* Effect of low-dose cyclosporin A on systemic lupus erythematosus disease activity. *Arthritis Rheum* 1994; 37(4): 551-558.