Systemic lupus erythematosus

Alberta Hoi, Talia Igel, Chi Chiu Mok, Laurent Arnaud

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Department of Rheumatology, Monash Health, School of Clinical Sciences, Monash University, Melbourne, VIC, Australia (A Hoi PhD FRACP, T Igel MBBS BMedSc); Department of Medicine, Tuen Mun Hospital, Hong Kong Special Administrative Region, China (C C Mok MD FRCP); Department of Rheumatology, National Reference Center for Autoimmune Diseases, INSERM UMR-S 1109, Hôpitaux Universitaires de Strasbourg, Strasbourg, France (Prof L Arnaud MD PhD)

Correspondence to: Assoc Prof Alberta Hoi, Department of Rheumatology, Monash Health, School of Clinical Sciences, Monash University, Melbourne, VIC 3168, Australia **alberta.hoi@monash.edu**

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease characterised by the presence of autoantibodies towards nuclear antigens, immune complex deposition, and chronic inflammation at classic target organs such as skin, joints, and kidneys. Despite substantial advances in the diagnosis and management of SLE, the burden of disease remains high. It is important to appreciate the typical presentations and the diagnostic process to facilitate early referral and diagnosis for patients. In most patients, constitutional, mucocutaneous, and musculoskeletal symptoms represent the earliest complaints; these symptoms can include fatigue, lupus-specific rash, mouth ulcers, alopecia, joint pain, and myalgia. In this Seminar we will discuss a diagnostic approach to symptoms in light of the latest classification criteria, which include a systematic evaluation of clinical manifestations (weighted within each domain) and autoantibody profiles (such as anti-double-stranded DNA, anti-Sm, hypocomplementaemia, or antiphospholipid antibodies). Non-pharmacotherapy management is tailored to the individual, with specific lifestyle interventions and patient education to improve quality of life and medication (such as hydroxychloroquine or immunosuppressant) adherence. In the last decade, there have been a few major breakthroughs in approved treatments for SLE and lupus nephritis, such as belimumab, anifrolumab, and voclosporin. However the disease course remains variable and mortality unacceptably high. Access to these expensive medications has also been restricted across different regions of the world. Nonetheless, understanding of treatment goals and strategies has improved. We recognise that the main goal of treatment is the achievement of remission or low disease activity. Comorbidities due to both disease activity and treatment adverse effects, especially infections, osteoporosis, and cardiovascular disease, necessitate vigilant prevention and management strategies. Tailoring treatment options to achieve remission, while balancing treatment-related comorbidities, are priority areas of SLE management.

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease, characterised by the presence of autoantibodies towards nuclear antigens, immune complex deposition, and chronic inflammation at classic target organs, such as skin, joints, and kidneys. The disease course is variable, and persistent inflammation has the potential to lead to organ damage and, in severe cases, serious health consequences and premature mortality.

Lupus epidemiology

SLE has been reported to affect more than 3·4 million people worldwide.[1] The disease predominantly affects women, with a ratio of about 9 women to 1 man. Although SLE can occur at any age, it most commonly affects women of childbearing age, typically between 15 years and 44 years; childhood-onset SLE (usually defined as onset before age 18 years) tends to have a more severe disease course.

The true global incidence and prevalence of SLE is difficult to ascertain, due to inherent variations in case definition in epidemiological studies and a shortage of epidemiological data on SLE in many countries.[2] Much of the current literature looks at data derived from national registries, which rely heavily on case identification using International Classification of Disease coding, or similar. The most robust analysis of SLE epidemiology comes from North America and Europe.[3] Overall, the observational data have demonstrated substantial variation in both incidence and prevalence. These studies have also identified key demographic groups who have increased risk for the development of SLE and worse prognosis. Recent analyses of epidemiological studies from the past 5 years in North America have reaffirmed the discrepancies between sex and ethnicity, with rates up to ten times higher in females than in males,[4] and twice as high in Black people than in White people.[5] Black women had the highest incidence of the disease.[6] Black people were the most likely to develop SLE at a younger age and have renal involvement.[5] These discrepancies are mirrored in several studies that showed Native Americans, Black Africans, Indigenous Australians, and Indigenous New Zealanders had higher rates of disease than their White counterparts.[3] Furthermore, data from Asian countries continue to show higher risk of SLE-related complications in local ethnic groups, predominantly with the development of severe renal disease.[7] There is a disproportionate burden of SLE, and

Search strategy and selection criteria

We searched for original clinical studies and reviews in MEDLINE (via PubMed), published between June 1, 2018, and May 30, 2023, in the English language. We used the terms "lupus erythematosus, systemic" or the search terms "systemic lupus erythematosus", "lupus" or "SLE", in combination with the search terms "epidemiology", "pathophysiology", "diagnosis", "classification", "treatment goal", "lupus low disease activity state", "non-pharmacological treatment", "pharmacotherapy", "treatment strategies", or "prognosis". We searched for publications in the past 5 years, but did not exclude older publications that were the original studies and were commonly referenced and highly regarded.

poor disease outcomes, in low-income and middle-income countries (LMICs) with lower socioeconomic status.[2] As race is a sociocultural—rather than a biological—construct, the aforementioned associations might reflect a possible role of unmeasured confounders, such as socioeconomic status. Health disparities are strongly affected by socioeconomic factors, such as scarce resources for diagnosis, timely referral to specialists, surveillance of disease activity and complications, and accessibility to novel therapies. With few exceptions, mortality rates for patients with SLE in LMICs are substantially higher than those in high-income countries.[8]

Pathophysiology

There have been several major advances in the understanding of the pathogenesis of SLE in recent years.[9] Previous genome-wide association studies have identified more than 100 genetic variants associated with the disease, many of which are directly involved in signalling of the immune pathways.[10] One of the strongest risk alleles for SLE is the signal transducer and activator of transcription (*STAT*) 4 gene, which regulates important transcription factors involved in the interferon signalling pathway.[11] Specific risk alleles might confer more severe end organ manifestations, such as the apolipoprotein L1 gene in patients with African ancestry.[12] Both innate and adaptive immune dysregulation are featured in the pathophysiology of SLE. A few key pathways have been identified (figure 1) as major drivers of autoimmunity, such as impaired clearance of cell debris that could induce a loss of self-tolerance; there are also pathways directed towards interaction between immune cells and their mediators, which contribute to the perpetuation of autoimmunity and chronic inflammation, such as the dysregulation of type 1 interferon response.[13]

The interferon signature, which was coined to describe the overexpression of interferon-regulated genes, is frequently observed in patients with SLE, and has been implicated in disease initiation and perpetuation.[14] Other studies have shown significantly elevated expression of *STAT1* and *STAT2* in B cells and monocytes in people with SLE, reiterating the importance of dysregulated homoeostasis of type 1 interferon effects in SLE.[15] In addition to type 1 interferons, there are other cytokines and costimulatory signalling molecules that are relevant in lupus pathogenesis, which can be targeted to ameliorate their effects on immune cells.[16,17]

These intricate immune pathways highlight the multifaceted nature of lupus pathogenesis. As knowledge of these pathways evolves, researchers have been able to identify novel therapeutic targets, and lay foundations for personalised medicine in the future.[9,18] Emerging insights also help to shape rational therapeutic strategies that could target dual pathways to achieve sustained remission and improved outcomes for patients.

A structured approach to SLE diagnosis

Diagnostic ambiguity can pose a challenge in primary care. Constitutional (such as fatigue), musculoskeletal, or mucocutaneous symptoms represent the earliest complaints in most patients who might eventually be diagnosed with SLE. In some patients, however, involvement of other organ systems (such as lupus nephritis) can be the first manifestation of the disease. It is important to have a systematic approach to evaluate a patient's history, including all symptoms, duration, and any family history of autoimmune diseases. The following guide serves to provide some tips for the generalist when patients present with manifestations that are compatible with an SLE diagnosis. The use of an autoantibody profile can considerably assist the diagnostic process and help with differential diagnoses. Early referral to a rheumatologist can greatly assist with the diagnostic process.

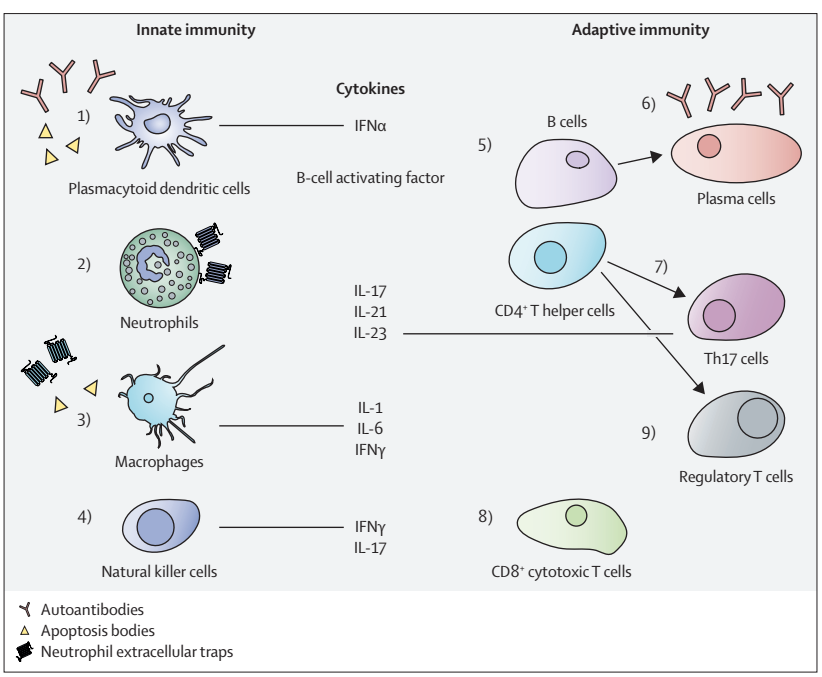


Figure 1: **Key cellular and humoral drivers of systemic lupus erythematosus pathogenesis**
Lupus pathogenesis involves dysregulation of both innate and adaptive immune responses, with several cellular and humoral elements playing key roles. (1) Activated by self-DNA and RNA within immune complexes or apoptotic bodies, plasmacytoid dendritic cells are primary sources of type I interferons (eg, IFNα), which amplify and perpetuate the cycle of autoreactive cells and autoantibody production. (2) Neutrophils and their products (eg, neutrophil extracellular traps) are potent sources of nucleic acids, which activate plasmacytoid dendritic cells and prime T cells by reducing their activation threshold. (3) Macrophages contribute to both the initiation and propagation of lupus. A defect in the ability of macrophages to clear apoptotic cells can lead to accumulation of apoptotic material, serving as a source of autoantigens. Macrophages are key producers of proinflammatory cytokines (eg, IL-1, IL-6, and IFNγ), serve as antigen-presenting cells, and release inflammatory mediators that cause tissue damage and fibrosis. (4) Natural killer cells play an important role in regulating the activity and survival of other immune cells and produce cytokines (eg, IFNγ and IL-17). (5) Autoreactive CD4⁺ T cells and B cells amplify the immune response, and their activation relies on appropriate engagement of costimulatory molecules. (6) The process for the maturation of plasma cells is dependent on the proliferation and differentiation of B cells under the influence of cytokines (eg, B-cell activating factor). Subsequent class switching and somatic hypermutation are important processes in B cells, which require T-cell help in the germinal centre. (7) Th17 cells, a subset of CD4 T helper cells producing cytokines such as IL-17 or IL-21, promote inflammation and differentiation into plasma cells. Th17 cells are activated, expanded, and sustained under the influence of IL-23. (8) CD8⁺ cytotoxic T cells can mediate tissue damage in the skin, kidney, or brain. (9) Regulatory T cells, a subset of CD4 T cells, are essential for maintaining immune tolerance and preventing autoimmune responses. Th17 cells=T helper 17 cells.

Fatigue

Although fatigue is not part of the SLE classification criteria because of its non-specific nature, it is a common presenting symptom that should prompt clinicians to look for other organ involvement. Fatigue occurring with one of the common musculoskeletal or mucocutaneous manifestations should prompt clinical suspicion for SLE. Some target organ involvement, such as renal or haematological manifestations of SLE, can present with predominantly constitutional symptoms in early disease.

	Weight
Clinical domains and criteria	
Constitutional	
Fever: temperature ≥38·3°C	2
Haematological	
Leucopenia: $<4 \times 10^9$ per L	3
Thrombocytopenia: $<100 \times 10^9$ per L	4
Autoimmune haemolysis: positive direct Coomb's test, and evidence of haemolysis (reticulocytosis, low haptoglobin, and elevated indirect bilirubin or lactate dehydrogenase)	4
Neuropsychiatric	
Delirium	2
Psychosis: characterised by delusions, hallucination, or both, in the absence of delirium	3
Seizure: primary generalised or partial or focal seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus (clinical or biopsy proven)	4
Acute cutaneous lupus: localised form is the classic fixed, flat, or raised erythema over malar eminences, but tends to spare the nasolabial fold; can be generalised in distribution	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis: should have two or more of the following features, including typical description of pericarditis chest pain, pericardial rub, or electrocardiogram changes	6
Musculoskeletal	
Joint involvement: inflammatory joint pain characterised by synovitis involving two or more joints, or tenderness in two or more joints and morning stiffness	6
Renal	
Proteinuria: >0·5 g/24 h or equivalent spot urine protein–creatinine ratio	4
Renal biopsy class II or V lupus nephritis	8
Renal biopsy class III or IV lupus nephritis	10
Immunology domains and criteria	
Antiphospholipid antibodies	
At least moderate titre anti-cardiolipin antibodies (any isotype), or positive anti-β2-glycoprotein 1 antibodies or lupus anticoagulant	2
Complement proteins	
Low C3 or low C4	3
Low C3 and low C4	4
SLE-specific antibodies	
Anti-double-stranded DNA antibody in an immunoassay with demonstrated 90% or greater specificity for SLE against relevant disease controls or anti-Sm antibody	6

Information taken from the most recent European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) guideline. EULAR/ACR 2019 Classification Criteria of SLE is a useful framework to understand the spectrum of clinical and immunological disease typically associated with SLE. Attribution is important in the application of these criteria, and therefore a criterion should not be counted if there is a more probable explanation than SLE. Occurrence of a criterion on at least one occasion is sufficient. For SLE classification, at least one clinical criterion and ten or more points are required, but only the highest weighted criterion within each domain is counted towards the total score; additional criteria items within the same domain are not counted. Entry criterion of using this classification criteria is the presence of positive antinuclear antibodies at a titre of ≥1:80 on Hep-2 cells or equivalent (ever). SLE=systemic lupus erythematosus.

Table 1: **Summary of key criteria and weightings towards SLE classification**

Common musculoskeletal features

Joint involvement is another common presenting symptom in patients with SLE, and up to 90% of patients will have musculoskeletal symptoms during the course of the disease.[19] Inflammatory arthralgia in SLE can be migratory, transient, or persistent, and most typically affects the hands, wrists, and knees. Imaging studies have revealed that tendon involvement, synovitis, and even erosions (as evident on MRI) are prevalent.[20] Classic Jaccoud arthropathy (traditionally characterised by non-erosive deformities on x-ray, and often reversible subluxation of the metacarpophalangeal joints), is rare, appearing in fewer than 5% of patients with SLE.[21]

Mucocutaneous features

Although it is common for patients with SLE to have mucocutaneous features, the disease spectrum is diverse. The classic butterfly-shaped rash over the cheeks and nose, called the malar rash, represents an acute lupus-specific rash. Patients can have other types of skin lesions, which can differ in the depth of the inflammatory infiltrate (eg, deep, potentially scarring lesions, as in discoid lupus erythematosus) or morphology (eg, classic ring-shaped red patches with scaly borders, as in subacute cutaneous lupus erythematosus). Additionally, mucous membrane involvement can lead to mouth ulcers. Photosensitivity and non-scarring alopecia are also common features.

Classification criteria to minimise diagnostic ambiguity

One of the most common challenges reported by primary care physicians and patients is related to diagnostic ambiguity. Many patients report the frustration of the difficulties of obtaining a confident diagnosis of SLE in real-world practices.[22] Classification criteria are used primarily for research purposes to establish a homogeneous cohort that can help with understanding disease course and prognosis, but can also be used by clinicians to determine whether a patient has sufficient clinical and serological features to fulfil the diagnosis of SLE. A summary of the key criteria and their relative weighting towards the classification of SLE, from the latest version by the European League Against Rheumatism (EULAR) and American College of Rheumatology in 2019, is shown in table 1.[23] The clinical domains and criteria captured in these classification criteria are not an exhaustive list of clinical manifestations seen in patients with SLE, but reflect clinical features that are most specifically associated with SLE.

Serological profile

In terms of serological domain, the move to include an ever positive (historic) ANA test (ANA titre more than or equal to 1:80) as an entry criterion for SLE in this new classification criteria has been much debated, but a consensus has generally been reached that the presence of ANAs is a fundamental hallmark of SLE.[24] Some autoantibodies (such as anti-Sm and anti-double-stranded DNA [anti-ds] DNA) have high specificity for SLE, whereas other autoantibodies, such as anti-Ro/SSA, anti-La/SSB, anti-RNP, and antiphospholipid antibodies (including anti-cardiolipin and anti-β2-glycoprotein 1 antibodies) have an association with SLE, but are less specific; these autoantibodies can be used in the diagnostic process, but other autoimmune diseases must be considered (figure 2).

Other lupus mimics and lupus-spectrum immune disorders

Part of the challenge in lupus diagnosis is that not all clinical features occur simultaneously, and there can often be considerable time elapsed between manifestations. For most patients, constitutional (including fatigue), mucocutaneous, and musculoskeletal symptoms represent the earliest complaints. There have been many terms used to describe early disease (such as early lupus, incomplete lupus, or subcriteria lupus), where there might be some clinical and serological features consistent with SLE, but patients do not fulfil the classification criteria. Although most of these patients do not progress to SLE, 5–10% of cases do evolve into full SLE or different connective tissue diseases, such as Sjögren's syndrome, systemic sclerosis, or spondyloarthritis.[25,26] It remains difficult to predict which patients will progress, and monitoring by a rheumatology service can therefore help early disease identification and improve patient outcomes.[25–27] Risk factors, such as a younger age at presentation, serositis, presence of anti-dsDNA antibodies, or emerging biomarkers (eg, interferon score), might help to identify patients at high risk of SLE.[25,26] An alternative diagnostic label, such as undifferentiated connective tissue disease, can be used for patients who have ongoing symptoms and a disease duration of at least 3 years, but do not fulfil classification criteria for one of these conditions.[28,29]

Another common mimic for SLE is fibromyalgia, particularly in patients who have undifferentiated symptoms and misattribution of positive ANAs. However, studies of fibromyalgia in SLE have shown a high prevalence of coexistence of both conditions in the same individual.[30,31] Although fibromyalgia and related central pain sensitisation syndromes are poorly understood conditions, their common occurrence in SLE has prompted researchers to propose a model of so-called type 1 versus type 2 SLE symptoms to facilitate discussion with patients regarding the attribution and management of their symptoms.[30,32] Type 1 symptoms have been proposed to include inflammatory manifestations that are conventionally accepted as part of lupus disease activity, such as arthritis, serositis, or dermatitis, whereas type 2 symptoms include non-inflammatory symptoms, such as fatigue, widespread pain, mood disturbance, and cognitive dysfunction, which overlap with fibromyalgia.[30,32–34]

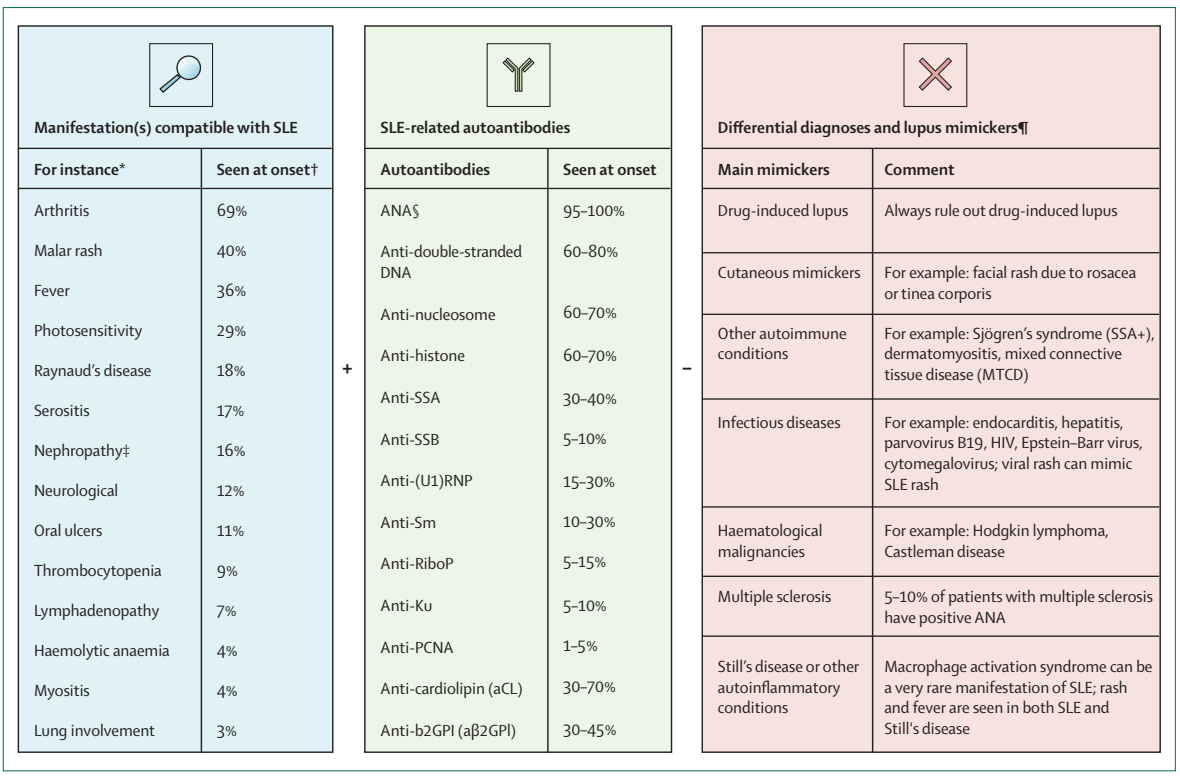
Non-pharmacological management

Non-pharmacological therapy plays an important role in SLE management, despite a shortage of comparative studies on its effectiveness. We encourage early discussion of lifestyle interventions with patients, as these interventions will probably have ongoing benefits on the physical, social, and psychological domains of patients' quality of life.[35] One of the most important interventions is for smoking cessation, since cigarette smoking has been identified as a significant risk factor for the development of SLE, with evidence suggesting cessation could dramatically reduce this risk.[36,37] Moreover, continued smoking after diagnosis with SLE is associated with an increased inflammatory burden, leading to more frequent flares, worsened disease control (particularly in cutaneous disease), and decreased efficacy of treatments.[38] Early referral to smoking cessation help services should be considered.[39]

Sun protection is crucial for patients with SLE, and interventions encompass discussion with patients regarding sensible clothing, attention to ultraviolet exposure, and the use of sunscreen.[40] Although photosensitivity is predominantly a cutaneous reaction, some patients report systemic symptoms after sun exposure, such as joint pain, weakness, fatigue, or headaches.[41] However, data using the Nurses' Health Study suggest no strong link between high ultraviolet exposure and incident SLE risk.[42] Still, individual sun sensitivity varies, and a tailored protection strategy, in consultation with an SLE specialist, is advised.

Early studies have shown that exercise improves psychological function and reduces fatigue.[43,44] Exercise is safe and well tolerated by most patients with SLE.[45] Much less discussed is the role of psychological interventions. A systematic review and meta-analysis suggested that psychological interventions in patients with SLE could reduce anxiety, depression, and disease activity. Although these studies were small, there was a consistent benefit in improving effects on mental health, fatigue, and physical function, and such interventions might even improve treatment satisfaction and adherence.[46]

Fatigue is a very common concern for patients with SLE, with 53–80% of patients identifying this as a primary manifestation of disease, even though it is not part of the classification criteria. Clinicians should, therefore, have a systematic approach to managing fatigue, given its multifactorial nature (figure 3).[50] Physical activity, weight loss, addressing sleep and mood disturbance, and pain management have all been shown to improve fatigue in patients with SLE.[51]



Manifestation(s) compatible with SLE

For instance*	Seen at onset†
Arthritis	69%
Malar rash	40%
Fever	36%
Photosensitivity	29%
Raynaud's disease	18%
Serositis	17%
Nephropathy‡	16%
Neurological	12%
Oral ulcers	11%
Thrombocytopenia	9%
Lymphadenopathy	7%
Haemolytic anaemia	4%
Myositis	4%
Lung involvement	3%

+

SLE-related autoantibodies

Autoantibodies	Seen at onset
ANA§	95–100%
Anti-double-stranded DNA	60–80%
Anti-nucleosome	60–70%
Anti-histone	60–70%
Anti-SSA	30–40%
Anti-SSB	5–10%
Anti-(U1)RNP	15–30%
Anti-Sm	10–30%
Anti-RiboP	5–15%
Anti-Ku	5–10%
Anti-PCNA	1–5%
Anti-cardiolipin (aCL)	30–70%
Anti-b2GPI (aβ2GPI)	30–45%

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Differential diagnoses and lupus mimickers¶

Main mimickers	Comment
Drug-induced lupus	Always rule out drug-induced lupus
Cutaneous mimickers	For example: facial rash due to rosacea or tinea corporis
Other autoimmune conditions	For example: Sjögren's syndrome (SSA+), dermatomyositis, mixed connective tissue disease (MTCD)
Infectious diseases	For example: endocarditis, hepatitis, parvovirus B19, HIV, Epstein–Barr virus, cytomegalovirus; viral rash can mimic SLE rash
Haematological malignancies	For example: Hodgkin lymphoma, Castleman disease
Multiple sclerosis	5–10% of patients with multiple sclerosis have positive ANA
Still's disease or other autoinflammatory conditions	Macrophage activation syndrome can be a very rare manifestation of SLE; rash and fever are seen in both SLE and Still's disease

Figure 2: **Making a diagnosis of SLE**
Reproduced from @Lupusreference.[47] SLE=systemic lupus erythematosus. *Any tissue or organ can be targeted by SLE. †Based on data from Cervera and colleagues.[48] ‡Renal biopsy generally needed to confirm SLE. §Lack of ANA is uncommon in SLE and strongly argues against this diagnosis; ANA usually present years before clinical disease onset. ¶Based on data from Chasset and colleagues.[49]

Medication non-adherence is a substantial barrier to achieving and maintaining remission in SLE, especially given the chronicity of disease. Up to 75% of patients report occasional non-adherence to their medication, depending on the assessment methods.[52] Studies have sought to identify the potential barriers to medication adherence with the aim to provide practical solutions for patients. Frequently reported barriers to adherence include, but are not limited to, forgetfulness, concern regarding medication adverse effects, financial reasons, or disagreement with medical professionals with regard to the role of medications in halting disease progression.[53,54] Unsurprisingly, in one study, patients who were non-adherent reported more barriers to medication adherence than patients who were sufficiently adherent.[53]

Although these barriers certainly contribute to medication non-adherence, often poor adherence is inadvertent, due to low health literacy, or as a result of restricted access to health care due to socioeconomic status. Patient activation is an important feature of patient engagement that specifically involves skills that can lead to patients taking independent action to maintain and improve their health. There is a movement to promote patient activation through education for better health literacy and self-efficacy, which are important aspects of chronic disease management.[55] Teaching patients how to navigate the health-care system can improve patients' ratings on self-efficacy.[56]

Pharmacotherapy

Drug therapies in SLE take into account factors such as dominant organ involvement, level of disease activity, and disease severity (mild, moderate, or severe), as well as a patient's individual circumstances (such as pregnancy planning), in a shared decision-making process (table 2).[57] Treatment goals now focus on early control of disease activity, the prevention of flare, and minimisation of comorbidities and treatment-related toxicity, especially from glucocorticoids. Achieving a lupus low disease activity state, or remission, is associated with improved long-term outcomes, such as prevention of flare, reducing damage accrual, and improving quality of life and survival.[58,59]

The 2023 EULAR guideline has broadened its recommendations to include some novel therapeutic agents such as belimumab, anifrolumab, and voclosporin, but hydroxychloroquine is still the quintessential SLE medication that is widely used, due to its broad benefits for symptoms, flare, and damage prevention, and is therefore recommended for all patients (unless contraindicated, for instance due to hypersensitivity to

hydroxychloroquine).[60–63] Improved understanding of hydroxychloroquine-related retinopathy has led to a revised screening guideline for safety in long-term hydroxychloroquine use. The risk of toxicity has been estimated to be less than 1% in those taking hydroxychloroquine for less than 5 years, increasing to approximately 5% after 5 years, and up to 20% after 20 years of therapy.[64,65] The risk of retinopathy can be mitigated by adhering to the optimal long-term dose target of 5·0 mg/kg per day (actual bodyweight) and regular retinal screening after 5 years of use. Extra attention should be paid to patients with renal impairment, tamoxifen use, and pre-existing macular disease.[66] The optimal dose of hydroxychloroquine should take into account a patient's disease activity status, risk for flare, background immunosuppression, and history of non-adherence. Hydroxychloroquine blood concentration, where available, might provide additional information to assess therapeutic adherence and optimise hydroxychloroquine dosing.[67–69]

Glucocorticoids remain a mainstay of treatment for active SLE due to their ability to rapidly control disease activity, induce remission, and treat flares. However, glucocorticoids have a long list of adverse effects, particularly in the metabolic, infective, ocular, cerebrovascular, cardiovascular, and musculoskeletal systems.[70–73] To counter these risks, many lupus nephritis studies propose a lower initial glucocorticoid dose with more rapid tapering.[74–76] The latest EULAR guideline has suggested that, ideally, glucocorticoids should be discontinued where possible, but when glucocorticoid discontinuation is not feasible, the maintenance dose should not exceed 5 mg/day (prednisone equivalent).[57,77]

Timely initiation and maintenance of immunomodulatory agents can reduce disease activity and expedite glucocorticoid tapering. Escalation from glucocorticoids to conventional immunosuppressants such as methotrexate, azathioprine, and mycophenolate (either mycophenolate mofetil or mycophenolic acid) is generally used in patients with clinically significant, but perhaps non-organ-threatening, disease. Rheumatologist involvement early in the disease process can facilitate identification of organ involvement and recognition of flares and persistent disease activity, and thereby implement an appropriate level of immunosuppression.

In lupus nephritis, mycophenolate is as effective as cyclophosphamide, and has become standard induction immunosuppression therapy in most centres.[78,79] Calcineurin inhibitors, such as cyclosporin, tacrolimus, or the newer generation voclosporin, have proven efficacy in lupus nephritis.[80] The AURORA 1 study used a multi-targeted approach of combining voclosporin and mycophenolate to bring on disease remission more rapidly than mycophenolate alone.[74]

The addition of biologics, such as belimumab or anifrolumab, has improved disease activity control in clinical trials of patients with persistently active SLE, despite standard of care. Belimumab is a human monoclonal antibody against B-cell activating factor that inhibits activation, proliferation, and survival of B cells. In phase 3 trials, treatment with intravenous or subcutaneous belimumab plus standard therapy was effective in reducing overall disease activity and reducing flares, with improvement in quality of life;[81] there was also a corresponding improvement in serological profile. More recently, belimumab has shown significant efficacy in improving renal response in patients with lupus nephritis, with a greater number of patients reaching the primary efficacy endpoint (defined as a reduction in urinary protein–creatinine ratio ≤0·7, estimated glomerular filtration rate of <20% below preflare value, and no use of rescue therapy) over 2 years.[81,82]

Rituximab, an anti-CD20 monoclonal antibody, has been used for over a decade for refractory SLE, despite the failure of its phase 3 studies (such as EXPLORER or LUNAR) to meet their primary endpoints.[83,84] In these phase 3 studies, there were observations of reduced time to severe flare, an increased proportion of partial renal response, and improved laboratory parameters. In real-world observational studies, rituximab has been used mainly in treatment-refractory cases, but these studies build the experience and foundation for other B-cell depletion therapies that might come in the future.

Anifrolumab is the first human monoclonal antibody against the type 1 interferon receptor that has been

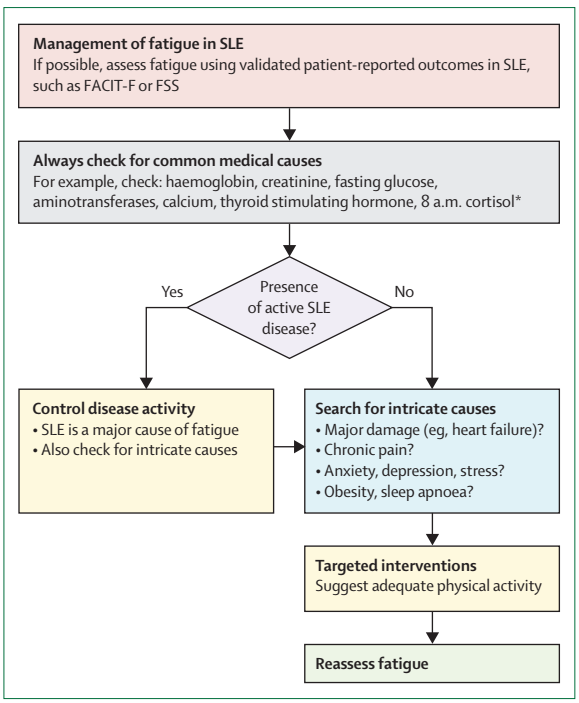

Figure 3: **Strategies to manage fatigue in patients with SLE**
Reproduced from Mertz et al.[50] FACIT-F=Functional Assessment of Chronic Illness Therapy—Fatigue. FSS=Fatigue Severity Scale. SLE=systemic lupus erythematosus. *In patients who stopped or tapered glucocorticoids <5 mg/day during the last 6 months.

	Typical indications	Benefits	Grade of recommendation*	Monitoring and precaution, including pregnancy consideration
Non-steroidal anti-inflammatory drugs	Arthritis, fever, serositis	Improvement in symptoms of fever, headaches, arthralgias, and serositis[90]	B	Avoid in chronic kidney disease, history of arterial thrombosis, and multiple vascular risk factors; rare association with aseptic meningitis; using in early pregnancy is associated with an increased risk of miscarriage, avoid use after 20 weeks of gestation due to association with oligohyramnios
Glucocorticoids	Low dose for mild disease and maintenance; moderate to high dose for major organ disease (eg, nephritis or neuropsychiatric disease)	Rapid control of inflammatory activity; in lupus nephritis, at a dose of 0·5 mg/kg per day prednisone-equivalent, renal response rates are between 33% and 81% depending on other concomitant immunosuppression[91,92]	C	Exclude infection before administration; monitor blood pressure, and lipid and glucose concentrations; monitor for and prevent osteoporosis and infections; effects on birth defect and adverse pregnancy outcomes have been inconsistent
Hydroxychloroquine	Indicated in all patients with SLE, unless contraindicated	Improved skin and joint disease, with a 2·5-fold increase in flare after hydroxychloroquine withdrawal;[93] benefits include protection against irreversible tissue damage as a result of disease or its treatment (damage accrual) and adverse pregnancy outcomes, favourable cardiovascular profile, and beneficial immunomodulatory effects	A	Baseline ophthalmological examination and regular surveillance for retinopathy; generally considered safe for use in pregnancy as benefits outweigh risk, dose should not exceed 400 mg daily; a large number of observational studies have not found an association between hydroxychloroquine use and congenital malformations[94]
Methotrexate	Arthritis, myositis, skin lesions, serositis	Improved arthritis, skin lesions, and hypocomplementaemia, and lower mean Systemic Lupus Erythematosus Disease Activity Index score;[95] good medication persistence[96]	B	Might aggravate photosensitivity; monitor liver and renal function and cell counts; consider baseline chest radiograph and lung function to exclude clinically significant pre-existing interstitial lung disease or other chronic lung conditions; contraindicated for use in pregnancy due to its risk on spontaneous abortion and teratogenic risk
Azathioprine	Lupus nephritis, more serious organ disease, need for glucocorticoid-sparing effects; compatible with pregnancy	Improvement in renal response (serum creatinine or proteinuria);[97-99] safe for use in pregnancy	B	Close monitoring of leukocyte and neutrophil counts when first used; regular blood tests and liver function tests; selective use is acceptable during pregnancy
Mycophenolate mofetil or mycophenolic acid	Standard induction immunosuppressant for lupus nephritis, refractory skin, and more severe organ disease	Improvement in renal response, including remission, similar to cyclophosphamide;[79,100] superior to azathioprine in achieving clinical remission in patients with non-renal active SLE[101]	B	Monitor for gastrointestinal intolerance, cell counts, and liver function; teratogenic effect from exposure to mycophenolate in pregnancy
Calcineurin inhibitors including cyclosporin, tacrolimus, and voclosporin	Lupus nephritis, refractory haematological, and more severe organ disease	Improvement in renal response, including remission[80,102]	B	Monitor blood pressure, electrolytes, renal function, and for symptoms of neurotoxicity; selective use, particularly for older calcineurin inhibitors (such as cyclosporin and tacrolimus), is acceptable in pregnancy
Cyclophosphamide	Lupus nephritis, neuropsychiatric, and other serious major organ diseases	Improvement in renal response, including remission;[100,103] in patients with refractory disease, clinically significant improvement in physician global assessment and Systemic Lupus Erythematosus Disease Activity Index score and durable response in all organ systems[104]	C	Intravenous regimen generally preferred due to lower toxicity; monitor leukocyte and neutrophil counts; prophylaxis against pneumocystis pneumonia; contraindicated for use in pregnancy—unless a life-threatening situation—due to potential teratogenic effects
Belimumab	Moderate to severe SLE manifestations not responding to standard of care, might have country-specific restriction	More likely to have at least a 4-point reduction in the SLE Responder Index	A	Monitor cell counts, immunoglobulin concentration (for hypogammaglobulinaemia), and for infusion reaction; no recommendation regarding use in pregnancy due to scarcity of published data on pregnancy outcomes
Rituximab	Refractory SLE manifestations, particularly lupus nephritis, neuropsychiatric lupus, and cytopenia; other off-label use for a range of extra-renal disease activity	Improvement in renal and non-renal responses; patients with thrombocytopenia, neurolupus, and cutaneous lupus appear to have better response than those with predominantly joint manifestation[105,106]	C	Prophylaxis for occult hepatitis B reactivation; monitor cell counts and immunoglobulin concentration; no recommendation regarding use in pregnancy due to scarcity of published data on pregnancy outcomes
Anifrolumab	Moderate to severe SLE manifestations not responding to standard of care as adjunctive therapy to standard immunosuppressant (such as azathioprine, methotrexate, or mycophenolate)	Improvement or stability in organ-specific disease activity as defined by British Isles Lupus Assessment Group index[85]	B (A†)	Monitor for reactivation of shingles and respiratory tract infections; no recommendation regarding use in pregnancy due to scarcity of published data on pregnancy outcomes

SLE=systemic lupus erythematosus. *Grade of recommendation in accordance with European League Against Rheumatism: A=consistent level 1 (randomised clinical trials) studies; B=consistent level 2 or 3 (cohort or case-control) studies; C=level 4 (case series) studies, or extrapolations from level 2 or 3 studies; D=level 5 (expert opinion) evidence, or inconsistent or inconclusive studies of any level. †The 2023 update of the European League Against Rheumatism recommendations for the management of systemic lupus erythematosus has given anifrolumab a grade A recommendation, based on results of the TULIP studies, two phase 3 randomised clinical trials; TULIP2 met its primary endpoint but TULIP1 did not.

Table 2: **Pharmacotherapies in SLE**

approved for the treatment of moderate to severe SLE, on the basis of improvement in disease activity, using the British Isles Lupus Assessment Group-based composite lupus assessment response.[85,86] In clinical trials, most patients had musculoskeletal or mucocutaneous domain involvement. Effects in patients with refractory cutaneous lupus were particularly rapid and substantial.[87,88]

Belimumab and anifrolumab were approved by the US Food and Drug Administration, in 2011, and 2021, respectively, for the treatment of SLE. However, for these monoclonal antibodies, their relatively small treatment effects and conflicting results using different outcome measures have led to some uncertainty regarding their potential cost-effectiveness in health care. An international collaboration of SLE clinicians and academics, patient representatives, industry partners, and regulatory experts—called the Treatment Response Measure for SLE Taskforce—has been formed in an attempt to address the desperate need for a better clinical outcome assessment for SLE trials that is fit for purpose (table 2).[89]

Treatment strategies

The optimal treatment algorithm that incorporates existing and novel therapies, either as monotherapy or combination, is yet to be determined. As hydroxychloroquine has such good protective effects on multiple facets of SLE, it is generally used alone, or in combination with another immunosuppressant. In many parts of the world, access to novel biologic immunomodulatory therapies, such as belimumab and anifrolumab, is still difficult. Most patients with SLE are treated with combination therapy, such as hydroxychloroquine (a conventional immunosuppressant) and a glucocorticoid.[96] Treatment should ideally avoid the use of long-term glucocorticoids, but the best strategy to achieve this is still unclear. New combination therapy, such as using a multitargeted approach combining mycophenolate and tacrolimus, has shown superior efficacy over intravenous cyclophosphamide in several open-label studies in lupus nephritis, particularly in patients in China.[107,108]

Sequential therapy has also been explored for patients with severe SLE. The term was first used as some patients who relapsed on rituximab had substantially elevated B-cell activating factor and anti-dsDNA levels.[109] This finding prompted studies to investigate sequential therapy using rituximab followed by belimumab.[110,111] Other alternative approaches, such as more potent B-cell depleting strategies, could replace sequential therapy in the future.

Pregnancy considerations

SLE predominantly affects women of childbearing age. Most women with SLE will have a healthy pregnancy, but there is an increased risk of both maternal and fetal complications, such as pre-eclampsia, fetal growth restriction, or prematurity.[112,113] Clinicians can help patients manage this process with appropriate counselling, risk evaluation, and an active approach to control disease activity and any complications that might arise. A good communication dialogue between the treating physician and the obstetrician is crucial during antenatal visits. Key considerations for pharmacotherapy in pregnancy are outlined in table 2.

Pre-conception counselling

All patients who are planning a pregnancy are encouraged to have a full consultation with their rheumatologist to discuss their plan as early as possible, allowing the rheumatologist to assess disease activity, overall health status, autoantibody profile, and previous obstetric history. Antiphospholipid antibody status should be assessed, including testing for lupus anticoagulant and anticardiolipin and anti-β2-glycoprotein 1 antibodies. Data from the PROMISSE study have shown that lupus anticoagulant was associated with an increased risk of poor pregnancy outcomes;[114] other studies have suggested that triple antibody positivity has the highest risk of poor pregnancy outcomes.[115,116] Medications might be first reviewed during a preconception counselling session, to take into account disease control, risk to the developing fetus of continued use during pregnancy, and any additional treatment that might be required. The rheumatologist might recommend an immunosuppressant change to minimise potential risks to the fetus. Data from disease registries on the potential teratogenic effects of medication in men trying to conceive are generally reassuring, despite a scarcity of studies. Although based on mostly observational data, the prognosis of fetal and maternal outcomes is considered to be best when the patient's disease has been quiescent for at least 6 months before the pregnancy.

Disease optimisation during pregnancy

In an ideal situation, disease remission before conception should be the target.[117] Close monitoring by the treating rheumatologist or nephrologist is important to identify and address any flares promptly. During the second and third trimesters, the development of pre-eclampsia can be difficult to differentiate from active lupus nephritis. The timing of the onset of hypertension (before 20 weeks of gestation makes pre-eclampsia unlikely), presence of active urinary sediment, or rising serological activity (rising anti-dsDNA and dropping complements) are all useful features to suggest active lupus nephritis; whereas rising uric acid is typically associated with pre-eclampsia.[118] Overall, the use of hydroxychloroquine has been shown to be beneficial in preventing lupus flare during pregnancy.[119]

Fetal and pregnancy monitoring

Fetal monitoring in women with anti-Ro/SSA is recommended. The risk of congenital heart block can be as low as 2% if patients have no previous history. Weekly fetal echocardiogram from 16 weeks of gestation to at

least 24 weeks is recommended.[120] The American College of Rheumatology has provided a conditional recommendation that low-dose aspirin be considered for patients with SLE from 12 weeks of gestation, to prevent or delay onset of pre-eclampsia.[121,122] The additional use and intensity of anticoagulants depends on previous clinical history, including whether the patient has had obstetric or thromboembolic antiphospholipid syndrome, bearing in mind the general hypercoagulable state of pregnancy. Low-molecular-weight heparin is the drug of choice during pregnancy, as warfarin is teratogenic.[123]

Management of comorbidities in SLE

Patients with SLE can have a high burden of comorbidities.[124] These comorbidities are mainly driven by a combination of disease activity, disease duration, and adverse effects from treatments.[125,126] SLE damage accrual captures many of these comorbidities in patients from the time of their diagnosis of SLE, and includes irreversible tissue damage that is a result of the disease or its treatment. Not only do these comorbidities affect a patient's quality of life, but they also add to the challenges in managing SLE, due to the need for specific screening and interventions. Additionally, treatments can lead to potential drug interactions and further complications. The accrual of comorbidities has a direct effect on mortality.[127,128]

Infections

The increased risk of infection in patients with SLE has been attributed to immune dysfunction, high disease activity, and medication use (such as glucocorticoids and immunosuppressants). Antimalarial use has been shown to reduce risk of infection in patients with SLE.[129] The strongest risk factor for recurrent infection is a previous history of infection.[130] Multiple international guidelines recommend immunisation to minimise the effect of infections in the population with SLE.[57,131,132] Screening and treatment for active hepatitis B and C infection before starting immunosuppressive therapies should be routine, and prophylaxis against pneumocystis pneumonia should be considered for patients at high risk.[133] Screening for HIV is also considered good practice in many situations, based on individual patient factors and regional prevalence. Vaccination against seasonal influenza, pneumococcus, SARS-CoV-2, herpes zoster virus, and human papillomavirus are all relevant, with schedules based on local governing health body recommendations.[131] Patients should be educated on this heightened risk of infection, and encouraged to use personal protective equipment, such as masks, in high-risk situations.

Bone health

Glucocorticoid-related comorbidities account for a substantial portion of the burden on patients with SLE.[134] One of the major preventable comorbidities relates to bone health, and regular monitoring of serum 25-hydroxyvitamin D concentrations to guide supplementation is important.[135] In patients with SLE, premature menopause affects fertility, bone density, cardiovascular health, and quality of life, and is associated with certain disease factors, such as specific autoantibodies and the use of any immunosuppressant (and not solely with cyclophosphamide).[136] Recommendations on the use of bone mineral density scans to monitor bone health in patients with SLE take into account the patient's age, menopausal status, and other risk factors, such as the duration and dose exposure of glucocorticoid.[137]

Diabetes risk

Regular monitoring of glycated haemoglobin can assess for steroid-induced diabetes, particularly for patients on long-term glucocorticoids.

Cardiovascular risk

The burden of coronary heart disease and cerebrovascular disease is high in patients with SLE, due to an accelerated risk of atherosclerosis.[138] There is emerging evidence to suggest coronary microvascular dysfunction might play a role in patients with cardiac symptoms without obstructive coronary artery disease.[139] Cardiac involvement can be subclinical, or can present with atypical symptoms.[140] Expert lupus bodies recommend tight blood pressure control (target <130/80 mm Hg), and commencement of statin therapy if LDL is greater than 100 mg/dL (2·6 mmol/L).[141] The safety of hormone replacement therapy in patients with SLE in terms of cardiovascular risk remains unclear due to the small number of studies available.

Renal protection

Regular monitoring of proteinuria, renal function, and blood pressure control are essential to minimise progression of chronic renal disease. Adjunctive renoprotection measures (such as using inhibitors of the renin–aldosterone system, with or without the addition of non-steroidal mineralocorticoid receptor antagonists or SGLT2 inhibitors) are common strategies. The exact mechanisms of the renoprotective effect are still to be determined, but probably extend beyond just good blood pressure or proteinuria control.[142]

Prognosis

The disease course of SLE remains variable. Despite therapeutic advancements, patients frequently have disease exacerbations (flares) of varying severity. Studies have shown considerable variation in the rates of lupus low disease activity state attainment of between 25% and 75% by 12 months, depending on the cohorts.[143,144] Long-term outcomes have improved over the past decades, but there are still notable unmet clinical needs, including access to better therapies for patients with persistently active disease, comorbidity burden, and progressive

damage accrual. Progressive damage accrual is an important concept of long-term prognosis and patient management, as it refers to the cumulative—and often irreversible—organ damage that occurs as a result of chronic inflammation and autoimmunity in SLE, which is separate from acute flares or immediate disease activity. Mortality from SLE remains unacceptably high, with an overall risk three times higher than the general population, with no further improvement in survival since the mid-1990s, and major worldwide inequities due to heterogeneous access to care.[8,145] Two-thirds of deaths are due to complications of SLE disease or treatment (eg, infective complications as a result of excessive chronic corticosteroid therapy or use of potent immunosuppressants), compared with a third of cases due to active disease.[146]

Future directions

Reduction of diagnosis delay and development of more effective therapeutic strategies are the two key priorities to improve SLE prognosis. Trials focused on glucocorticoid-sparing strategies will be important to move further towards safer glucocorticoid use, by reducing dose and duration of treatment. With regard to emerging therapies, there are ongoing studies concerning discovery of novel targets and refining ways to manipulate established targets. The evolving therapeutic landscape focuses on targeting B cells, T cells, the interferon pathway, toll-like receptor signalling, or the complement system. Additionally, there is a growing understanding of the distinct mechanisms that cause target organ damage. Researchers have not yet been able to leverage on the promise of personalised medicine, and future studies to examine the use of existing or novel biomarkers to predict therapeutic outcomes at an individual level remain a priority as there are no biomarkers that can reliably predict therapeutic outcomes. There is a pressing need for an improved clinical outcome measure that can be used in SLE clinical trials to assess clinically meaningful responses to treatment. Improving access to care and SLE drugs is a major challenge, especially in LMICs, or in subpopulations such as childhood-onset SLE.[147] These barriers can lead to delayed diagnoses, inadequate treatment, and suboptimal patient outcomes. Finally, further health services research to examine the role of social support, education, and self-efficacy is another key priority that could improve patient satisfaction and adherence.

Contributors

AH and TI contributed to the Seminar planning, search strategy, and data extraction. TI wrote the original draft, and AH, CCM, and LA contributed to the editing, revision, and preparation of the final manuscript.

Declaration of interests

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References

1 Tian J, Zhang D, Yao X, Huang Y, Lu Q. Global epidemiology of systemic lupus erythematosus: a comprehensive systematic analysis and modelling study. *Ann Rheum Dis* 2023; **82:** 351–56.
2 Carter EE, Barr SG, Clarke AE. The global burden of SLE: prevalence, health disparities, and socioeconomic impact. *Nat Rev Rheumatol* 2016; **12:** 605–20.
3 Barber MRW, Drenkard C, Falasinnu T, et al. Global epidemiology of systemic lupus erythematosus. *Nat Rev Rheumatol* 2021; **17:** 515–32.
4 Weckerle CE, Niewold TB. The unexplained female predominance of systemic lupus erythematosus: clues from genetic and cytokine studies. *Clin Rev Allergy Immunol* 2011; **40:** 42–49.
5 Somers EC, Marder W, Cagnoli P, et al. Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan Lupus Epidemiology and Surveillance programme. *Arthritis Rheumatol* 2014; **66:** 369–78.
6 Dall'Era M, Cisternas MG, Snipes K, Herrinton LJ, Gordon C, Helmick CG. The incidence and prevalence of systemic lupus erythematosus in San Francisco County, California: the California lupus surveillance project. *Arthritis Rheumatol* 2017; **69:** 1996–2005.
7 Shim JS, Sung YK, Joo YB, Lee HS, Bae SC. Prevalence and incidence of systemic lupus erythematosus in South Korea. *Rheumatol Int* 2014; **34:** 909–17.
8 Scherlinger M, Mertz P, Sagez F, et al. Worldwide trends in all-cause mortality of autoimmune systemic diseases between 2001 and 2014. *Autoimmun Rev* 2020; **19:** 102531.
9 Hoi A. pathogenesis of systemic lupus erythematosus: insights from translational research. Cham: Springer, 2021.
10 Armstrong DL, Zidovetzki R, Alarcón-Riquelme ME, et al. GWAS identifies novel SLE susceptibility genes and explains the association of the HLA region. *Genes Immun* 2014; **15:** 347–54.
11 Hagberg N, Joelsson M, Leonard D, et al. The *STAT4* SLE risk allele rs7574865[T] is associated with increased IL-12-induced IFN-γ production in T cells from patients with SLE. *Ann Rheum Dis* 2018; **77:** 1070–77.
12 Blazer A, Dey ID, Nwaukoni J, et al. Apolipoprotein L1 risk genotypes in Ghanaian patients with systemic lupus erythematosus: a prospective cohort study. *Lupus Sci Med* 2021; **8:** e000460.
13 Crow MK. Pathogenesis of systemic lupus erythematosus: risks, mechanisms and therapeutic targets. *Ann Rheum Dis* 2023; **82:** 999–1014.
14 Rönnblom L, Leonard D. Interferon pathway in SLE: one key to unlocking the mystery of the disease. *Lupus Sci Med* 2019; **6:** e000270.
15 Gallucci S, Meka S, Gamero AM. Abnormalities of the type I interferon signalling pathway in lupus autoimmunity. *Cytokine* 2021; **146:** 155633.
16 Karnell JL, Albulescu M, Drabic S, et al. A CD40L-targeting protein reduces autoantibodies and improves disease activity in patients with autoimmunity. *Sci Transl Med* 2019; **11:** eaar6584.
17 Liu D, Xu H, Shih C, et al. T-B-cell entanglement and ICOSL-driven feed-forward regulation of germinal centre reaction. *Nature* 2015; **517:** 214–18.
18 Felten R, Scherlinger M, Mertz P, Chasset F, Arnaud L. New biologics and targeted therapies in systemic lupus: from new molecular targets to new indications. A systematic review. *Joint Bone Spine* 2023; **90:** 105523.
19 Ball EM, Bell AL. Lupus arthritis—do we have a clinically useful classification? *Rheumatology (Oxford)* 2012; **51:** 771–79.
20 Wright S, Filippucci E, Grassi W, Grey A, Bell A. Hand arthritis in systemic lupus erythematosus: an ultrasound pictorial essay. *Lupus* 2006; **15:** 501–06.

21 Santiago MB, Galvão V. Jaccoud arthropathy in systemic lupus erythematosus: analysis of clinical characteristics and review of the literature. *Medicine (Baltimore)* 2008; **87:** 37–44.

22 Bruce IN, Buie J, Bloch L, et al. Lupus spectrum ambiguity has long-term negative implications for patients. *Lupus Sci Med* 2023; **10:** e000856.

23 Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol* 2019; **71:** 1400–12.

24 Pisetsky DS, Bossuyt X, Meroni PL. ANA as an entry criterion for the classification of SLE. *Autoimmun Rev* 2019; **18:** 102400.

25 Dyball S, Rodziewicz M, Mendoza-Pinto C, Bruce IN, Parker B. Predicting progression from undifferentiated connective tissue disease to definite connective tissue disease: a systematic review and meta-analysis. *Autoimmun Rev* 2022; **21:** 103184.

26 Md Yusof MY, Psarras A, El-Sherbiny YM, et al. Prediction of autoimmune connective tissue disease in an at-risk cohort: prognostic value of a novel two-score system for interferon status. *Ann Rheum Dis* 2018; **77:** 1432–39.

27 Choi MY, Barber MR, Barber CE, Clarke AE, Fritzler MJ. Preventing the development of SLE: identifying risk factors and proposing pathways for clinical care. *Lupus* 2016; **25:** 838–49.

28 Marwa K, Anjum F. Undifferentiated connective tissue disease. Treasure Island, FL: StatPearls, 2023.

29 Antunes M, Scirè CA, Talarico R, et al. Undifferentiated connective tissue disease: state of the art on clinical practice guidelines. *RMD Open* 2019; **4** (suppl 1): e000786.

30 Wolfe F, Petri M, Alarcón GS, et al. Fibromyalgia, systemic lupus erythematosus (SLE), and evaluation of SLE activity. *J Rheumatol* 2009; **36:** 82–88.

31 Gräfe A, Wollina U, Tebbe B, Sprott H, Uhlemann C, Hein G. Fibromyalgia in lupus erythematosus. *Acta Derm Venereol* 1999; **79:** 62–64.

32 Eudy AM, Reeve BB, Coles T, et al. The use of patient-reported outcome measures to classify type 1 and 2 systemic lupus erythematosus activity. *Lupus* 2022; **31:** 697–705.

33 Eudy AM, Rogers JL, Corneli A, et al. Intermittent and persistent type 2 lupus: patient perspectives on two distinct patterns of type 2 SLE symptoms. *Lupus Sci Med* 2022; **9:** e000705.

34 Fava A, Petri M. Systemic lupus erythematosus: diagnosis and clinical management. *J Autoimmun* 2019; **96:** 1–13.

35 Fangtham M, Kasturi S, Bannuru RR, Nash JL, Wang C. Non-pharmacologic therapies for systemic lupus erythematosus. *Lupus* 2019; **28:** 703–12.

36 Speyer CB, Costenbader KH. Cigarette smoking and the pathogenesis of systemic lupus erythematosus. *Expert Rev Clin Immunol* 2018; **14:** 481–87.

37 Parisis D, Bernier C, Chasset F, Arnaud L. Impact of tobacco smoking upon disease risk, activity and therapeutic response in systemic lupus erythematosus: a systematic review and meta-analysis. *Autoimmun Rev* 2019; **18:** 102393.

38 Chasset F, Francès C, Barete S, Amoura Z, Arnaud L. Influence of smoking on the efficacy of antimalarials in cutaneous lupus: a meta-analysis of the literature. *J Am Acad Dermatol* 2015; **72:** 634–39.

39 Raymond WD, Hamdorf M, Furfaro M, Eilertsen GO, Nossent JC. Smoking associates with increased BAFF and decreased interferon-γ levels in patients with systemic lupus erythematosus. *Lupus Sci Med* 2021; **8:** e000537.

40 Ahluwalia J, Marsch A. Photosensitivity and photoprotection in patients with lupus erythematosus. *Lupus* 2019; **28:** 697–702.

41 Foering K, Chang AY, Piette EW, Cucchiara A, Okawa J, Werth VP. Characterisation of clinical photosensitivity in cutaneous lupus erythematosus. *J Am Acad Dermatol* 2013; **69:** 205–13.

42 Barbhaiya M, Hart JE, Malspeis S, et al. Association of ultraviolet B radiation and risk of systemic lupus erythematosus among women in the Nurses' Health Studies. *Arthritis Care Res (Hoboken)* 2023; **75:** 1409–15.

43 Lu L, Koo S, McPherson S, Hull MA, Rees CJ, Sharp L. Systematic review and meta-analysis: associations between metabolic syndrome and colorectal neoplasia outcomes. *Colorectal Dis* 2022; **24:** 681–94.

44 Yuen HK, Cunningham MA. Optimal management of fatigue in patients with systemic lupus erythematosus: a systematic review. *Ther Clin Risk Manag* 2014; **10:** 775–86.

45 Blaess J, Goepfert T, Geneton S, et al. Benefits and risks of physical activity in patients with systemic lupus erythematosus: a systematic review of the literature. *Semin Arthritis Rheum* 2023; **58:** 152128.

46 Zhang J, Wei W, Wang CM. Effects of psychological interventions for patients with systemic lupus erythematosus: a systematic review and meta-analysis. *Lupus* 2012; **21:** 1077–87.

47 @Lupusreference. Oct 23, 2020. https://x.com/Lupusreference/status/1319589539967631361?s=20 (accessed June 5, 2023).

48 Cervera R, Khamashta MA, Font J, et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. *Medicine (Baltimore)* 1993; **72:** 113–24.

49 Chasset F, Richez C, Martin T, Belot A, Korganow AS, Arnaud L. Rare diseases that mimic systemic lupus erythematosus (lupus mimickers). *Joint Bone Spine* 2019; **86:** 165-71.

50 Mertz P, Schlencker A, Schneider M, Gavand PE, Martin T, Arnaud L. Towards a practical management of fatigue in systemic lupus erythematosus. *Lupus Sci Med* 2020; **7:** e000441.

51 Cornet A, Andersen J, Myllys K, Edwards A, Arnaud L. Living with systemic lupus erythematosus in 2020: a European patient survey. *Lupus Sci Med* 2021; **8:** e000469.

52 Costedoat-Chalumeau N, Pouchot J, Guettrot-Imbert G, et al. Adherence to treatment in systemic lupus erythematosus patients. *Best Pract Res Clin Rheumatol* 2013; **27:** 329–40.

53 Hardy C, Gladman DD, Su J, Rozenbojm N, Urowitz MB. Barriers to medication adherence and degree of nonadherence in a systemic lupus erythematosus (SLE) outpatient population. *Rheumatol Int* 2021; **41:** 1457–64.

54 Costedoat-Chalumeau N, Tamirou F, Piette JC. Treatment adherence in systemic lupus erythematosus and rheumatoid arthritis: time to focus on this important issue. *Rheumatology (Oxford)* 2018; **57:** 1507–09.

55 Fortin PR, Da Costa D, Neville C, et al. Challenges of perceived self-management in lupus. *Arthritis Care Res (Hoboken)* 2022; **74:** 1113–21.

56 White AA, Ba A, Faith TD, et al. The care-coordination approach to learning lupus self-management: a patient navigator intervention for systemic lupus inpatients. *Lupus Sci Med* 2021; **8:** e000482.

57 Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019; **78:** 736–45.

58 Golder V, Kandane-Rathnayake R, Hoi AY, et al. Association of the lupus low disease activity state (LLDAS) with health-related quality of life in a multinational prospective study. *Arthritis Res Ther* 2017; **19:** 62.

59 Golder V, Kandane-Rathnayake R, Huq M, et al. Prospective validation of the lupus low disease activity state (LLDAS)—a treat to target endpoint for systemic lupus erythematosus. *Lancet Rheumatol* 2019; **1:** e95–102.

60 Mok CC, Penn HJ, Chan KL, Tse SM, Langman LJ, Jannetto PJ. Hydroxychloroquine serum concentrations and flares of systemic lupus erythematosus: a longitudinal cohort analysis. *Arthritis Care Res (Hoboken)* 2016; **68:** 1295–302.

61 Akhavan PS, Su J, Lou W, Gladman DD, Urowitz MB, Fortin PR. The early protective effect of hydroxychloroquine on the risk of cumulative damage in patients with systemic lupus erythematosus. *J Rheumatol* 2013; **40:** 831–41.

62 Alarcón GS, McGwin G, Bertoli AM, et al. Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L). *Ann Rheum Dis* 2007; **66:** 1168–72.

63 Dima A, Jurcut C, Chasset F, Felten R, Arnaud L. Hydroxychloroquine in systemic lupus erythematosus: overview of current knowledge. *Ther Adv Musculoskelet Dis* 2022; **14:** 1759720X211073001.

64 Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology* 2016; **123:** 1386–94.

65 Almeida-Brasil CC, Hanly JG, Urowitz M, et al. Retinal toxicity in a multinational inception cohort of patients with systemic lupus on hydroxychloroquine. *Lupus Sci Med* 2022; **9:** e000789.

66 Yusuf IH, Sharma S, Luqmani R, Downes SM. Hydroxychloroquine retinopathy. *Eye (Lond)* 2017; **31:** 828–45.

67 Jorge AM, Mancini C, Zhou B, et al. Hydroxychloroquine dose per ophthalmology guidelines and the risk of systemic lupus erythematosus flares. *JAMA* 2022; **328:** 1458–60.

68 Garg S, Unnithan R, Hansen KE, Costedoat-Chalumeau N, Bartels CM. Clinical significance of monitoring hydroxychloroquine levels in patients with systemic lupus erythematosus: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)* 2021; **73:** 707–16.

69 Fasano S, Messiniti V, Iudici M, Coscia MA, Ciccia F. Hydroxychloroquine daily dose, hydroxychloroquine blood levels and the risk of flares in patients with systemic lupus erythematosus. *Lupus Sci Med* 2023; **10:** e000841.

70 Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum* 2000; **43:** 1801–08.

71 Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. *Am J Med* 1994; **96:** 115–23.

72 Ugarte-Gil MF, Mak A, Leong J, et al. Impact of glucocorticoids on the incidence of lupus-related major organ damage: a systematic literature review and meta-regression analysis of longitudinal observational studies. *Lupus Sci Med* 2021; **8:** e000590.

73 Felten R, Arnaud L. Is it possible to stop glucocorticoids in systemic lupus? *Joint Bone Spine* 2020; **87:** 528–30.

74 Rovin BH, Teng YKO, Ginzler EM, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2021; **397:** 2070–80.

75 Furie RA, Aroca G, Cascino MD, et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2022; **81:** 100–07.

76 Mok CC, Teng YKO, Saxena R, Tanaka Y. Treatment of lupus nephritis: consensus, evidence and perspectives. *Nat Rev Rheumatol* 2023; **19:** 227–38.

77 Mathian A, Pha M, Haroche J, et al. Withdrawal of low-dose prednisone in SLE patients with a clinically quiescent disease for more than 1 year: a randomised clinical trial. *Ann Rheum Dis* 2020; **79:** 339–46.

78 Mok CC. Mycophenolate mofetil for non-renal manifestations of systemic lupus erythematosus: a systematic review. *Scand J Rheumatol* 2007; **36:** 329–37.

79 Touma Z, Gladman DD, Urowitz MB, Beyene J, Uleryk EM, Shah PS. Mycophenolate mofetil for induction treatment of lupus nephritis: a systematic review and meta-analysis. *J Rheumatol* 2011; **38:** 69–78.

80 Peleg Y, Bomback AS, Radhakrishnan J. The evolving role of calcineurin inhibitors in treating lupus nephritis. *Clin J Am Soc Nephrol* 2020; **15:** 1066–72.

81 Furie R, Rovin BH, Houssiau F, et al. Two-year, randomised, controlled trial of belimumab in lupus nephritis. *N Engl J Med* 2020; **383:** 1117–28.

82 Furie R, Rovin BH, Houssiau F, et al. Safety and efficacy of belimumab in patients with lupus nephritis: open-label extension of BLISS-LN study. *Clin J Am Soc Nephrol* 2022; **17:** 1620–30.

83 Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomised, double-blind, phase 2/3 systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum* 2010; **62:** 222–33.

84 Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with rituximab study. *Arthritis Rheum* 2012; **64:** 1215–26.

85 Morand EF, Furie R, Tanaka Y, et al. Trial of anifrolumab in active systemic lupus erythematosus. *N Engl J Med* 2020; **382:** 211–21.

86 Furie R, Morand EF, Askanase AD, et al. Anifrolumab reduces flare rates in patients with moderate to severe systemic lupus erythematosus. *Lupus* 2021; **30:** 1254–63.

87 Blum FR, Sampath AJ, Foulke GT. Anifrolumab for treatment of refractory cutaneous lupus erythematosus. *Clin Exp Dermatol* 2022; **47:** 1998–2001.

88 Morand EF, Furie RA, Bruce IN, et al. Efficacy of anifrolumab across organ domains in patients with moderate-to-severe systemic lupus erythematosus: a post-hoc analysis of pooled data from the TULIP-1 and TULIP-2 trials. *Lancet Rheumatol* 2023; **4:** e282–92.

89 Connelly K, Eades LE, Koelmeyer R, et al. Towards a novel clinical outcome assessment for systemic lupus erythematosus: first outcomes of an international taskforce. *Nat Rev Rheumatol* 2023; **19:** 592–602.

90 Horizon AA, Wallace DJ. Risk:benefit ratio of nonsteroidal anti-inflammatory drugs in systemic lupus erythematosus. *Expert Opin Drug Saf* 2004; **3:** 273–78.

91 Ruiz-Irastorza G, Danza A, Khamashta M. Glucocorticoid use and abuse in SLE. *Rheumatology (Oxford)* 2012; **51:** 1145–53.

92 Illei GG, Austin HA 3rd, Crane M, et al. Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves long-term renal outcome without adding toxicity in patients with lupus nephritis. *Ann Intern Med* 2001; **135:** 248–57.

93 Canadian Hydroxychloroquine Study Group. A randomised study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. *N Engl J Med* 1991; **324:** 150–54.

94 Schreiber K, Giles I, Costedoat-Chalumeau N, et al. Global comment on the use of hydroxychloroquine during the periconception period and pregnancy in women with autoimmune diseases. *Lancet Rheumatol* 2023; **5:** e501–06.

95 Carneiro JR, Sato EI. Double blind, randomised, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus. *J Rheumatol* 1999; **26:** 1275–79.

96 Kandane-Rathnayake R, Louthrenoo W, Luo SF, et al. Patterns of medication use in systemic lupus erythematosus: a multicentre cohort study. *Arthritis Care Res (Hoboken)* 2022; **74:** 2033–41.

97 Grootscholten C, Ligtenberg G, Hagen EC, et al. Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomised controlled trial. *Kidney Int* 2006; **70:** 732–42.

98 Arends S, Grootscholten C, Derksen RH, et al. Long-term follow-up of a randomised controlled trial of azathioprine/methylprednisolone versus cyclophosphamide in patients with proliferative lupus nephritis. *Ann Rheum Dis* 2012; **71:** 966–73.

99 Fu Q, Wu C, Dai M, et al. Leflunomide versus azathioprine for maintenance therapy of lupus nephritis: a prospective, multicentre, randomised trial and long-term follow-up. *Ann Rheum Dis* 2022; **81:** 1549–55.

100 Rathi M, Goyal A, Jaryal A, et al. Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis. *Kidney Int* 2016; **89:** 235–42.

101 Ordi-Ros J, Sáez-Comet L, Pérez-Conesa M, et al. Enteric-coated mycophenolate sodium versus azathioprine in patients with active systemic lupus erythematosus: a randomised clinical trial. *Ann Rheum Dis* 2017; **76:** 1575–82.

102 Zheng Z, Zhang H, Peng X, et al. Effect of tacrolimus *vs* intravenous cyclophosphamide on complete or partial response in patients with lupus nephritis: a randomised clinical trial. *JAMA Netw Open* 2022; **5:** e224492.

103 Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005; **353:** 2219–28.

104 Petri M, Jones RJ, Brodsky RA. High-dose cyclophosphamide without stem cell transplantation in systemic lupus erythematosus. *Arthritis Rheum* 2003; **48:** 166–73.

105 Sans-Pola C, Danés I, Bosch JA, Marrero-Álvarez P, Cortés J, Agustí A. Off-label use of rituximab in patients with systemic lupus erythematosus with extrarenal disease activity: a retrospective study and literature review. *Front Med (Lausanne)* 2023; **10:** 1159794.

106 Rydén-Aulin M, Boumpas D, Bultink I, et al. Off-label use of rituximab for systemic lupus erythematosus in Europe. *Lupus Sci Med* 2016; **3:** e000163.

107 Choi CB, Won S, Bae SC. Outcomes of multitarget therapy using mycophenolate mofetil and tacrolimus for refractory or relapsing lupus nephritis. *Lupus* 2018; **27:** 1007–11.

108 Mok CC, Ho LY, Ying SKY, Leung MC, To CH, Ng WL. Long-term outcome of a randomised controlled trial comparing tacrolimus with mycophenolate mofetil as induction therapy for active lupus nephritis. *Ann Rheum Dis* 2020; **79:** 1070–76.

109 Carter LM, Isenberg DA, Ehrenstein MR. Elevated serum BAFF levels are associated with rising anti-double-stranded DNA antibody levels and disease flare following B cell depletion therapy in systemic lupus erythematosus. *Arthritis Rheum* 2013; **65:** 2672–79.

110 Atisha-Fregoso Y, Malkiel S, Harris KM, et al. Phase 2 randomised trial of rituximab plus cyclophosphamide followed by belimumab for the treatment of lupus nephritis. *Arthritis Rheumatol* 2021; **73:** 121–31.

111 van Schaik M, Arends EJ, Soonawala D, et al. Efficacy of belimumab combined with rituximab in severe systemic lupus erythematosus: study protocol for the phase 3, multicentre, randomised, open-label Synbiose 2 trial. *Trials* 2022; **23:** 939.

112 Clowse ME, Jamison M, Myers E, James AH. A national study of the complications of lupus in pregnancy. *Am J Obstet Gynecol* 2008; **199:** 127.

113 Park JS, Chung MK, Lim H, Lee J, Lee CH. Risk of pregnancy complications and low birth weight offsprings in Korean women with rheumatic diseases: a nationwide population-based study. *J Korean Med Sci* 2022; **37:** e18.

114 Yelnik CM, Laskin CA, Porter TF, et al. Lupus anticoagulant is the main predictor of adverse pregnancy outcomes in aPL-positive patients: validation of PROMISSE study results. *Lupus Sci Med* 2016; **3:** e000131.

115 Laurent C, Ricard L, Nguyen Y, et al. Triple positive profile in antiphospholipid syndrome: prognosis, relapse and management from a retrospective multicentre study. *RMD Open* 2023; **9:** e002534.

116 Lazzaroni MG, Fredi M, Andreoli L, et al. Triple antiphospholipid (aPL) antibodies positivity is associated with pregnancy complications in aPL carriers: a multicentre study on 62 pregnancies. *Front Immunol* 2019; **10:** 1948.

117 Tani C, Zucchi D, Haase I, et al. Are remission and low disease activity state ideal targets for pregnancy planning in systemic lupus erythematosus? A multicentre study. *Rheumatology (Oxford)* 2021; **60:** 5610–19.

118 Iozza I, Cianci S, Di Natale A, et al. Update on systemic lupus erythematosus pregnancy. *J Prenat Med* 2010; **4:** 67–73.

119 Eudy AM, Siega-Riz AM, Engel SM, et al. Effect of pregnancy on disease flares in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2018; **77:** 855–60.

120 De Carolis S, Garufi C, Garufi E, et al. Autoimmune congenital heart block: a review of biomarkers and management of pregnancy. *Front Pediatr* 2020; **8:** 607515.

121 Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol* 2020; **72:** 529–56.

122 Davidson KW, Barry MJ, Mangione CM, et al. Aspirin use to prevent preeclampsia and related morbidity and mortality: US Preventive Services Task Force recommendation statement. *JAMA* 2021; **326:** 1186–91.

123 Ambati A, Knight JS, Zuo Y. Antiphospholipid syndrome management: a 2023 update and practical algorithm-based approach. *Curr Opin Rheumatol* 2023; **35:** 149–60.

124 Gergianaki I, Garantziotis P, Adamichou C, et al. High comorbidity burden in patients with SLE: data from the community-based lupus registry of Crete. *J Clin Med* 2021; **10:** 998.

125 Bruce IN, O'Keeffe AG, Farewell V, et al. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort. *Ann Rheum Dis* 2015; **74:** 1706–13.

126 Sutton EJ, Davidson JE, Bruce IN. The Systemic Lupus International Collaborating Clinics (SLICC) damage index: a systematic literature review. *Semin Arthritis Rheum* 2013; **43:** 352–61.

127 Segura BT, Bernstein BS, McDonnell T, et al. Damage accrual and mortality over long-term follow-up in 300 patients with systemic lupus erythematosus in a multi-ethnic British cohort. *Rheumatology (Oxford)* 2020; **59:** 698.

128 Murimi-Worstell IB, Lin DH, Nab H, et al. Association between organ damage and mortality in systemic lupus erythematosus: a systematic review and meta-analysis. *BMJ Open* 2020; **10:** e031850.

129 Pimentel-Quiroz VR, Ugarte-Gil MF, Harvey GB, et al. Factors predictive of serious infections over time in systemic lupus erythematosus patients: data from a multi-ethnic, multinational, Latin American lupus cohort. *Lupus* 2019; **28:** 1101–10.

130 Ko T, Koelmeyer R, Li N, et al. Predictors of infection requiring hospitalisation in patients with systemic lupus erythematosus: a time-to-event analysis. *Semin Arthritis Rheum* 2022; **57:** 152099.

131 Oku K, Hamijoyo L, Kasitanon N, et al. Prevention of infective complications in systemic lupus erythematosus: a systematic literature review for the APLAR consensus statements. *Int J Rheum Dis* 2021; **24:** 880–95.

132 Pons-Estel BA, Bonfa E, Soriano ER, et al. First Latin American clinical practice guidelines for the treatment of systemic lupus erythematosus: Latin American Group for the Study of Lupus (GLADEL, *Grupo Latino Americano de Estudio del Lupus*)-Pan-American League of Associations of Rheumatology (PANLAR). *Ann Rheum Dis* 2018; **77:** 1549–57.

133 Fragoulis GE, Nikiphorou E, Dey M, et al. 2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2023; **82:** 742–53.

134 Petri M, Bechtel B, Dennis G, et al. Burden of corticosteroid use in patients with systemic lupus erythematosus: results from a Delphi panel. *Lupus* 2014; **23:** 1006–13.

135 Sen D, Keen RW. Osteoporosis in systemic lupus erythematosus: prevention and treatment. *Lupus* 2001; **10:** 227–32.

136 Ceccarelli F, Orefice V, Perrone G, et al. Premature ovarian failure in patients affected by systemic lupus erythematosus: a cross-sectional study. *Clin Exp Rheumatol* 2020; **38:** 450–54.

137 Buckley L, Humphrey MB. Glucocorticoid-induced osteoporosis. *N Engl J Med* 2018; **379:** 2547–56.

138 Conrad N, Verbeke G, Molenberghs G, et al. Autoimmune diseases and cardiovascular risk: a population-based study on 19 autoimmune diseases and 12 cardiovascular diseases in 22 million individuals in the UK. *Lancet* 2022; **400:** 733–43.

139 Weber BN, Stevens E, Barrett L, et al. Coronary microvascular dysfunction in systemic lupus erythematosus. *J Am Heart Assoc* 2021; **10:** e018555.

140 Burkard T, Trendelenburg M, Daikeler T, et al. The heart in systemic lupus erythematosus: a comprehensive approach by cardiovascular magnetic resonance tomography. *PLoS One* 2018; **13:** e0202105.

141 Drosos GC, Vedder D, Houben E, et al. EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases, including systemic lupus erythematosus and antiphospholipid syndrome. *Ann Rheum Dis* 2022; **81:** 768–79.

142 Morales E, Sandino J, Galindo M. Lupus nephropathy beyond immunosuppression: searching for nephro and cardioprotection. *Front Nephrol* 2023; **3:** 1105676.

143 Hao Y, Oon S, Ji L, et al. Determinants and protective associations of the lupus low disease activity state in a prospective Chinese cohort. *Clin Rheumatol* 2022; **41:** 357–66.

144 Morand EF, Abreu G, Furie RA, Golder V, Tummala R. Lupus low disease activity state attainment in the phase 3 TULIP trials of anifrolumab in active systemic lupus erythematosus. *Ann Rheum Dis* 2023; **82:** 639–45.

145 Lee YH, Choi SJ, Ji JD, Song GG. Overall and cause-specific mortality in systemic lupus erythematosus: an updated meta-analysis. *Lupus* 2016; **25:** 727–34.

146 Fors Nieves CE, Izmirly PM. Mortality in systemic lupus erythematosus: an updated review. *Curr Rheumatol Rep* 2016; **18:** 21.

147 Barber MRW, Falasinnu T, Ramsey-Goldman R, Clarke AE. The global epidemiology of SLE: narrowing the knowledge gaps. *Rheumatology (Oxford)* 2023; **62** (suppl 1)**:** i4–9.