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SYSTEMIC LUPUS ERYTHEMATOSUS – PAST, PRESENT AND EMERGING THERAPIES

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ABSTRACT

Background Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by immune dysregulation, autoantibody production, and immune complex-mediated tissue damage. Despite advances in disease management, SLE remains associated with substantial morbidity, increased mortality, and significant therapeutic challenges.

Objective This narrative review summarizes the current understanding of SLE epidemiology, pathogenesis, diagnosis, and treatment, with a particular focus on established therapeutic strategies and emerging treatment modalities.

Methods A comprehensive literature search was conducted using publicly available scientific databases. Clinical guidelines, systematic reviews, meta-analyses, and original research articles were selected based on their relevance to SLE pathogenesis, diagnosis, and treatment.

Results Current management of SLE aims to achieve remission or low disease activity through the use of hydroxychloroquine, glucocorticoids, conventional immunosuppressive agents, and targeted biologic therapies, including belimumab and anifrolumab. Improved understanding of SLE immunopathogenesis has facilitated the development of novel therapeutic approaches. Among these, hematopoietic stem cell transplantation and chimeric antigen receptor (CAR) T-cell therapy have demonstrated encouraging results in patients with severe or treatment-refractory disease. However, their widespread implementation is currently limited by safety concerns, treatment-related toxicity, high cost, limited clinical experience, and the absence of long-term efficacy and safety data.

Conclusions Although recent therapeutic advances have improved clinical outcomes in SLE, many patients continue to experience refractory disease and treatment-related complications. Emerging therapies offer the potential for more targeted and durable disease control, but further large-scale clinical studies with extended follow-up are required to establish their long-term efficacy, safety, and place in future treatment algorithms.

KEYWORDS

Systemic Lupus Erythematosus, Treatment, CAR T-cell, Biologic Therapy

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Introduction

Systemic Lupus Erythematosus (SLE) is a rare, chronic, inflammatory disease affecting multiple organs. The disease can affect virtually any organ, including the skin, joints, kidneys, cardiovascular system, and central nervous system, resulting in substantial morbidity and increased mortality,

Epidemiology

Globally, the incidence of SLE ranges from 1,5 to 11 cases per 100,000 person-years, while its prevalence varies between 13 and 7,7 cases per 100,000 individuals. Across all international regions, women are consistently more affected by SLE than men. Men are diagnosed at a later age than women. Black, Hispanic and Asian populations are more affected by SLE, exhibiting higher incidence and prevalence rates compared with white populations. Mortality rates among patients with SLE are two to three times higher than those observed in the general population. The most reported causes of death are infection, cardiovascular disease and renal disease, but not cancer. [1, 2]

Etiopathogenesis

The pathogenesis of SLE involves abnormal activation of both the innate and adaptive immune systems, leading to an immune response directed against nucleic acid-containing cellular particles. This process is characterized by the overproduction of antinuclear antibodies (ANAs), which recognize and bind to these self-antigens, including anti-Sm and anti-double-stranded DNA (anti-dsDNA) antibodies. In addition, patients may produce antiphospholipid (aPL) and anti-β2-glycoprotein I antibodies (anti-β2GPI), which are not classified as ANAs. These antibodies are produced by plasma cells and plasmablasts, which constitute the antibody-producing terminal stage of B-cell differentiation and play a crucial role in the inflammatory processes and tissue damage associated with SLE.

The pathogenesis of SLE is also driven by a loss of immune tolerance, resulting in the survival of self-reactive T and B lymphocytes. Impaired clearance of cellular debris and self-antigens promotes the formation of immune complexes (ICs) composed of nucleic acids, nucleic acid-binding proteins, and autoantibodies. These ICs deposit in tissues, triggering inflammation and tissue damage. Furthermore, IC-mediated activation of the immune system induces the production of pro-inflammatory cytokines, particularly interferon- α , thereby amplifying the inflammatory response and perpetuating disease progression. [3, 4]

In addition to autoantibody-mediated inflammation, dysregulation of the complement system is an important contributor to SLE pathogenesis. Activation of the complement system through the classical, alternative, or lectin pathways culminates in the formation of the membrane attack complex (MAC). In SLE, complement dysregulation contributes to defective clearance of ICs and apoptotic debris, as well as enhanced inflammation and tissue damage, thereby promoting disease development and progression. [5]

Type I interferons (IFNs), particularly IFN- α , are key mediators of SLE pathogenesis, as they serve as immunomodulators that bridge innate and adaptive immune responses. Alterations in nucleic acid metabolism can stimulate type I IFN production through the activation of cytosolic nucleic acid sensors, which play a critical role in SLE pathogenesis. Elevated circulating levels of type I IFNs have been reported in approximately 50% of patients, while an even larger proportion exhibit increased expression of type I IFN-responsive genes in peripheral blood cells, reflecting enhanced IFN signaling activity. [6-8] Environmental triggers, such as ultraviolet (UV) light exposure, can further enhance type I IFN responses at both local and systemic levels. [9]

Environmental factors play an important role in triggering SLE in genetically susceptible individuals. Factors such as UV radiation and certain drugs can induce DNA damage or modify DNA methylation, generating immunostimulatory self-nucleic acids that activate the immune system. Viral infections, particularly Epstein-Barr virus (EBV), have also been strongly associated with SLE development. EBV can promote type I IFN production, B-cell activation, and immune dysregulation, thereby contributing to autoimmunity. In addition, alterations in the gut microbiome may influence SLE pathogenesis. Increased intestinal permeability and translocation of microbial products can stimulate immune responses and promote autoantibody production through mechanisms such as molecular mimicry. [10]

Diagnosis

Clinical presentations of SLE differ considerably among patients and may involve multiple organ systems. The diagnosis of SLE remains challenging due to its clinical heterogeneity and the lack of universally accepted diagnostic criteria with both high sensitivity and specificity. The 1997 American College of Rheumatology (ACR) classification criteria were widely used for the classification of SLE and included 11 clinical and immunological criteria: non-erosive arthritis, serositis (pleuritis or pericarditis), malar rash, discoid rash, photosensitivity, oral ulcers, hematological disorder, renal disorder, neurological disorder, immunological abnormalities, and positive antinuclear antibodies (ANAs). To improve the classification of SLE, the criteria were revised in 2019 through a joint initiative of the European Alliance of Associations for Rheumatology (EULAR) and ACR. The updated criteria introduced ANA positivity as an obligatory entry criterion and implemented a weighted scoring system encompassing clinical and immunological manifestations. In addition, autoimmune hemolysis, non-scarring alopecia, fever and low complement levels (C3 and/or C4) were incorporated, whereas malar rash and photosensitivity were removed as individual criteria. Compared with the 1997 ACR criteria, the 2019 EULAR/ACR criteria demonstrated substantially improved sensitivity while maintaining a comparable specificity. Consequently, the revised criteria provide greater accuracy in the classification of SLE. Nevertheless, both classification systems may be less effective in identifying early diseases, as many clinical and immunological manifestations accumulate over time. The requirement for multiple criteria to be fulfilled can therefore make classification more straightforward in patients with established or advanced SLE. It is important to note that the ACR classification criteria encompass the most common manifestations of SLE but do not capture the full spectrum of disease presentations. To address some of these limitations, alternative classifications systems have been developed, including the Systemic Lupus International Collaborating Clinics (SLICC) criteria, which provide broader coverage of cutaneous and neuropsychiatric manifestations of SLE and may be more useful for early disease classification due to their higher sensitivity. [4, 11]

Table 1. 2019 EULAR/ACR Criteria for the Classification of Systemic Lupus Erythematosus

Clinical Criteria	Weight	Immunological Criteria	Weight
Constitutional Fever	2	Antiphospholipid antibodies Anti-cardiolipin antibodies OR Anti- β 2GPI antibodies OR Lupus anticoagulant	2
Hematologic Leukopenia	3	Complement proteins Low C3 OR low C4	3
Thrombocytopenia	4	Low C3 AND low C4	4
Autoimmune hemolysis	4		
Neuropsychiatric Delirium	2	SLE-specific antibodies Anti-dsDNA antibody OR Anti-Smith antibody	6
Psychosis	3		
Seizure	5		
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		

Patients are eligible for these criteria only if they have a positive ANA test $\geq 1:80$

SLE classification requires at least one clinical criterion and 10 points.

Methodology

A comprehensive literature search was conducted using publicly available scientific databases, including PubMed. Articles published between 1929 and 2026 were identified using combinations of the following keywords: “systemic lupus erythematosus”, “treatment”, “epidemiology”, “diagnosis”, “history”, “biologic therapy”, “CAR T-cell”, “guidelines”. Clinical guidelines, systematic reviews, meta-analyses, and original research articles were included. Publications were selected based on their relevance to article topic and their contribution to the current understanding of the field.

Results

History

For many years there was no effective treatment of SLE. In the 19th century, a variety of topical therapies, including salicylic acid and iodoform, were used to treat cutaneous lupus, although most were likely ineffective. Later, during the late 19th and early 20th centuries, lupus treatment expanded to include cauterization, X-ray therapy, topical radium salt applications, and UV phototherapy. It should be noted that the term lupus was historically used to describe a range of conditions that are now classified as distinct diseases.

The development of modern lupus therapy began with the introduction of antimalarial drugs, starting with quinine in 1894, followed by mepacrine and later hydroxychloroquine, whose efficacy was confirmed in the first randomized placebo-controlled trial in 1965. [12] Owing to their broad therapeutic benefits, antimalarials became a cornerstone of SLE treatment.

Subsequent therapeutic advances included limited trials of gold salts [13] and, more importantly, the introduction of cortisone and synthetic corticosteroids in the 1950s [14], which revolutionized the management

of inflammatory diseases and play an important role in SLE treatment till today. Topical corticosteroids also improved the treatment of cutaneous lupus manifestations.

Following the post-war development of immunosuppressive agents, cyclophosphamide demonstrated efficacy in SLE and was later validated in randomized clinical trials. [15] Other immunosuppressants, including azathioprine [16] and mycophenolate mofetil [17], were subsequently introduced and established through clinical studies, further expanding therapeutic options for lupus management.

At the end of the 20th century, the development of biologic and targeted therapies marked a new era in the treatment of SLE. ‘An antibody directed against the CD21’ called Rituximab was first introduced in SLE in 2001. Although major randomized trials did not meet their primary endpoints, registry data supported its clinical usefulness. [18, 19] The identification of elevated B lymphocyte stimulator (BlyS) levels in SLE led to development of belimumab, which demonstrated efficacy in phase III clinical trials [20] and became first approved biologic therapy for SLE.

Advances in understanding SLE pathophysiology also highlighted the central role of interferons, leading to the development of targeted therapies such as anifrolumab, a monoclonal antibody directed against type I interferon receptor. Proving its efficacy in the phase III TULIP program [21, 22], anifrolumab was registered by European Medicines Agency since 2022.

Current treatment recommendations

First European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of SLE were published in 2008. [23] Updated guidelines for management of SLE were released in 2019. [24] The most recent recommendations were published in 2023. Since the 2019 update, advances in SLE research and treatment have progressed rapidly. With more therapies currently in development and improvements in clinical trial design, SLE management is expected to continue advancing, likely requiring more frequent guideline updates in the future. [25]

Current management strategies for SLE focus on achieving a specific treatment goal, ideally remission according to the definition in DORIS criteria [26], or alternatively, a low disease activity state, such as the Lupus Low Disease Activity state (LLDAS). [27]

Based on the latest EULAR recommendations, hydroxychloroquine is advised for all patients, with a target dose at 5 mg/kg/day, however dosing should be tailored according to the patient’s risk of flare and retinal toxicity, with individuals at greater risk of retinal damage requiring more frequent ophthalmologic monitoring. Initial dose above 5 mg/kg/day may be considered, provided it does not exceed 400 mg/day, in certain patients, such as those with moderate to severe disease, however the dose should then be reduced to the recommended range once clinical improvement is achieved. [25]

Glucocorticoids can be used in the treatment of SLE according to the principle of using the lowest possible dose for the shortest possible duration. Dosing should be guided by the severity and type of organ involvement, with the goal of tapering to ≤ 5 mg/day prednisone equivalent (compared with ≤ 7.5 mg/day prednisone equivalent in the 2019 recommendations) and discontinuing treatment whenever possible. Recent recommendations emphasize minimizing glucocorticoid exposure because of its association with adverse outcomes, supporting the use of the lowest effective dose for the shortest duration as bridging therapy. Pulses of intravenous methylprednisolone up to 1000mg per day for 1-3 days can be considered in patients with moderate-to-severe disease. [25]

If the tapering of glucocorticoids ≤ 5 mg prednisone equivalent is impossible or patients do not respond to hydroxychloroquine use of immunosuppressive/immunomodulating drugs, such as azathioprine, methotrexate, mycophenolate or/and biological drugs such as belimumab or anifrolumab should be considered. Although approved biological therapies are considerably more expensive, their effectiveness has been demonstrated in high-quality randomized controlled trials, unlike conventional immunosuppressive agents, for which comparable evidence remains limited. [25]

Intravenous cyclophosphamide may be considered in severe organ-threatening or life-threatening SLE, because of its high efficacy, although its use is limited by gonadal toxicity. [25]

Rituximab is used off-label in SLE and is generally reserved for refractory disease (it may be introduced earlier in selected cases such as immune cytopenias). Although there is no universally accepted definition of refractory SLE, it generally refers to disease that fails to respond to multiple classes of immunosuppressive therapy. [25]

EULAR recommendations also include plasma exchange, hematopoietic stem cell transplantation, and experimental therapies, such as CAR T-cell therapy as potential options for patients who do not respond to the aforementioned therapies. [25]

Non-pharmacological strategies play an important role in improving long-term outcomes in SLE, as highlighted in EULAR recommendations. These include sun protection, smoking cessation, a healthy balanced diet, regular physical activity, and measures to support bone health. [28] Patients with SLE should particularly avoid excessive sun exposure because of photosensitivity, while smoking cessation is strongly encouraged, as smoking may reduce the effectiveness of antimalarial and biologic therapies in addition to its other harmful effects. [29, 30]

Current evidence suggests that nutritional interventions may provide supportive benefits in Systemic Lupus Erythematosus management. For example, vitamin D supplementation may reduce inflammation, and support disease control and bone health. Omega-3 fatty acids have been associated with lower disease activity, reduced inflammation and oxidative stress, improved lipid profile and endothelial function, and better quality of life. Vitamin E may help regulate antibody production, while a low glycemic-index diet may promote weight loss and reduce fatigue. Overall, these interventions were well tolerated, although larger, high-quality studies are still needed to confirm their long-term effects on disease activity, comorbidities, and quality of life. [31, 32]

Exercise and regular physical activity are among the most extensively studied non-pharmacological interventions in SLE and have been shown to improve patient outcomes. Physical activity may reduce fatigue and improve aerobic capacity. Exercise programs should always be individualized, taking into account the patient's overall health, cardiorespiratory status, potential contraindications, and personal preferences to ensure an appropriate balance between risks and benefits. Educating patients about the positive effects of physical activity, such as improved aforementioned reduced fatigue and improved aerobic capacity, but also improved muscle strength and limb function, may improve adherence to exercise programs. Physical activity is generally safe in SLE and this should be clearly communicated to healthcare providers and caregivers to reduce unnecessary barriers to participation. [28, 33]

Emerging Therapies

Hematopoietic Stem Cells (HSCs)

Hematopoietic Stem Cell Transplantation (HSCT) is a therapeutic intervention widely used in the treatment of hematological malignancies and other blood disorders. The procedure restores hematopoiesis through the infusion of healthy hematopoietic stem cells, which are capable of self-renewal and differentiation into all blood cell lineages, following the ablation or suppression of the recipient's bone marrow. The therapeutic rationale for HSCT in SLE is to reset the immune system by eliminating autoreactive immune cells through conditioning therapy and subsequently regenerating a self-tolerant hematopoietic and immune system from transplanted hematopoietic stem cells. HSCT can be classified into two main types: autologous transplantation, in which HSCs are collected from and subsequently reinfused into the recipient, and allogeneic transplantation, in which stem cells are obtained from a genetically compatible donor of the same species. Allogeneic and autologous HSCT differ substantially in both their therapeutic potential and risk profiles. Allogeneic HSCT may induce durable remission through graft-versus-autoimmunity effect, whereby donor immune cells eliminate autoreactive lymphocytes. However, its clinical use is limited by an increased risk of complications, particularly graft-versus-host disease (GVHD), as well as the requirement for prolonged immunosuppressive therapy. In contrast, autologous HSCT utilizes the patient's own stem cells, resulting in a lower risk of GVHD and transplant-related mortality. Nevertheless, in autoimmune diseases, disease relapse remains a concern owing to the potential reconstitution of autoreactive immune cell populations. The European Society for Blood and Marrow Transplantation (EBMT) currently recommends autologous HSCT utilizing peripheral blood stem cells as the standard transplantation strategy for autoimmune rheumatic diseases, including SLE. [34] A total of 215 autologous HSCT procedures for SLE were reported in the EBMT-ADWP Registry between 1994 and 2021. [35] Current EBMT recommendations consider HSCT for the treatment of SLE as "clinical option". However, they emphasize that, given the rapidly evolving landscape of highly effective alternative therapies, the indications and eligibility criteria for HSCT are subject to ongoing revision. [34] Although robust evidence is currently lacking to support HSCT as a standard treatment strategy in SLE, it may still be considered a viable option in selected patients. Larger trials with long-term follow-up, comparing HSCT with other therapies used in the treatment of SLE, are needed to resolve outstanding questions. [36]

Chimeric Antigen Receptor T Cells

Chimeric Antigen Receptor (CAR) T-cell therapy involves the genetic modification of autologous T lymphocytes to recognize and eliminate specific target cells. The therapeutic process comprises the collection of the patient's T cells by apheresis, followed by genetic engineering and ex vivo expansion, and culminates in the reinfusion of the modified T cells into the patient. The initial reported case described a 20-year-old woman with severe, treatment-refractory SLE who attained complete clinical and serological remission after receiving CAR T-cell therapy. [37] Building on these findings, the investigators extended their study to five patients, all of whom experienced remission of SLE clinical manifestations within three months following treatment. [38] Despite encouraging preliminary results, several challenges limit the widespread implementation of CAR T-cell therapy for SLE. B-cell depletion has emerged as a potentially curative strategy, however, profound impairment of antibody production may increase susceptibility to infectious complication. While CAR T-cell infusion itself may be associated with cytokine release syndrome and neurotoxicity. In addition, the high cost of the therapy, limited clinical experience, small patients cohorts, and the lack of long-term follow-up currently restrict its broader application. Further large-scale studies with extended follow-up are needed to establish the long-term efficacy and safety of CAR T-cell therapy in SLE.

Conclusions

Despite significant advances in the management of SLE, many patients continue to experience persistent disease activity, recurrent flares, treatment-related toxicity, and progressive organ damage. Although conventional immunosuppressive agents and recently approved biologic therapies have improved clinical outcomes, unmet therapeutic needs remain, particularly for patients with refractory disease. Emerging therapeutic strategies, including targeted biologics and cellular therapies such as CAR T-cell therapy, offer the potential for more precise and durable disease control. While early clinical data are encouraging, further large-scale studies with long-term follow-up are required to establish their efficacy, safety, and optimal integration into current treatment algorithms. Continued advances in the understanding of SLE immunopathogenesis are expected to drive the development of personalized therapeutic approaches and improve long-term patient outcomes.

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