

Treatment of systemic lupus erythematosus

SUMMARY

Systemic lupus erythematosus should be suspected in individuals with one or more classic symptoms. Diagnosis is made clinically and supported by serology.

Reducing sun exposure is central to the management of lupus.

Hydroxychloroquine is first-line treatment unless contraindicated and is useful in almost all manifestations of lupus. Other treatments are titrated against type and severity of organ involvement.

Monoclonal antibodies have a limited role in the management of lupus.

Introduction

Systemic lupus erythematosus (also known as lupus) is a chronic, relapsing-remitting autoimmune disease characterised by autoantibody production. It may present at any stage of life, but is most common in women of childbearing age, with a female to male ratio of 9:1. Lupus has a wide spectrum of presentations, including skin, psychiatric and kidney manifestations.

When to suspect lupus

Lupus should be considered in any individual with one or more typical manifestations, but especially women of childbearing age. Classic symptoms include photosensitive rash, mouth ulcers, small joint arthritis, or unexplained cytopenias and venous or arterial clotting. Serositis and neurologic involvement are observed less commonly (Box).¹

How to confirm diagnosis

The variable manifestations of lupus make diagnosis difficult and serology can be useful (see Box). Almost all patients (99%) have antinuclear antibodies at diagnosis. However, they are nonspecific and present in approximately 5% of the healthy population at titres of 1:320.² More specific for lupus is the presence of anti-double-stranded DNA antibodies, particularly when detected by the radionucleotide Farr assay. These are observed in approximately 70% of patients with lupus.³ Anti-Smith antibodies are uncommon but specific for lupus and associated with nephritis and cytopenias.⁴ Antiphospholipid antibodies are found in 40% of patients and are classically associated with an elevated risk of thrombosis and miscarriage.⁵ Antibodies against the extractable nuclear antigens Ro(SSA), La(SSB) and ribonuclear protein are common but nonspecific in the diagnosis of lupus. Antinuclear antibodies combined with lupus-specific antibody positivity can support the diagnosis. These

are incorporated in the Systemic Lupus International Collaborating Clinics diagnostic criteria (Box).¹

Pathogenesis

The pathogenesis of lupus is a composite of complex genetic risk and environmental influences. While immunologic abnormalities ranging from complement to B-cell dysregulation are reported, increased type 1 interferon activity is observed in 85% of patients at any point in time.⁶ This is central to the disease. Reflecting this complex pathogenesis, several distinct biologic pathways have been targeted in the treatment of lupus.

Management of lupus

The management of lupus includes three goals:

- preventing flares and their symptomatic impact
- reducing chronic accumulation of organ damage
- minimising toxicity from immunosuppression.

All patients should minimise sun exposure and use hydroxychloroquine unless contraindicated. For lupus activity that is resistant to these measures, antiproliferative immunosuppressants and corticosteroids are effective. The choice of antiproliferative is influenced by the organ involved. Cyclophosphamide is used for severe life- and organ-threatening lupus. Biologic drugs have a limited role but drugs such as rituximab may be used for manifestations refractory to other treatments.

Non-drug approaches

Ultraviolet exposure can flare both cutaneous and systemic symptoms such as arthritis. Sunscreens (SPF 50+) should be used as well as avoiding exposure during peak hours.⁷

Smoking cessation may help with treatment-resistant skin lesions.⁸ It may also mitigate the elevated cardiovascular risk associated with lupus.⁹

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Box **Diagnostic criteria for systemic lupus***

Clinical criteria

Acute cutaneous – lupus malar rash, bullous lupus, toxic epidermal necrolysis variant of lupus, maculopapular lupus rash, photosensitive lupus rash

Chronic cutaneous – discoid lupus rash, hypertrophic (verrucous) lupus, lupus panniculitis, mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus

Oral or nasal ulcers – palate, buccal, tongue, or nasal in the absence of other causes

Non-scarring alopecia – in the absence of other causes

Arthritis – synovitis involving 2 or more joints, characterised by swelling or effusion or tenderness in 2 or more joints and at least 30 minutes of morning stiffness

Serositis – typical pleurisy for more than one day, pleural effusions, pleural rub or typical pericardial pain for more than one day, pericardial effusion, pericardial rub or pericarditis by ECG

Renal involvement – urine protein:creatinine ratio or 24-hour urine protein with >500 mg protein/24 hours or red cell casts

Neurological symptoms – seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, acute confusional state

Haemolytic anaemia – in the absence of other causes

Leucopenia – in the absence of other causes

Thrombocytopenia – in the absence of other causes

Immunological criteria

Antinuclear antibodies

Anti-dsDNA antibodies – above reference range (or >2-fold if tested by ELISA)

Anti-Smith antibodies

Antiphospholipid antibodies – positive lupus anticoagulant, false-positive rapid plasma reagin test, medium- or high-titre cardiolipin antibody, positive anti-b2-glycoprotein

Low complement C3, C4, CH50

Positive Direct Coombs test – in the absence of haemolytic anaemia

* For a positive diagnosis, patients must have 4 or more of the listed criteria, with at least 1 clinical and 1 laboratory criterion

dsDNA double-stranded DNA

ELISA enzyme-linked immunosorbent assay

Source: reference 1

doses (400 mg daily).¹⁶ In addition to improving skin symptoms, hydroxychloroquine reduces flares of systemic lupus¹⁷ and lupus nephritis.¹⁸ It also lowers cholesterol and thromboembolic risk in patients with antiphospholipid antibodies.^{19,20} Consequently, sustained hydroxychloroquine therapy minimises accrual of organ damage²¹ and glucocorticoid-induced osteoporosis, and improves overall survival.²²

The major complications of hydroxychloroquine therapy are ocular. Transient and reversible corneal deposits occur in about 10% of people.²³ Irreversible retinopathy can also develop and typically manifests as visual disturbances, photophobia or light flashes. The risk of retinal toxicity is cumulative and may be as high as 20% at 20 years with recommended hydroxychloroquine doses.²⁴ A maximal daily hydroxychloroquine dose of less than 5 mg/kg (up to 400 mg/day) is recommended, along with regular screening by an ophthalmologist to detect toxicity before visual changes (Table 1).²⁴⁻²⁶ Less common adverse effects include cardiac, cutaneous and neuropsychiatric manifestations.²⁷ Hydroxychloroquine is safe to use in pregnancy and should be continued.²⁸

Corticosteroids

Almost all patients will be treated with corticosteroids at some point.²⁹ They are effective in controlling systemic lupus but their sustained use is limited by substantial toxicity. Corticosteroids are used transiently to control systemic disease flares or when disease activity cannot be controlled by other drugs alone. Due to toxicity, they should never be used on their own.

The adverse effects are dose-dependent and include an increased risk of infection, cancer, osteoporosis and avascular necrosis, steroid-induced diabetes, accelerated atherosclerosis and mood disturbances.³⁰ Cardiovascular risk is significantly increased in lupus and the use of corticosteroids increases this further.³¹ Indeed, no study has established a safe lowest dose in systemic lupus so when possible they should be withdrawn.³²

The toxicity of corticosteroids needs to be balanced against the threat of organ injury if they are not used. For mild disease, lower doses are often sufficient. High doses are typically reserved for debilitating or life-threatening involvement such as lupus nephritis or neuropsychiatric lupus (Table 2).³³ Once disease remission is achieved, the dose should be tapered.

For cutaneous lesions, topical corticosteroids are the mainstay of treatment. Higher potency creams have superior efficacy over low-potency creams.³⁴ However, they increase the risks of telangiectasia and skin atrophy and are used intermittently depending on the severity and location of the lesions. Topical steroids are useful for mouth ulcers but increase the risk of candidiasis.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective for symptom relief in lupus-associated arthritis and myalgias.¹⁰ However, they increase the risk of allergic reactions¹¹ and aseptic meningitis.¹² In the presence of lupus nephritis, they increase the risk of acute kidney injury¹³ and death when used in patients with end-stage kidney disease.¹⁴

Hydroxychloroquine

Hydroxychloroquine should be used in all patients with lupus unless contraindicated. It is an antimalarial drug that inhibits toll-like receptors 7 and 9. These are potent drivers of type 1 interferon production.¹⁵ Hydroxychloroquine is useful in both cutaneous and systemic lupus. Approximately half of patients with cutaneous lupus fail to respond to standard doses (200 mg daily) and may benefit from higher

Table 1 Monitoring for patients receiving lupus treatments

Drug	Monitoring
Hydroxychloroquine	Baseline fundal exam of the eye, then annual screening after 5 years treatment ²⁴
Corticosteroids	Baseline and annual bone densitometry ³ Annual diabetes check ^{3,25} Periodic ophthalmology review for cataracts and glaucoma
Azathioprine	TMPT activity before starting treatment Full blood count at 2–4 weeks for 2–3 months, then every 3 months
Methotrexate	Full blood count and liver function test every 2–4 weeks for 3 months, then every 2–3 months until 6 months. Monitor every 3 months when patient is stable ^{7,26}
Mycophenolate	Full blood count at 2–4 weeks, then every 3 months
Cyclophosphamide	Full blood count every 2 weeks for a month, then monthly
Rituximab	Optional: check CD19+ B cells to confirm depletion

TMPT thiopurine methyltransferase

Table 2 Steroid doses and indications in lupus

EULAR grading	Dose: prednisolone equivalent (mg)	Typical indications	Duration and tapering
Low dose	<7.5	Maintenance	If starting on low dose, give for 2–4 weeks. Tapering not required
Medium dose	7.5–30	Mild disease: cutaneous, musculoskeletal, haematological, or constitutional symptoms	Medium–high dose for 2–4 weeks then taper over 1–2 months
High dose	30–100		
Very high dose	>100	Induce remission of severe disease	
Pulse therapy	>250		

EULAR European League Against Rheumatism
Source: reference 33

Antiproliferative drugs

Three antiproliferative immunosuppressants are primarily used in systemic lupus – azathioprine, methotrexate and mycophenolate. For non-renal manifestations such as arthritis and rash where hydroxychloroquine or topical corticosteroids are insufficient, methotrexate is effective.³⁵ While evidence is stronger for methotrexate, azathioprine is also useful and has the benefit of being safe in pregnancy. Thiopurine methyltransferase activity should be tested before azathioprine is used to avoid bone marrow suppression in patients with a deficiency.

Mycophenolate is effective in non-renal disease that is refractory to corticosteroids,³⁶ and is superior

to azathioprine.³⁷ However, it is contraindicated in pregnancy. For systemic lupus with kidney involvement, mycophenolate is superior to azathioprine so it is first-line maintenance therapy when tolerated.³⁸

Cyclophosphamide

Cyclophosphamide is an alkylating drug that is beneficial in treating severe lupus. Oral regimens result in higher cyclophosphamide exposure and carry a greater risk of infection and bone marrow suppression than the intravenous preparation. High-dose mycophenolate is as effective as cyclophosphamide in controlling aggressive nephritis and is increasingly used as first-line therapy³⁸ given the lower rates of hair loss and infertility.

Biologic drugs

A range of new biological therapies has been investigated in patients with lupus. Many have not shown significant benefit to date.³⁹⁻⁴⁸

Rituximab

Rituximab is a B-cell depleting antibody against CD20. Despite initial reports of excellent responses to this drug, trials have failed to show a benefit in non-renal³⁹ and renal lupus.⁴⁰ However, it continues to be used in refractory disease and registry data suggest a benefit.^{49,50}

Belimumab

Belimumab antibody inhibits B-cell activating factor (BAFF). This target has shown significant pre-clinical promise given its role in promoting autoreactive B-cell activation and proliferation.⁵¹ Two multicentre trials, BLISS-52⁴³ and BLISS-76,⁴⁴ assessed the efficacy of belimumab at 52 and 76 weeks. While reaching statistical significance, both trials observed a modest reduction in overall disease activity at 52 weeks and no significant benefit at 76 weeks. The benefit was largely due to improvements in musculoskeletal and cutaneous symptoms.⁵² Its role in non-renal disease that is unresponsive to conventional drugs.

Anifrolumab

Anifrolumab blocks the interferon alpha receptor 1. Initial lupus studies observed benefits in disease activity. However, placebo-controlled trials (TULIP 1 and TULIP 2) failed to demonstrate benefit when conventional measures of lupus activity were used, and only marginally significant benefit when modified lupus scores were used.^{53,54}

Pregnancy

Pregnancy can present challenges in women with lupus, so pregnancy planning and counselling are important.⁵⁵ Fertility rates are normal in lupus, unless compromised by cyclophosphamide⁵⁶ or worsening renal failure. Recent evidence is conflicting regarding increased disease flares during pregnancy.^{57,58} However, the risks of pre-eclampsia⁵⁹ and miscarriage⁶⁰ are significantly higher. Secondary antiphospholipid syndrome confers added perinatal risk warranting specialist care.

When treating pregnant women, corticosteroids and azathioprine are generally safe. Mycophenolate, methotrexate and cyclophosphamide are contraindicated in pregnancy. Cyclophosphamide should be stopped three months before attempting to conceive and both men and women receiving cyclophosphamide should be on appropriate contraception. Egg harvesting or sperm banking should be considered before treatment.

Conclusion

Lupus has a wide range of clinical manifestations and should be considered as a diagnosis when two or more symptoms occur in women of childbearing age. All patients should receive hydroxychloroquine with appropriate monitoring. Antiproliferative drugs are useful for maintenance therapy, while high-dose steroids and cyclophosphamide are reserved for severe disease. The role of biologic drugs is an area of ongoing research. <

Conflict of interest: none declared

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