Advances in systemic lupus erythematosus

Rym Abida
Su-Ann Yeoh
David A Isenberg

Rym Abida MD is an internal medicine resident, Faculty of medicine of Tunis, Tunis El Manar University, Tunisia. Competing interests: none declared.

Su-Ann Yeoh BMedSci BMBS MRCP is a Clinical Research Fellow, University College London and Specialty Registrar in Rheumatology, University College Hospital London, UK. Competing interests: none declared.

David A Isenberg MD FRCP FAMS is Academic Director of Rheumatology at University College London, UK. Competing interests: none declared.

Abstract
Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a heterogeneous course and systemic involvement. It is the result of a complex pathogenic pathway that culminates in autoantibody formation. The interaction between environmental triggers and genetic susceptibility is key in this process. Genome-wide association study technology has allowed the recognition of >80 loci associated with SLE that lead to the formation of key proteins, each contributing a small increase to the risk. Advances in the management of the disease include new validated standardized tools to capture disease activity, damage and quality of life, for clinical and research purposes. The prognosis of SLE has much improved in the last 50 years because of better general management and specific treatment, including better use of immunosuppressive agents and development of a new group of drugs – biological therapies.

Keywords
Disease activity index
management
MRCP
pathogenesis
systemic lupus erythematosus
treatment

Key points
•Systemic lupus erythematosus (SLE) is a complex disease, more common in women, with multisystemic involvement.
•There is a higher prevalence of SLE in patients with African heritage, with more severe disease and poorer clinical outcomes.
•Classification criteria and tools to measure disease activity should be used in clinical practice.
• The European League Against Rheumatism and the American College of Rheumatology classification criteria (2019) is a cumulative multicriteria weighted system with an immunological entry criterion that has slightly better sensitivity and specificity than previous classification criteria.
•Effective biological agents for treating different features of SLE are slowly becoming available and may have an important corticosteroid-sparing effect.

Introduction
Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disease with a highly heterogeneous pattern of clinical and serological manifestations. Its course differs in different individuals and is unpredictable within the same patient over time, which makes it interesting and challenging to manage. The pathogenesis of SLE is the result of interactions between genes, hormones and the environment, but its precise aetiology is mostly unknown. More than 80 risk genes for the disease have been described. Certain genetic features are also associated with increased disease activity.

In the last 35 years, major efforts have been made to define key aspects of the condition, notably disease activity and damage, using standardized indices. These tools are essential for comparing different cohorts, assessing disease progression and prognosis, and measuring response to treatment. This approach is particularly important now that new biological drugs are beginning to show encouraging signs of efficacy in lupus. This review focuses mostly on the recent advances in understanding and managing SLE.

Understanding

Epidemiology

SLE is a rare disease. Its incidence is estimated to be 0.3-31.5 per 100,000 person per year, and its prevalence worldwide exceeds 50-100 per 100,000 depending on ethnicity, with the highest prevalence being among Afro-carribeans[1,] The incidence may be increasing, probably because of greater awareness of the disease. The prevalence has also been thought to be increasing, which may reflect an improvement in survival rates as well as chronicity.

SLE is more frequent and more severe in African, Hispanic, Chinese and Asian descendants. These patients have more haematological, serosal, neurological and renal manifestations in general, although clinical profiles vary in specific populations. Study of the LUMINA (Lupus in Minorities: Nature vs Nurture) and other cohorts have concluded that, especially in African-American and Hispanic populations, there is an association with high disease activity and damage. Besides ethnicity, other predictors of damage are age, disease duration, disease activity and corticosteroid use.

Socioeconomic status is also associated with a worse prognosis, particularly with respect to the later manifestations of the disease. Poor social support is more commonly found among ethnic minorities, which makes it difficult to distinguish if this is an independent contributor to disease severity.[1]

SLE is more frequent among women of childbearing age, in a ratio that varies between populations but is on average 10:1. Although the age of diagnosis also depends on ethnicity, it is most commonly described to occur between the third and fourth decades of life. Males and female patients show little difference in their disease manifestations or severity, although presentation at the extremes of life is associated with increased severity.

Pathogenesis

There is a complex interaction between gene susceptibility, hormonal influences and environmental triggers with a breakdown of immune tolerance, resulting in autoantibody production and consequent dysregulation of the inflammatory response, leading to induction and maintenance of the disease.

Genetic factors

A genetic component in SLE pathogenesis was first suggested by evident concordance between monozygotic twins in 24–69% of cases, compared with 1–5% in dizygotic twins, and also by the different prevalence in various ethnic groups. An 8–20-fold increased risk of developing SLE has been reported in siblings of SLE patients.

In the last decade, with the development of genome-wide association study technology, >80 loci with common variants have been shown to have a confirmed association with SLE. These genes lead to the formation of key proteins involved in innate and adaptive immunity. Each appears to make a small contribution to the complex pathogenesis of lupus, suggesting that they work cumulatively. Gene-centred DNA sequencing studies have revealed two main independent molecular pathways involved in SLE: T-lymphocyte differentiation and innate immunity mediated by human leucocyte antigen (HLA) and interferon (IFN), respectively.

One of the chromosomal regions having the strongest association with SLE is the HLA locus, especially the class II region containing HLA-DRB1, -DQA1 and -DQB1. There are also associations of some of these loci with specific clinical features (e.g. DRB1 and renal disease) and serological features (e.g. DR2 and anti-Sm antibodies, and DR3 and anti-Ro antibodies).

In the last decade, the importance of the interferon (IFN) signature in the pathogenesis of SLE has been recognized. IFNα is a key mediator in activation of the innate response and also in the adaptive immune system (normally in response to a viral infection). It enhances natural killer cell activity, stimulates maturation of antigen-presenting cells, prevents apoptosis of T cells, suppresses T regulatory cells and promotes B cell differentiation and antibody production. In patients with SLE, IFNα expression is increased in the absence of appropriate stimuli, because of overexpression of the regulating genes, and IFNα concentration is associated with disease activity.

Although hormonal influences have a greater importance in determining the higher prevalence of SLE in women, some X-chromosome-linked genes have been described that might contribute to this (e.g., *IRAK1*, its neighbour gene *MECP2* and presence of CD40L).

It is also now recognized that post-translational modifications are likely to be contributors to the complex inheritance and incomplete concordance between homozygotic twins. In SLE, epigenetic modifications such as abnormalities in DNA methylation and histones have been reported. For example, an elevated interleukin (IL)-6 concentration may contribute to the proliferation of B cells via DNA methylation.

Environmental influences and triggers

The importance of the environment has been suggested by epidemiological studies. The 'prevalence gradient hypothesis' describes a higher prevalence of SLE in the Afro-Caribbean population living in Europe and North America, whereas the prevalence in Western Africa may be low.[1] However, this observation could result from an environmental influence on the manifestations of SLE or from inadequate health systems in Western Africa that fail to recognize the condition.

Infections can modulate the immune system protecting against autoimmunity, but can also trigger the disease. An association between SLE and Epstein–Barr virus (EBV) infection has been described in children; this virus can trigger a flare because of antigenic mimicking (EBV protein EBNA-1 can cross-react with the self-antigen Ro). An association between cytomegalovirus and SLE has also been suggested.

Oestrogens increase the risk of the disease and are a recognized trigger for flares, which probably contributes to the higher prevalence of SLE in women. Women treated with hormonal replacement therapy (but less so with oral contraceptives) have a higher risk of developing SLE and also a higher risk of mild to moderate flare; in addition, associations between SLE and early menarche, menstrual irregularities and early or surgical menopause have been described.

Other environmental triggers reported include ultraviolet light, cigarette smoking and silica. Drugs implicated in drug-induced lupus include hydralazine, D-penicillamine, minocycline, lithium and more recently (albeit rarely) tumour necrosis factor (TNF)-α blocking agents (infliximab, adalimumab, etanercept).

Pathological mechanisms

The complex pathogenesis of SLE seems to involve almost every component of the immune system that culminates in antibody formation. The principal mechanisms are listed here.

B and T cell signalling abnormalities include an abnormal T cell receptor complex, alterations on proteins that influence the T cell response to inflammation in various ways (such as mitogen-activated protein kinase), decreased concentrations of blunting molecules such as Lyn (LCK/Yes-related novel tyrosine kinase), impaired signalling via the B cell inhibitory receptor FcgRIIB, and a faster response to a B cell proliferation stimulus such as a proliferation-inducing ligand (APRIL) or B lymphocyte stimulator (BLyS).

Autoantigen-specific T cells have been described. T cells stimulate B cell proliferation and are necessary for the secretion of high-affinity class-switched immunoglobulin (Ig) G antibodies, in a process called T lymphocyte help. These antibodies are strongly associated with tissue damage in SLE. T regulatory cells, which suppress T helper cells and B cells, are impaired in SLE.

Dysregulated apoptosis and defective clearance of cellular debris increases autoantigen exposure and tolerance breakdown. In SLE, apoptosis (particularly of T lymphocytes) is dysregulated in a Fas/Fas ligand-dependent pathway that is hyperexpressed and correlates with SLE activity and autoantibody concentrations. Abnormalities in the innate immune system, including that of phagocytes and complement, are also linked to impaired recognition and clearance of apoptotic bodies. Subsequently, abnormal prolonged exposure of nuclear antigens that undergo multiple alterations creates neoepitopes or uncovers hidden epitopes. The remaining apoptotic bodies then go through a process called secondary necrosis that leads to the release of even more nuclear material.

Neutrophil extracellular traps (NETs), a mechanism of defence against microorganisms, also play an important role in perpetuating the inflammation and exposure of double-stranded (ds) DNA because they are not promptly degraded in SLE. The lower degradation of NETs in SLE correlates with disease activity.

Antibody formation occurs, with pathogenic potential. The presence of hyperactive and hyper-responsive B and T cells and the prolonged exposure to nuclear antigens leads to the formation of autoantibodies directed against nuclear structures that are the immunological hallmark of SLE.

Autoantibodies have been reported to be found in the serum up to 10 years before symptom onset in 85% of SLE patients. Deposition of autoantibodies and complement with inflammation is identified in biopsies of various tissues from patients with SLE. The most widely studied antibody is anti-dsDNA, the serum concentration of which often correlates with disease activity. A rapid rise in anti-dsDNA antibody levels, especially if accompanied by a fall in C3, often predicts a clinical flare. Other antibodies have been identified in biopsies and serum from patients with SLE; the presence of each of these correlates with specific clinical manifestations (Table 1).

However, the pathogenic role of the autoantibodies in SLE is not entirely clear. They are found in kidney biopsies, where they bind directly to renal cells or via immune complexes with circulating nuclear components, which are then deposited in the renal glomerular basement membrane (leading to inflammation). However, the hypothesis of secondary binding to an already inflamed tissue is not excluded. In this case, the presence of autoantibodies would be a marker, not a cause, of inflammation. Another suggestion is that anti-dsDNA antibodies are binding to nucleosomes; in other words, dsDNA is linked to histones, and the histones (which are positively charged) are responsible for binding to negatively charged regions of renal tissue – the so-called histone bridge theory. Autoantibodies lead to the formation of immune complexes that directly induce B cells to produce more autoantibodies and enhance the Toll-like receptor–IFN1 pathway, which also stimulates B cells to differentiate into plasmablasts.

It is important to bear in mind that different autoantibodies have different specificities and sensitivities. Table 1 shows the autoantibodies that may be present in SLE. Anti-nuclear antibody (ANA) has 95% sensitivity but lacks specificity. It is present in up to 20% of the normal healthy population, as well as in other types of autoimmune disease, malignancies, infections and medication use. A higher ANA titre, especially 1:640 and above, is considered significant and might suggest the presence of an autoimmune condition. A homogenous pattern of ANA is seen in patients with SLE and linked to anti-dsDNA and anti-nucleosome antibodies, whereas a speckled pattern is linked to antibodies against extractable nuclear antigens.

Anti-Sm and anti-dsDNA are both rare in other rheumatic diseases and are highly specific, but have low and moderate sensitivity, respectively. Anti-Sm antibodies, which are three times as common in black than white patients, are associated with higher mortality and morbidity. Anti-dsDNA enzyme-linked immunoassay (ELISA) is used in clinical practice to monitor lupus activity, unlike with anti-Sm, whose levels do not correlate with disease activity. DNA *Crithidia* assay is another test that can be used in the diagnostic process; which is more specific than ELISA.

Classification criteria

The American College of Rheumatology (ACR) classification criteria, first published in 1971 and subsequently revised in 1982 and in 1997, have been the most widely used. In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) group published validated criteria that have higher sensitivity than the revised ACR criteria. They also have lower specificity (although not statistically significant), which might lead to the inclusion of more patients in clinical trials. The SLICC classification criteria addressed some changes reflecting a better understanding of the disease and its manifestations - mucocutaneous and neurological involvement were redefined, ANA, anti-dsDNA, anti-Sm and antiphospholipid antibodies were considered different criteria enabling each antibody to contribute to SLE classification, and low complement was added as a new criterion.

Nevertheless, the revised ACR and SLICC criteria may fail to identify patients at early stages of the disease, and a further attempt has been made recently to achieve a classification criteria that would enable patient with early SLE to be included in clinical studies and trials. Thus in 2019, the European League Against Rheumatism (EULAR) collaborated with the ACR to create a criteria set that has a slightly higher sensitivity than the ACR and higher specificity than the SLICC[2]. Unfortunately, it also excludes the possibility of SLE being diagnosed in the absence of a positive anti-nuclear antibody. This ACR/EULAR criteria consists of a cumulative weighted multicriteria system that classifies a patient with SLE when the score is ≥10 but only if the entry criteria (ANA positive at a titre of ≥1:80) is fulfilled (Figure 1). To address this disadvantage, further research using the three sets of criteria has been proposed for clinical practice[1].

Management

Clinical features

SLE has an unpredictable course. It progresses in acute flares and periods of remission, although there are probably long periods of subclinical inflammatory activity. It can affect virtually every organ and system in the body, and during the flares more than one organ is usually affected (Table 2). In mild forms, the joints and skin are the main organs affected. In moderate forms, other organs are involved, but it is severe disease, notably of the kidneys and heart, that can be life-threatening.

Renal involvement occurs in 30–40% of patients with SLE, usually early in the disease course. It has been shown that anti-dsDNA, anti-Sm, complement and anti-C1q antibodies are strongly associated with renal involvement. It is imperative that blood pressure measurement and urine analysis are performed as part of the clinical assessment of patients with SLE. Renal biopsy is performed to identify the presence of lupus nephritis (LN), which has six classes according to the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification: class I, minimal mesangial proliferative LN; class II, mesangial proliferative LN; class III, focal LN; class IV, diffuse LN; class V, membranous LN; and class VI, advanced sclerosis. A revision of this classification has been suggested and awaits validation. Besides glomerular involvement, tubulointerstitial lesions (e.g. interstitial fibrosis and tubular atrophy) can be observed and are associated with poorer outcomes. It is also important to be aware of other potential causes of renal impairment in SLE patients as a result of concurrent diseases or nephrotoxic drugs.

Neuropsychiatric SLE is highly diverse, comprising central and peripheral nervous system manifestations and focal to more diffuse syndromes. This diversity results in diagnostic difficulty, particularly because this can be present without abnormalities in the typical markers of active lupus such as anti-dsDNA and complement. Disruption of the blood–brain barrier has been thought to be important for the development of neuropsychiatric SLE. Headaches are a common neurological complaint in SLE patients but are not specific or linked to active disease. However, it is important to assess for the presence of red flag signs suggesting a subarachnoid haemorrhage, venous sinus thrombosis and meningitis. Reduction in cognitive function, ‘brain fog’ and depression are other common complaints.

Gastrointestinal symptoms are common in SLE, but are usually mild and related to infective causes or are an adverse effect of treatment for SLE. Gastrointestinal manifestations of SLE, which can result from gut vasculitis, can result in increased morbidity if not identified and treated. Lupus enteritis is a potentially fatal gastrointestinal manifestation, with symptoms varying from those of an acute abdomen to pseudo-obstruction or protein-losing enteropathy. Associations between SLE and autoimmune gastrointestinal diseases are rarely reported. A review by Alves et al. (see Further reading) reported that inflammatory bowel disease can present before or after the diagnosis of SLE, with a prevalence of 0.4–0.7% for ulcerative colitis and <0.4% for Crohn's disease. Primary biliary cirrhosis occurs in 0.3–2.4% of patients with SLE. Autoimmune hepatitis has been reported in 3–10% of patients with SLE, with a higher incidence in patients with juvenile SLE. Other autoimmune diseases can coexist with SLE; these include secondary Sjögren's syndrome, overlap syndromes with features of rheumatoid arthritis and scleroderma, hypothyroidism and antiphospholipid syndrome.

The prognosis of SLE has markedly improved in the last 50 years, with a current 5-year survival rate of >90%. This is mainly due to the result of advances in immunosuppressive therapy, dialysis and transplantation, and in general management, including antihypertensive drugs and statins. In addition, the recognition and management of co-morbidities, such as osteoporosis and cardiovascular disease, have improved. However, the mortality rate is still increased compared to the general population, with an all-cause mortality of approximately 2.6 times that of the general population.

In the last 40 years, it has been recognized that cardiovascular disease is a major cause of death in SLE, particularly later in the course of the disease. Classical cardiovascular risk factors contribute to this increased risk, notably smoking (20% of patients in most cohorts continue to smoke), hypertension and dyslipidaemia. In addition, the sustained inflammation in autoimmune diseases leads to accelerated atherosclerosis. Thromboembolic events are also more common in SLE.

Patients with SLE have been found to have an increased risk of certain malignancies. In a large multicentre international study by Bernatsky et al., SLE patients were found to be three times more likely to develop haematological malignancies, in particular, non-Hodgkin's lymphoma and leukaemia, and there is also a small increased risk of lung, thyroid and vulval cancers[3]. The pre-cancerous stage, cervical dysplasia, has been reported to have a higher incidence in patients with SLE, especially in those who have been treated with cyclophosphamide. This highlights the importance of SLE patients adhering to national cervical screening programmes. Interestingly, there is a lower risk of developing breast, endometrial and ovarian cancers in women, and prostate cancers in men.

Susceptibility to infections, the most common being respiratory tract infections, has been thought to be the result of an impaired immune response. This susceptibility is further compounded by increased lupus activity, hypocomplementemia, leukopenia, corticosteroid use (≥7.5 mg/day) and immunosuppressants such as cyclophosphamide. The mortality rate from infections in patients with SLE has been reported to be nearly five times that of the general population. In contrast, hydroxychloroquine may have a protective effect against infection.

It is now believed that the persistence of high mortality rates among SLE patients is related to their particular susceptibility to adverse outcomes. Identifying the most vulnerable patients can prevent the occurrence of complications and improve the overall morbidity and mortality in SLE. To capture this aspect, a new frailty index has been created using the SLICC inception cohort in order to stratify the vulnerability risk among SLE patients (see Further reading).

Pregnancy morbidity is higher in patients with SLE and includes miscarriages, intrauterine growth restriction and pre-term birth; the presence of LN and antiphospholipid syndrome further increase this risk. The risk of neonatal heart block is estimated to be 2% with anti-Ro antibody-positive mothers, increasing further to 15% in the next pregnancy if neonatal heart block was present in the previous pregnancy. Good control of the SLE for at least 4 months before conception optimizes pregnancy outcomes.

It is important to review the vaccination status in patients with SLE. In general, 'live' vaccinations for patients on immunosuppressants or >10 mg of prednisolone should be avoided. However, non-live vaccinations have been thought to be safe in SLE patients taking immunosuppressive drugs. It is advised that patients with SLE are given the appropriate immunizations, especially against pneumococcus, and the yearly influenza vaccine. In addition, in certain age groups, immunizations as per national vaccination schedules, such as the human papillomavirus and meningococcus vaccination, should be given. Passive immunization may also be considered in some cases, e.g. high-risk exposure to tetanus, especially among patients receiving B cell depleting agents.

Indices

Since the 1980s, new tools have been created to capture disease activity (as a global or individual organ/system score), damage and quality of life in patients with SLE. Standard measures of these aspects are critical when comparing different groups of patients and assessing the response to drugs. The correlation between indices measuring different aspects of the disease is poor, suggesting that they are complementary and should all be measured. The two most popular indices capturing disease activity are the British Isles Lupus Assessment Group (BILAG) index and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[4].

Clinical trials in SLE

Invariably, there are two kinds of clinical trials in SLE - firstly, those involving patients with LN, where the outcome measures and endpoints are tangible, reproducible and can be comparable between different studies (such as proteinuria, creatinine level, progression to end-stage renal disease). The other type of clinical trial involving non-renal SLE lacks these concrete endpoints, but are essential to perform as approximately 60-70% of SLE patients do not have renal disease. As an example, comparison of drug efficacy in different trials can be challenging if different disease activity scores were used as endpoints. To address this issue, composite scores have been created, the most widely used activity indices are the SLE Responder Index (SRI) and BILAG-Based Combined Lupus Assessment (BICLA). They combine the BILAG index, the SELENA-SLEDAI and Physician Global Assessment (PGA) in slightly different ways.

Treatment

The treatment of SLE depends on the organ and systems involved and the severity of disease, and can vary from topical medicines for skin disease and non-steroidal anti-inflammatory diseases for musculoskeletal disease to aggressive systemic immunosuppression. It is now clear that associated diseases such as osteoporosis and cardiovascular disease should be prevented and diagnosed and treated early. Osteoporosis is strongly associated with SLE, and the World Health Organization suggests regular dual X-ray absorptiometry for a correct diagnosis of osteoporosis, to determine the fracture risk and monitor the effect of treatment.

Patients with SLE should also be screened for the presence of cardiovascular risk factors and cardiovascular disease. Modifiable risk-factors such as hypertension and hyperlipidaemia should be identified and concurrently managed. The importance of smoking cessation should be emphasized for reduction of cardiovascular risk and may improve cutaneous lupus. Angiotensin-converting-

enzyme (ACE) inhibitors should be considered, not only for blood pressure control (aiming for a diastolic blood pressure of <80 mmHg), but also to reduce the level of proteinuria in patients with LN and progression towards end-stage renal disease.

SLE patients, especially those with cutaneous manifestations, should be advised to reduce exposure to strong sunlight and to use adequate sun protection (SPF 50+).

Corticosteroids

Corticosteroids modify genomic and non-genomic pathways, the latter being activated at higher dosages (prednisolone >30 mg/day), leading to immunosuppressive and anti-inflammatory effects. The dose and route of administration of these drugs varies according to the organ(s) affected and the severity of the disease; there are no guidelines describing the ideal regimen. In mild disease, there is usually a response to prednisolone 5–15 mg/day or equivalent, and a sparing agent or antimalarial can also be used. In life-threatening and organ-threatening disease, methylprednisolone is used as a pulsed intravenous therapy. Some patients do not respond sufficiently to corticosteroid agents, and in some manifestations of SLE, a combination with an immunosuppressive drug is more effective. Close monitoring for adverse effects, especially with high doses of corticosteroids, is mandatory.

Hydroxychloroquine

The immunomodulatory properties of this drug mean it can be used to treat articular and skin flares, protect against the effects of ultraviolet light, improve sicca symptoms, treat milder disease and give a more favourable cardiovascular profile in different ways (reducing cholesterol, risk of diabetes mellitus and risk of development of carotid plaque, and having antithrombotic properties).

In patients with renal disease, it also facilitates the response to mycophenolate mofetil (MMF), and the EULAR 2019 guidelines suggest that it should be given to every lupus patient with nephritis. It was also shown that it prevents damage in the kidneys and central nervous system and, probably as a result of all of this, reduces mortality.

Although hydroxychloroquine (HCQ) is generally a very safe drug, prescribers should be aware of the rare adverse effect of retinal toxicity and initiate appropriate ophthalmology surveillance for this. Weight-based prescribing is important (200–400 mg/day, not exceeding ≤5 mg/kg actual body weight per day) to avoid exposure to high drug doses, which increases the risk of retinal toxicity. The British Society of Ophthalmology guidelines (2020) https://www.rcophth.ac.uk/wp-content/uploads/2020/12/Hydroxychloroquine-and-Chloroquine-Retinopathy-Monitoring-Executive-Summary.pdfrecommend that there is no need to do a formal baseline ophthalmic assessment. These should commence after 5 years of treatment. The risk of ocular toxicity is low within the first 5 years of treatment and It must be borne in mind however, that there may be risk factors such as renal impairment, old age or concomitant medications such as tamoxifen which may necessitate earlier or more frequent ocular surveillance. Cardiotoxicity is a serious but very rare adverse effect, described in case reports.

Immunosuppressives

Other immunosuppressive drugs are used in severe manifestations of SLE. LN is the most common life-threatening manifestation and attempts to improve its outcome have been ongoing for decades.

National Institutes of Health (NIH) studies in the 1980s established that cyclophosphamide-containing regimens were more effective than corticosteroids alone when treating LN. Importantly, in 2002, the Euro-Lupus Nephritis randomized-controlled trial (RCT) demonstrated that a low-dose cyclophosphamide regimen was as effective as the high-dose NIH regimens and had fewer (although not statistically significant) adverse effects. The Euro-Lupus regimen is currently the preferred cyclophosphamide regimen. However, because cyclophosphamide is very toxic even in low-doses regimens and because a significant percentage of patients are still treatment-resistant, new drugs have been tested.

The Aspreva Lupus Management Study (ALMS) RCT showed that MMF is a good option for the induction phase because it is as effective as cyclophosphamide. It also has fewer adverse effects than cyclophosphamide and is more effective than azathioprine. Importantly, cyclophosphamide and MMF are contraindicated in pregnancy and breastfeeding, and therefore azathioprine, although inferior to MMF, is preferred during pregnancy and fertility preservation.

Cyclophosphamide has been used to treat severe neurological, gastrointestinal and pulmonary manifestations. MMF is also effective in refractory haematological and dermatological manifestations. In the ALMS trial, it was shown that cyclophosphamide and MMF are similarly effective in controlling extra-renal disease in patients with renal lupus. For neuropsychiatric lupus, there is a lack of evidence

concerning the best treatment option, but corticosteroids alone or in combination with cyclophosphamide or azathioprine are recommended; other drugs are used in refractory cases.

Calcineurin inhibitors (CNI), tacrolimus and ciclosporin, inhibit the production of cytokines and lymphocyte proliferation, especially of T helper cells. The use of CNI as a monotherapy or combined with MMF (multitarget therapy) was proved to have favourable outcomes in active LN. Current guidelines suggest the use of multitarget therapy as a second line therapy in case of nephrotic range proteinuria. Ciclosporin can be used as a corticosteroid-sparing drug in patients with normal renal function. Voclosporin, a novel cyclosporin analogue, has shown its superior renal efficacy compared to a placebo in a phase III RCT (AURORA) without significant adverse outcomes. It is not yet used in widespread clinical practice.

Biological therapy

To date, the most logical and widely used biological option in SLE has been B cell depletion achieved by direct B cell elimination or inhibition of B cell survival agents.

Belimumab is a human monoclonal IgG1 that binds to BLyS (also known as BAFF, B cell activating factor), an important B cell stimulator protein. In March 2011, belimumab became the first drug in 50 years to be approved by the Food and Drug Administration for the treatment of SLE, and it has subsequently obtained National Institute for Health and Care Excellence approval. The BLISS-76 and BLISS-52 RCTs showed belimumab's efficacy in reducing disease activity and preventing flares; this was particularly shown for mucocutaneous and musculoskeletal manifestations and in a subset of autoantibody-positive patients (ANA titre ≥1:80 and/or anti-dsDNA antibody concentration ≥30 IU/ml) with a low C3 concentration. Recently, belimumab has proved its efficacy in the treatment of active LN: In the BLISS-LN RCT of 448 patients, the primary efficacy renal response over two years was significantly higher among patients receiving belimumab plus standard therapy compared to those with standard therapy alone.[5]

Rituximab is a chimeric mouse/human monoclonal antibody against CD20 on the surface of pre-B cells maturing to memory B cells. The binding triggers apoptosis of peripheral B cells without avoiding the regeneration from stem cells. It is licensed for non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis and granulomatosis with polyangiitis. In the UK, rituximab is currently widely used off-licence to treat SLE, funded by NHS England.

In many open-label studies, rituximab has shown efficacy in treating different features, such as fatigue, skin, arthritis, serositis and renal disease, in SLE. It is safe and well tolerated when used either alone or in combination or with cyclophosphamide.

Rituximab's corticosteroid-sparing effect is of great importance. A study of 50 LN patients, at the time of diagnosis (and before oral steroids were given), who were treated with the RITUXILUP (steroid-avoiding) protocol using rituximab and MMF, also demonstrated efficacy despite the lack of concomitant oral corticosteroids.

Disappointingly, two RCTs, EXPLORER and LUNAR, failed to show benefit from adding rituximab to continuing immunosuppressive treatment in patients with extra-renal and renal lupus, respectively. Inadequate trial design almost certainly played a part, as patients with severe and refractory disease were excluded and a high dose of corticosteroids was maintained, obscuring the efficacy of rituximab and its corticosteroid-sparing effect.

Given the fact that autoreactive B cell production implies different molecular targets, a new approach associating rituximab and belimumab, is currently used off-label. A reverse translational study has shown that this association significantly reduced low, medium and high avidity anti-dsDNA while rituximab reduced only medium avidity antibodies. A phase III RCT is ongoing (The BLISS BELIEVE study) comparing the use of combination of rituximab and belimumab to belimumab alone (NCT03312907).

Another therapeutic approach is based on the fact that rituximab treatment may induce an upregulation of BAFF levels which have been associated with incomplete remission or subsequent lupus relapse. Theoretically, adding an anti-BAFF treatment can interfere with this upregulation and improve outcomes. The BEAT Lupus study is a phase III RCT assessing the efficacy and safety of belimumab following rituximab prescription (ISRCTN47873); It appears that rituximab (two 1g infusions) followed by monthly belimumab achieved its primary endpoint of a reduction in IgG anti-dsDNA antibody levels compared to rituximab plus placebo ($p<0.001$) [Ehrenstein MR, via personal communication]. A key secondary endpoint, time to first severe flare, was also achieved ($p=0.03$).

Obinutuzumab, a third-generation humanized anti-CD20 antibody, appears to be a promising treatment. It has shown better outcomes compared with rituximab in murine lupus models. A recent phase II RCT of Obinutuzumab in LN (NOBILITY) met its endpoints and a phase III RCT (REGENCY) is now recruiting (NCT04221477).

Atacicept (which blocks the B cell activating factors BLyS and APRIL) has shown promising results in both flare-prevention and active disease RCTs. In the APRIL-SLE Phase II/III RCT, atacicept 150 mg was shown to be associated with a reduced flare rate. Unfortunately, two fatal pulmonary infections led to the premature termination of the atacicept group in the trial (deaths in small numbers of SLE patients have been reported in every SLE RCT). Subsequently, the ADDRESS II RCT, comparing atacicept 75 mg and 150 mg with placebo in treating moderately active SLE, has shown atacicept to be efficacious at reducing disease activity as well as in flare prevention, with no increase in the risk of serious adverse events.

Anifrolumab is a human monoclonal antibody to type I IFN receptor. Results with Anifrolumab are intriguing - two phase III RCTs have been conducted, TULIP-1 and TULIP-2. The primary endpoint in TULIP-1 was SRI 4 and BICLA in TULIP-2. TULIP-1 failed to meet its endpoints whereas in TULIP-2, significant favourable outcomes were seen. In an expert review (see Further reading), this discordance can be attributed to inadequate trial design and should be addressed by further studies.

A variety of other monoclonal antibodies including TNFα blockers, the IL-6 receptor blocker tocilizumab and abatacept (which blocks the links between antigen-presenting cells and T cells) have also been used in relatively small numbers of patients with variable benefit. Eculizumab, a fully humanized IgG2/IgG4 monoclonal antibody against C5 has also undergone Phase I trial. No biological drug apart from belimumab has been approved in the UK for the treatment of SLE, and further data are needed to support their use. Many other approaches are at phase II or phase III stages at present, including attempts to block the Fc Gamma II receptor and the CD40 ligand, but these approaches are not yet approved for lupus.

Remission

The international initiative treat-to-target for SLE was established to provide recommendations to treat according to a target identified for each patient. ‘Remission of systemic symptoms and organ manifestations’ was named as one of the targets. Treatment of SLE can be aimed to treat active disease, towards a lupus low disease activity state to remission with treatment, with the ultimate aim of remission off treatment.

Studies on remission in SLE have used various definitions of remission, including absence of clinical and serological activity, serological activity but clinically quiescent, and whether these states are achieved on or off treatment. A UK study by Medina Quinones et al., (see Further reading) reported complete disease remission of at least 3 years in 14.5% of patients, while another study by Zen et al. (see Further reading) reported prolonged disease remission of at least 5 years in 37%.

Because of the lack of a consensus on the definition of remission, a large international task force on Definitions of Remission in SLE (DORIS) have published eight key statements (Figure 2) and three principles for defining remission to try to harmonize research efforts (see further reading). The presence or absence of treatment has to be distinguished when defining remission. Remission in SLE remains a controversial topic, but there is evidence of improved outcomes and reduced damage accrual in patients with prolonged remission and lupus low disease activity state.

Pathogenic autoantibodies in SLE					
Autoantibodies	**Prevalence in SLE (%)**	**Sensitivity in SLE (%)**	**Specificity in SLE (%)**	**Clinical manifestations**	**Other diseases**
Anti-nuclear antibody	>95	High	Low		Scleroderma, Sjögren's syndrome, rheumatoid arthritis, polymyositis, dermatomyositis, drug-induced lupus, infection, malignancy, drugs, other autoimmune diseases
Anti-dsDNA	70–80	Moderate	High	Renal, skin	Rare in other diseases
Anti-nucleosome	60–90	High	High	Renal, skin	Undifferentiated connective tissue disease, autoimmune hepatitis, scleroderma, Sjögren's syndrome
Anti-Ro/SSA	30–40	Moderate	Moderate	Sicca symptoms, renal, skin, fetal heart abnormalities, rash in newborn	Sjögren's syndrome, rheumatoid arthritis, polymyositis, scleroderma
Anti-La/SSB	15–20	Moderate	Moderate	Fetal heart abnormalities	Sjögren's syndrome
Anti-Sm	10–30	Low	High	Renal, neuropsychiatric, associations with higher mortality	Rare in other diseases
Anti-U1-RNP	25	Moderate	Low	Raynaud's phenomenon, lung, neuropsychiatric, musculoskeletal	Undifferentiated connective tissue disease, scleroderma, polymyositis, rheumatoid arthritis, Sjögren's syndrome
Anti-ribosomal P	10–40	Moderate	Moderate	Neuropsychiatric, hepatitis	
Anti-NMDA	33–50			Neuropsychiatric	Anti-NMDA receptor encephalitis
Anti-phospholipid	20–40	Low	Low	Thrombosis, pregnancy loss	Malignancy, infection, drugs
Anti-C1q	30–50	Low	Low	Renal	Hypocomplementaemic urticarial vasculitis, Sjögren's syndrome, rheumatoid vasculitis

Pathogenic autoantibodies in SLE					
Autoantibodies	**Prevalence in SLE (%)**	**Sensitivity in SLE (%)**	**Specificity in SLE (%)**	**Clinical manifestations**	**Other diseases**
Anti-histone	70–80	Low	Low	Drug-induced lupus	Scleroderma, rheumatoid arthritis, Sjögren's syndrome, mixed connective tissue disease, vasculitis, malignancy, liver disease

Adapted from Rahman A, Isenberg DA. Systemic lupus erythematosus. *N Engl J Med 2008.* **358:**931; and Lloyd P, Doaty S, Hahn B. Aetiopathogenesis of systemic lupus erythematosus. In: *Systemic Lupus Erythematosus*. Oxford, UK: Oxford University Press; 2016.[3]

Table 1. Pathogenic autoantibodies in systemic lupus erythematosus (SLE).

Cumulative prevalence of clinical features in SLE

Clinical feature	Prevalence (%)
Dermatological	
Alopecia	70
Oral ulceration	50
Butterfly malar rash	40
Purpuric lesions	40
Vasculitic skin lesions	40
Discoid lupus	20
Livedo reticularis	20
Erythematous maculopapular eruption	<5
Relapsing nodular non-suppurative panniculitis	<5
Musculoskeletal	
Arthralgia/arthritis	90
Myalgia	50
Tenosynovitis	20
Myositis	5
Cardiopulmonary	
Valvular dysfunction	55
Pleurisy	35
Pleural effusion	25
Pulmonary hypertension	0.5–20
Pericarditis	15
Myocarditis	<15
Conduction disturbance	10
Interstitial alveolitis/pneumonitis	1–12
Interstitial fibrosis	3–13
Shrinking lung syndrome	<1
Coronary vasculitis	rare
Gastrointestinal	
Abdominal pain	8–40
Nausea	15
Intestinal vasculitis	0.2–14
Vomiting	<10
Diarrhoea	<10
Lupus hepatitis	9
Lupus pancreatitis	<4
Lupus peritonitis/abdominal serositis	Rare
Acute lupus cholecystitis	Rare

Clinical feature	Prevalence (%)
Renal	
Proteinuria	60
Casts	30
Haematuria	10
Neuropsychiatric	
Central nervous system	
Cognitive dysfunction	27–80
Headache (migraine, benign intracranial hypertension)	21–50
Anxiety	20
Seizures	20
Depression	15
Cerebrovascular disease	15
Hemiplegia	10
Cranial nerve lesions	10
Psychosis	10
Acute confusional state	<10
Cerebellar ataxia	5
Myelopathy	1–3
Aseptic meningitis	0.4–3
Demyelinating syndrome	0.2–2
Chorea/movement disorder	1
Peripheral nervous system	
Polyneuropathy	2.8–28
Cranial neuropathy	1.5–7
Mononeuropathy	1–7
Myasthenia gravis	0.2–2
Acute inflammatory demyelinating polyradiculopathy	<1
Haematological	
Anaemia	
Chronic disease	75
Iron deficiency	30
Autoimmune haemolytic	3–15
Lymphopenia	75
Leucopenia	30–60
Thrombocytopenia	15–25
Ophthalmic	
Retinal disease	3–29
Keratoconjuncivitis sicca	25

Clinical feature	Prevalence (%)
Anterior/posterior uveitis	0.1–4.8
Optic neuropathy: neuritis, ischaemic neuropathy, papilloedemia	1
Orbital inflammation, myositis, proptosis	n/a
Keratitis	n/a
Episcleritis/scleritis	n/a

n/a; not available.
Adapted from Morrow, J. et al.. Systemic lupus erythematosus. In: Autoimmune Rheumatic Disease. 2nd ed. Oxford University Press. 1999. 4:p. 59.

Table 2. Cumulative prevalence of clinical features in systemic lupus erythematosus (SLE)

2019 EULAR/ACR classification system for SLE

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Figure taken from Aringer M, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019;78:1151-9

Figure 1. 2019 EULAR/ACR classification system for systematic lupus erythematosus (SLE). §Additional criteria items within the same domain will not be counted. *Note: In an assay with at least 90% specificity against relevant disease controls. *Anti-β2GPI = anti–β2-glycoprotein I; anti-dsDNA = anti–double-stranded DNA.*

Key Statements on remission in SLE (according to the DORIS group)

Eight Statements on remission in SLE
Remission is a desirable outcome for the patient with SLE.
Remission in SLE includes, at the very least, the absence of symptoms and signs of SLE.
Remission in SLE is not the same as a cure
Remission in SLE is not the same as low disease activity.
Remission is a state that, if sustained, is associated with a low likelihood of adverse outcome.
'Serological activity' in SLE generally refers to the presence of anti-DNA antibodies and/or hypocomplementemia.
Treatment with antimalarials does not preclude the patient from being considered to be in remission.
Treatment with moderate-dose or high-dose steroids does preclude the patient from being considered in remission.

Adapted from van Vollenhoven R, *et al*. A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). *Annals of the Rheumatic Diseases* 2017;**76:**554-561.

Figure 2. Key Statements on remission in SLE (according to the DORIS group)

KEY REFERENCES

1 Fanouriakis A, Tziolos N, Bertsias G, Boumpas DT. Update on the diagnosis and management of systemic lupus erythematosus. Ann Rheum Dis, 2021;80:14-25.

2 Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019;78:1151-9

3 Bernatsky S, Ramsey-Goldman R, Labrecque J, Joseph L, Boivin J-F, Petri M, et al. Cancer risk in systemic lupus: an updated international multi-centre cohort study. J Autoimmun.2013;42:130-5.

4 Arora S, Isenberg DA, Castrejon I. Measures of Adult Systemic Lupus Erythematosus: Disease Activity and Damage. Arthritis Care Res. 2020;72:27-46.

5 Furie R, Rovin BH, Houssiau F, Malvar A, Teng YKO, Contreras G, et al. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. N Engl J Med. 2020;383:1117-28.

FURTHER READING

Gatto M, Zen M, Ghirardello A, Bettio S, Bassi N, Iaccarino L, et al. Emerging and critical issues in the pathogenesis of lupus. Autoimmun Rev. 2013;12:523-36.

Gordon C, Isenberg D(eds). Systemic lupus erythematosus. Oxford Medical Libraries, Oxford Rheumatology Library. Oxford: Oxford University Press, 2016.

Alves SC, Fasano S, Isenberg DA. Autoimmune gastrointestinal complications in patients with systemic lupus erythematosus: case series and literature review. Lupus 2016; 25: 1509e19.

Legge A, Kirkland S, Rockwood K, Andreou P, Bae S-C, Gordon C, et al. Construction of a Frailty Index as a Novel Health Measure in Systemic Lupus Erythematosus. J Rheumatol. 2020;47:72-81.

Goulden B, Isenberg D. Anti-IFNαR Mabs for the treatment of systemic lupus erythematosus. Expert Opin Biol Ther. 2020:1-10.

Medina-Quinones CV, Ramos-Merino L, Ruiz-Sada P, et al. Analysis of ~ complete remission in systemic lupus erythematosus patients over a 32-year-period. Arthritis Care Res (Hoboken) 2016; 68: 981e7.

Zen M, Iaccarino L, Gatto M, et al. Prolonged remission in Caucasian patients with SLE: prevalence and outcomes. Ann Rheum Dis 2015; 74: 2117e22.

Van Vollenhoven R, Voskuyl A, Bertsias G, Aranow C, Aringer M, Arnaud L, et al. A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). Ann Rheum Dis. mars 2017;76:554-61.

Please can you submit 3 new self-assessment questions for your article

The outcome for patients with SLE over the past 30 years has:

A. Improved from 5% 15-year survival to 30% 15-year survival.
B. Remained much the same about 85% 15-year survival.
C. Worsened, now 20% 15-year survival.
D. Improved to 100% 5-year survival.

B is correct, the others are false

Which of the following statements about SLE is true?

A. 30% of SLE patients have one or more additional autoimmune disease.
B. Autoimmune liver disease occurs in approximately 30% of SLE patients.
C. Approximately 30% of SLE patients have lupus nephritis.
D. 30% of SLE patients are male.
E. 30% of SLE patients with nephritis go into renal failure.

A and C are correct

Which monoclonal antibodies are widely used in the treatment of SLE?

A. Tocilizumab
B. Etanercept
C. Anifrolumab
D. Rituximab
E. Belimumab

D and E are correct