Lupus: Systemic lupus erythematosus (SLE)

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Lupus is a chronic inflammatory autoimmune disease with a wide range of clinical presentations resulting from its effect on multiple organ systems. Inflammation caused by lupus can affect many different body systems including joints, skin, kidneys, blood cells, brain, heart and lungs. Lupus can be difficult to diagnose because of its heterogeneity in presentation and ability to mimic other diseases. The clinical profile of lupus is challenging as the disease can be unpredictable, affecting various organs with variable degree of severity, and is complicated by the accrual of organ damage and comorbidities. [1, 2]

The four main types of lupus are neonatal and paediatric lupus erythematosus (NLE); discoid lupus erythematosus (DLE); drug-induced lupus (DIL); and systemic lupus erythematosus (SLE).[1, 2] The term "lupus" is commonly used to describe systemic lupus erythematosus (SLE), which is the most common type and more severe form of the condition. SLE is a complex autoimmune disease with a chronic relapsing-remitting course, and variable manifestations from mild mucocutaneous to life-threatening illness. [3, 4] It can affect any organ including the musculoskeletal, skin, hematologic, renal, neuropsychiatric, cardiovascular, and respiratory system.

The pathogenesis of systemic lupus erythematosus is complex, and the understanding of its pathogenesis is constantly evolving. While the exact aetiology is unknown, the condition is multifactorial in nature, arising from a combination of genetic, epigenetic and environmental factors, and it may be triggered in genetically-susceptible individuals by exposure to certain environmental risk factors.[9] Genetic, immunological, endocrine, and environmental factors influence the loss of immunological tolerance against self-antigens leading to the formation of pathogenic autoantibodies that cause tissue damage through multiple mechanisms.[11]

Long perceived as a rare disease, the overall worldwide trend for SLE is increasing in terms of prevalence and incidence. [7, 8] Females have a much higher incidence than males, with a female to male ratio of 9:1. [5, 6, 9] While the disease is much more common in females than males, it can follow a more aggressive course in males, with men demonstrating higher mortality rates than women. The disease predominantly affects young to middle-aged females, however, SLE can also present in older age groups, when it often follows a more indolent course. Neuropsychiatric lupus usually occurs in the first 10 years following diagnosis of SLE.[9] Systemic lupus erythematosus has long been recognised as having a heritable component, and numerous genome-wide association studies have identified more than 80 genetic predispositions.[13] High concordance rates in identical twins (reported to be as high as 50%) suggest a strong genetic contribution, although there is no obvious pattern of inheritance.[11] Environmental triggers have a role in SLE pathogenesis and include UV radiation exposure,

medications, smoking, environmental pollutants, low vitamin D levels and viruses such as the Epstein-Barr virus.[13]

The prevalence of SLE is variable dependent on ethnic origin, and ranges from 40–200 per 100,000 of population. Systemic lupus erythematosus is more common in people of African and Asian ancestry than in Europeans. [9] Pathologically, the disease is driven by loss of immune tolerance and abnormal B and T-cell function. Antinuclear antibodies are the hallmark serological feature, occurring in over 95% of patients with SLE at some point during their disease. [9]

Classification

There are multiple classification criteria for SLE. In 2019, the EULAR/ACR new classification criteria were developed using rigorous methodology with multidisciplinary and international input, and are reported to have excellent sensitivity and specificity. [14]

Figure 1: New EULAR/ACR Criteria for the Classification of SLE (2019)

Clinical domains	Points
Constitutional domain	
Fever	2
Cutaneous domain	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Arthritis domain	
Synovitis or tenderness in at least 2 joints	6
Neurologic domain	
Delirium	2
Psychosis	3
Seizure	5
Serositis domain	
Pleural or pericardial effusion	5
Acute pericarditis	6
Hematologic domain	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Renal domain	
Proteinuria > 0.5 g/24 hr	4
Class II or V lupus nephritis	8
Class III or IV lupus nephritis	10

Immunologic domains	Points
Antiphospholipid antibody domain	
Anticardiolipin IgG > 40 GPL *or* anti-β2GP1 IgG > 40 units *or* lupus anticoagulant	2
Complement proteins domain	
Low C3 *or* low C4	3
Low C3 *and* low C4	4
Highly specific antibodies domain	
Anti-dsDNA antibody	6
Anti-Sm antibody	6

REFERENCE: Aringer et al. Abstract #2928. 2018 ACR/ARHP Annual Meeting

- ✓ **Classification criteria are not diagnosis criteria**
- ✓ All patients classified as having SLE must have ANA ≥ 1:80 (entry criterion)
- ✓ Patients must have ≥ 10 points to be classified as SLE
- ✓ Items can only be counted for classification if there is no more likely cause
- ✓ Only the highest criterion in a given domain counts
- ✓ SLE classification requires points from at least one clinical domain

@Lupusreference

Aringer, M., Costenbader, K., Daikh, D., *et al.* (2019). 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Annals of the Rheumatic Diseases* 2019; 78:1151-1159.

Presentation, Signs & Symptoms & Manifestations

Systemic lupus erythematosus is a multisystem disease with several phenotypes, and clinical features can vary from a very mild disease with only mucocutaneous involvement, to severe life-threatening disease with multiorgan involvement.[11] More than 80% of patients with SLE have mucocutaneous involvement, which is one of the most well-recognised and identified clinical features. SLE skin lesions may be lupus specific, while several non-specific lesions are also noted. Lupus specific lesions include; Acute cutaneous lupus erythematosus **(ACLE)**, which includes localised, malar and generalised; Subacute cutaneous lupus erythematosus **(SCLE)**, which includes annular and papulosquamous and; Chronic cutaneous lupus

erythematosus **(CCLE)**, which includes classic discoid lupus erythematosus (DLE), hypertrophic/verrucous, lupus panniculitis/profundus, lupus tumidus, chilblains lupus, mucosal discoid lupus, and lichenoid discoid lupus.[11]

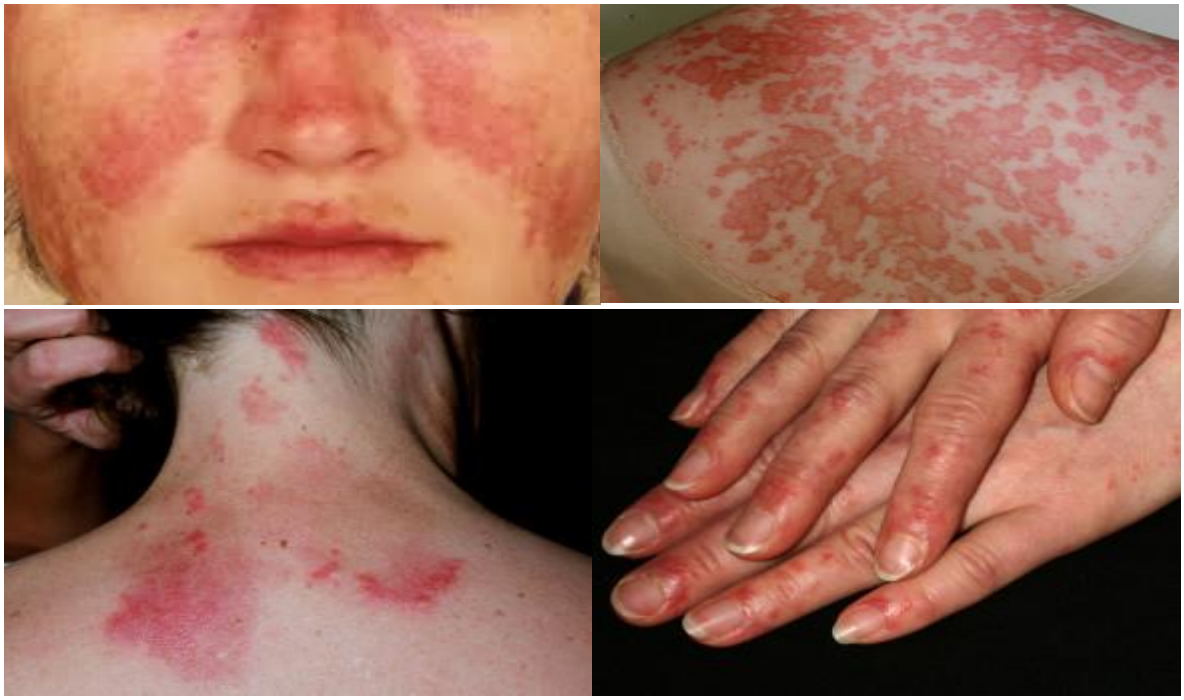
The hallmark acute cutaneous lupus erythematosus (ACLE) lesion is the malar or butterfly rash, which is an erythematous raised pruritic rash involving the cheeks and nasal bridge. The rash may be macular or papular and spares the nasolabial folds. It usually has an acute onset, but may last several weeks, and may cause induration and scaling. The malar rash may also fluctuate with lupus disease activity. Other rashes in this location that must be differentiated from the ACLE malar rash include rosacea, erysipelas, seborrheic dermatitis, and perioral dermatitis. Generalised ACLE leads to widespread maculopapular or macular rash in a photosensitive pattern. ACLE lesions usually heal without scarring.[11]

Subacute cutaneous lupus erythematosus (SCLE) rash is a photosensitive, widespread, nonscarring, nonindurated rash. It may be either papulosquamous resembling psoriasis or an annular/polycystic lesion with central clearing and peripheral scaling. SCLE lesions may last several months but usually heal without scarring. SCLE rash is seen in patients with a positive Anti-Ro (SSA) antibody in up to 90% of the cases. SCLE can also be caused by some drugs such as hydrochlorothiazide, and it has also been reported in patients with Sjogren syndrome and rheumatoid arthritis.[11]

The most common form of chronic cutaneous lupus erythematosus (CCLE) is Discoid lupus erythematosus (DLE). DLE may occur with or without SLE, and can be either localised (head and neck) or generalised (above and below the neck). DLE lesions are disk-shaped erythematous papules or plaques with adherent scaling and central clearing. DLE heals with scarring, and when present on the scalp can be associated with permanent alopecia. Mucosal DLE lesions can be seen in the oral cavity, and tend to be painful erythematous round lesions with white radiating hyperkeratotic striae.[11]

Signs and symptoms of SLE may develop suddenly or slowly, may be mild or severe, and may be temporary or permanent. Most people with lupus have mild disease characterised by episodes called flares. All organ systems can be involved in SLE and signs and symptoms depend on which body systems are affected by the disease. [11]

The most common signs and symptoms of SLE include: fatigue; fever; joint pain, stiffness and swelling; butterfly-shaped rash on the face that covers the cheeks and bridge of the nose or rashes elsewhere on the body; skin lesions that appear or worsen with sun exposure; fingers and toes that turn white or blue when exposed to cold or during stressful periods; shortness of breath; chest pain; dry eyes; headaches, confusion and memory loss. [2]
Common findings are skin lesions, such as malar rash or discoid lesions, photosensitivity, scarring or non-scarring patchy alopecia, mucocutaneous ulcers, polyarticular arthritis, nephritis with secondary hypertension and pedal oedema, and serositis manifesting as pleuro-pericarditis with pleural and pericardial effusions.[9]



Images: https://dermnetnz.org/topics/systemic-lupus-erythematosus-images

Other Manifestations

Photosensitivity is present in more than 90% of cases in SLE, and is characterised by abnormal skin reaction on exposure to Ultraviolet A/B and visible light, a reaction that may last weeks to months. Approximately 80% to 90% of patients with SLE experience musculoskeletal involvement during their disease course, and this may range from mild arthralgias to deforming arthritis. Lupus arthritis is typically a non-erosive, symmetrical inflammatory polyarthritis affecting predominantly the small joints of the hands, knees, and wrists, although any joint can be involved. [11]

Both the central (CNS) and peripheral (PNS) nervous systems may be involved in SLE, in addition to several psychiatric manifestations, although the diagnosis can be difficult. Other manifestations include renal involvement (lupus nephritis is a common complication of SLE), pulmonary involvement (pleuritis is the most common pulmonary manifestation); cardiovascular involvement (SLE may involve any layer of the heart including the pericardium, myocardium, endocardium and the coronary arteries); GI involvement (manifestations include oesophageal dysmotility, mesenteric vasculitis, lupus enteritis, peritonitis and ascites, protein-losing enteropathy, pancreatitis, and lupoid hepatitis).

Eye involvement is common, and keratoconjunctivitis sicca is frequently seen in SLE. Retinal vasculitis, optic neuritis, uveitis, scleritis, peripheral ulcerative keratitis, and episcleritis are other ocular manifestations. Patients with SLE are also more susceptible to drug-induced ocular damage including steroid-induced glaucoma or cataract and hydroxychloroquine

induced maculopathy. Ear involvement may lead to sudden sensorineural hearing loss. Adrenal infarction secondary to adrenal vessel thrombosis may be seen in patients with SLE and antiphospholipid antibody syndrome.[11]

Patients with SLE who are pregnant, with positive antiphospholipid antibodies are at a high risk of spontaneous abortions and foetal loss, pre-eclampsia and maternal thrombosis. Anaemia is present in more than 50 % of patients with SLE and most commonly in chronic disease. Other causes of anaemia in SLE may include iron deficiency anaemia, coomb's positive autoimmune haemolytic anaemia, red blood cell aplasia and microangiopathic haemolytic anaemia which may be associated with antiphospholipid antibody syndrome.[11]

Diagnosis

Diagnosis of systemic lupus erythematosus is challenging because symptoms vary greatly from person to person, and may change over time. While no single clinical feature or lab abnormality can confirm a diagnosis of SLE, diagnosis is based on clinical judgement and recognition of patterns of signs and symptoms supported by serological tests and following exclusion of other diagnoses.[11] Blood tests include Erythrocyte sedimentation rate (ESR), Anti-nuclear antibody, Anti-DNA antibody test, Antiphospholipid antibody test, Anti-Ro antibody test, Complement level test, FBC and Kidney and Liver function tests. X-ray, ultrasound scan (US), magnetic resonance imaging (MRI) scan or a computarised tomography (CT) scan may be carried out to check if SLE is affecting internal organs.[10, 12]

Treatment

Treatment of systemic lupus erythematosus includes the use of antimalarial drugs, corticosteroids, conventional immunosuppression with synthetic immunosuppressive medications, as well as biologic therapies and the detection and management of comorbidities. The goal of treatment is to prevent organ damage, achieve remission and to minimise damage attributable to medication side-effects. Choice of treatment is dictated by the organ system(s) involved and the severity of disease, and ranges from minimal treatment with NSAIDs and antimalarials to intensive treatment including corticosteroids and cytotoxic drugs**.** Other treatments include medication to control high blood pressure and high cholesterol. An increasing understanding of pathogenesis has facilitated a move towards the development of targeted biologic therapies, with the introduction of rituximab and belimumab into clinical practice.[9, 11,12]

The principle of 'treat to target' should be applied in systemic lupus erythematosus. Management strategies should be tailored to the organ system involved, with the addition of the general approaches as outlined in Figure 2. [13]

Figure 2: General management strategy for patients with systemic lupus erythematosus [13]

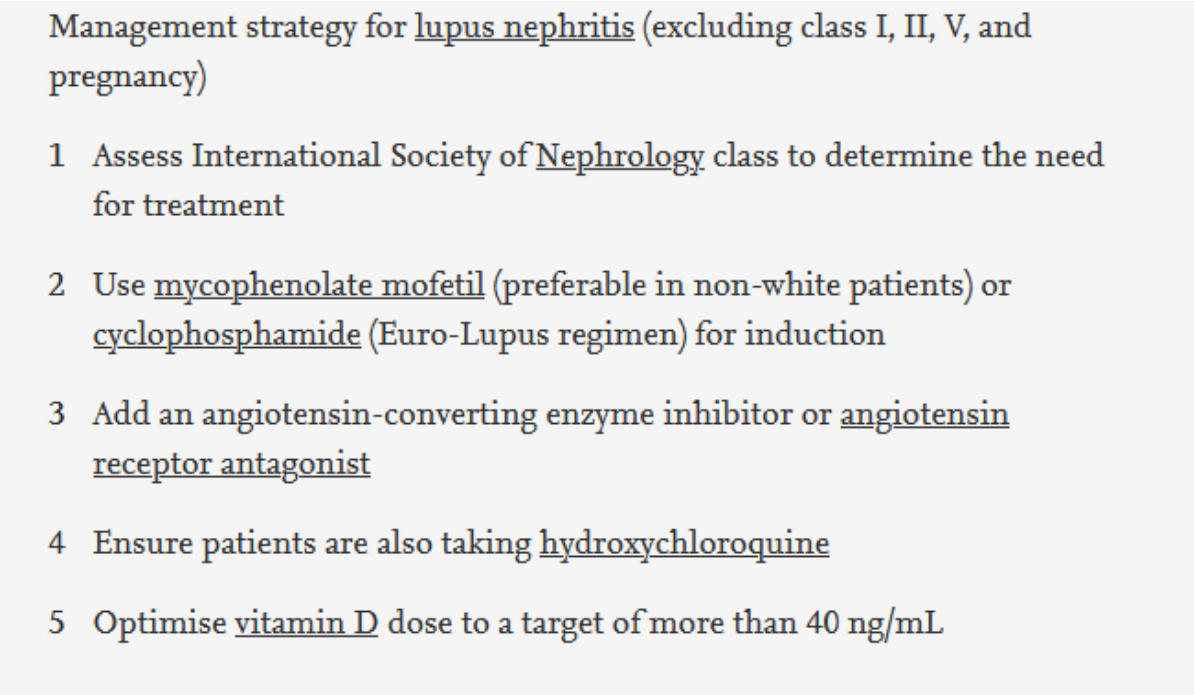
Durcan, L., O'Dwyer, T, Pettri, M. (2019). Management strategies and future directions for systemic lupus erythematosus in adults. The Lancet: Volume 393, Issue 10188, 8–14 June 2019, Pages 2332-2343

Hydroxychloroquine offers a survival advantage in SLE, and is important in the management of cutaneous disease and lupus arthritis. It works via numerous mechanisms, mediating immunomodulation without causing immunosuppression. It has a bolstering effect on therapy in lupus nephritis and has antithrombotic properties. Hydroxychloroquine has also been shown to improve pregnancy outcomes and reduce the risk of anti-Ro-related congenital heart block in neonates. Chloroquine is an alternative for patients who are allergic or intolerant to hydroxychloroquine, however, Chloroquine is associated with a higher risk of ocular toxicity. [1]

Lupus nephritis

Lupus nephritis affects up to 60% of SLE patients within a decade of diagnosis, with a negative effect on survival. It is clinically suggested by a spot urine protein-to-creatinine ratio of more than 0·5 g and should be confirmed by renal biopsy unless a strong contraindication exists. Lupus nephritis is classified and treatment targeted according to the *International Society of Nephrology and Renal Pathology Society Criteria*. Immunosuppressive therapies are generally not indicated in class I or VI lupus nephritis, unless necessitated by extrarenal disease activity. The aims of therapy are to preserve kidney function, prevent flares, avoid damage, and improve longevity and quality of life. [13]

Figure 3: Management strategy for lupus nephritis, excluding class I, II, V and pregnancy

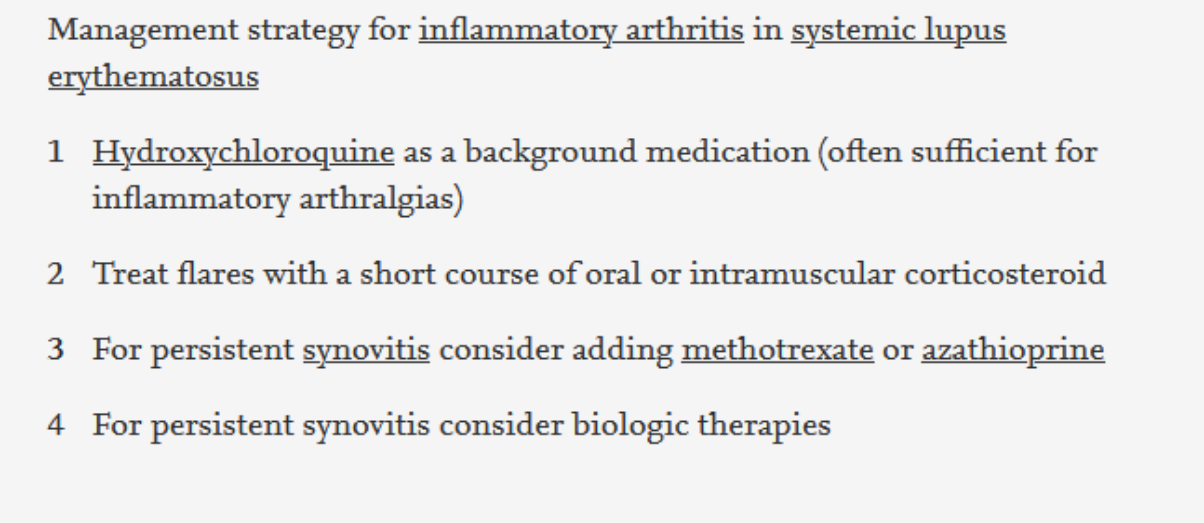


Durcan, L., O'Dwyer, T, Pettri, M. (2019). Management strategies and future directions for systemic lupus erythematosus in adults. The Lancet: Volume 393, Issue 10188, 8–14 June 2019, Pages 2332-2343

Musculoskeletal involvement

A range of articular manifestations associated with SLE vary from inflammatory arthralgias which affect the small joints of the hands and wrist, to synovitis. For inflammatory arthralgias, hydroxychloroquine therapy is often enough, whereas patients with synovitis often need further therapy.

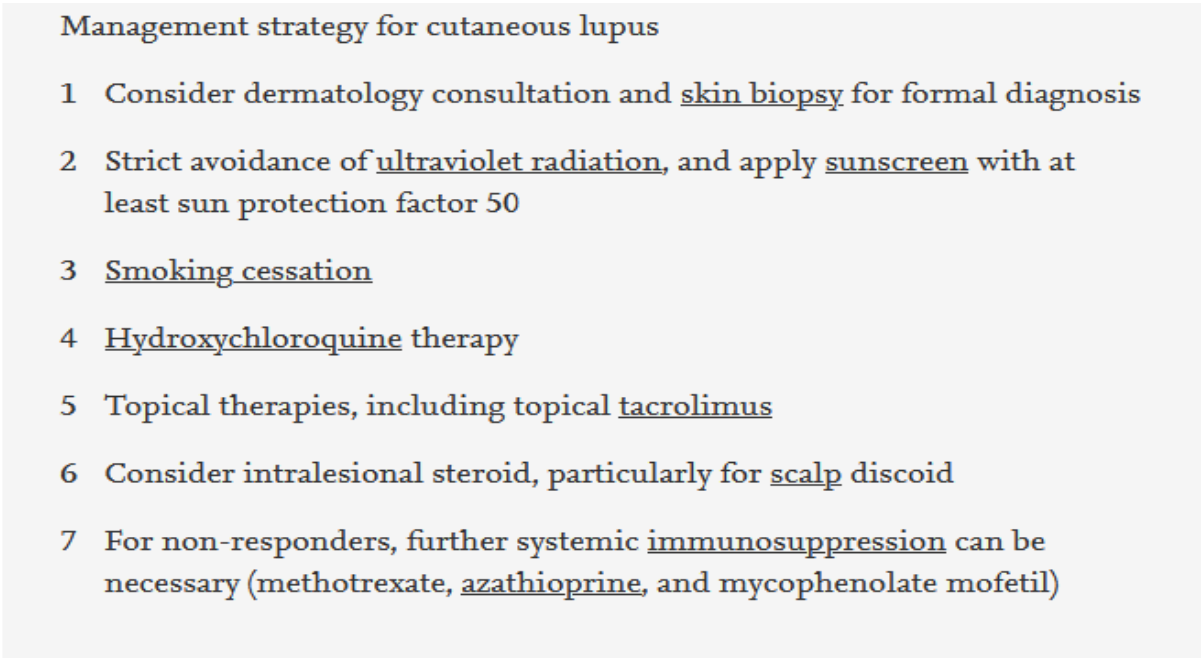
Figure 4: Management strategy for inflammatory arthritis in SLE



Durcan, L., O'Dwyer, T, Pettri, M. (2019). Management strategies and future directions for systemic lupus erythematosus in adults. The Lancet: Volume 393, Issue 10188, 8–14 June 2019, Pages 2332-2343

Cutaneous Lupus

Figure 5: Management strategy for cutaneous lupus



Durcan, L., O'Dwyer, T, Pettri, M. (2019). Management strategies and future directions for systemic lupus erythematosus in adults. The Lancet: Volume 393, Issue 10188, 8–14 June 2019, Pages 2332-2343

Patient education, lifestyle measures and emotional support play a central role and are important factors in the management of SLE. Smoking can worsen the symptoms of SLE and patients should be educated about the importance of smoking cessation. Photoprotection is important, and all patients with SLE should avoid direct sun exposure, and use broad-spectrum UV-A and UV-B sunscreens with a sun protection factor (SPF) of 30 or more. Vitamin D supplements are recommended. Patients with systemic lupus erythematosus experience significant stress related to their disease and its complications, and have higher rates of anxiety and depression. Support groups, involvement of psychiatry services and emotional and behavioural therapy may be required. [11]

Complications

Complications in patients with SLE usually occur because of organ damage caused by the disease, or due to the adverse effects of medications used to treat it. Medication-induced complications are common and require close monitoring and surveillance. Long-term corticosteroid use in SLE patients frequently leads to osteoporosis, leading to osteoporotic fractures. Other complications of long-term corticosteroid therapy include avascular necrosis, glaucoma, cataract, weight gain and poor control of diabetes mellitus. High dose corticosteroid use can also be associated with infections and acute psychosis. Long term use of hydroxychloroquine may rarely result in maculopathy and retinopathy that is irreversible, and close ophthalmology examinations are recommended. Cyclophosphamide use is associated with a significantly high risk of interstitial cystitis and bladder cancer even after drug discontinuation. SLE patients are immunocompromised and at a significantly high risk of infections which is one of the major causes of morbidity and mortality in systemic lupus erythematosus.[11]

Outlook

Systemic lupus erythematosus is a chronic inflammatory disorder with no cure. It can affect many organs and lead to a very poor quality of life without appropriate treatment and management. Due to earlier diagnosis and advancements in treatment, the outlook is now more promising than in the past, however, many patients are still at risk of life-threatening complications because of damage to internal organs and tissues, and some of the treatments used can also increase the risk of developing serious infections. An overreliance on corticosteroids contributes to much of the long-term organ damage. [10, 13]

Despite therapeutic advances, current management strategies are limited by high failure rates and toxicity, and the morbidity of SLE remains considerable. The overall probability of survival is 95% at 5 years after diagnosis, 91% after 10 years, 85% after 15 years, and 78% after 20 years.[13] Adverse outcomes are more common in males than females, and specific factors associated with adverse outcomes include poor adherence and attendance at clinic appointments, low income, and the presence of haemolytic anaemia, nephritis, hypertension,

antiphospholipid syndrome and low complement. Leading causes of mortality include cardiovascular disease, infections, and renal disease. At least 10% of patients with lupus nephritis progress to end stage kidney disease with a dramatic increase in mortality and decrease in quality of life. Relapses occur in up to 50% of patients, with only half achieving complete renal remission at 12 months.[13] Early diagnosis with therapy aimed at preventing organ damage, monitoring and screening for cardiovascular disease and infections with early intervention, can help improve patient outcomes and quality of life. Further scientific research and clinical trials aiming to find a cure or improve SLE outcomes, include targeting interferon pathways, medications that block B-cell or T-cell function, JAK inhibitors and treatment approaches involving mesenchymal or stem cells. [11, 13]

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