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Update on systemic lupus erythematosus: A review

Abdurahman Alloghbi[1], Yousef Al Obaisi[2], Hussain Alkhurayb[2], Amal M Shawabka[3], and Fahad S. Alshehri[2,4]*

[1]Department of Oncology, College of Medicine, King Khalid University, Abha, Saudi Arabia

[2]Pathology and Clinical Laboratory Medicine Administration, Haematology and Immunology Division, King Fahad Medical City, Riyadh, Saudi Arabia

[3]Department of Clinical Science, College of Medicine, Palestine Polytechnic University, Hebron, Palestine

[4]Department of Pathology and Clinical Laboratory Medicine, Haematology Division, King Faisal Medical City for Southern Region, Abha, Saudi Arabia

Abstract

Systemic lupus erythematosus (SLE) is a complex autoimmune and idiopathic condition that affects connective tissues. It is characterized by the formation of autoantibodies, the accumulation of immune complexes, inflammation, and, ultimately, irreversible organ damage. It can affect individuals of various ages, ethnicities, and genders. Nonetheless, nearly 90% of newly diagnosed SLE patients are women of reproductive age. The early mortality associated with SLE is primarily due to significant disease activity. However, subsequent mortality is linked to chronic illness and the use of immunosuppressive agents. Despite extensive research, the precise etiology of SLE remains partially understood; however, its onset involves a complex interplay of genetic predispositions, environmental stimuli, hormonal factors, and immune system abnormalities. The predominant clinical signs include fatigue, fever, weight loss, arthritis, pericarditis, anemia, and pulmonary complications. Diagnosing SLE requires a combination of clinical evaluations and laboratory testing, including antinuclear antibodies and anti-double-stranded DNA antibodies, among others. Managing SLE patients involves various approaches and lifestyle recommendations, including avoiding direct or reflected sunlight. This article presents an updated review of the mortality and pathophysiology of SLE. We also elucidate the clinical manifestations and the primary diagnostic and therapeutic strategies for this condition.

Keywords: Systemic lupus erythematosus; Clinical manifestations; Mortality, Diagnosis; Antinuclear antibodies

***Corresponding author:**
Fahad S. Alshehri
(fasaalshehri@moh.gov.sa)

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1. Introduction

Systemic lupus erythematosus (SLE) is a multifaceted autoimmune and idiopathic disorder that affects the connective tissues.[1] It is characterized by a prolonged pattern of relapses and remissions, accompanied by various symptoms. It results in various diseases that can range from moderate to severe and potentially life-threatening.[2] The cause of SLE is believed to be influenced by multiple factors. This condition is marked

by the development of autoantibodies, accumulation of immune complexes, inflammation, and ultimately, irreversible organ damage.[3] SLE can impact individuals of all ages, ethnicities, and genders.[4] However, over 90% of newly diagnosed SLE patients are women in their reproductive years.[5] It involves the activation of both innate and adaptive immune responses. The interplay between genetic and environmental factors leads to various immunological changes, resulting in ongoing immune reactions against one's nucleic acids.[6] Tissue damage caused by autoantibodies or immune complex deposits can affect several organs and systems, including the kidneys, heart, blood vessels, central nervous system, skin, lungs, muscles, and joints.[7-10] This damage can lead to significant illness and an increased risk of death.[11]

During the late 1940s, nearly 40% of individuals diagnosed with SLE experienced mortality within 3 years after the initial manifestation of symptoms.[12] Subsequently, the survival rates of individuals with SLE have significantly increased to over 90% for 5- and 10-year periods.[13] Based on the nationwide mortality database, the mortality rate of SLE between the years 1968 and 2013 accounted for the underlying cause of death in a total of 50,249 individuals across the United States (US).[14] During the period from 1999 to 2013, there were an additional 12,463 deaths in which SLE was identified as a contributing factor.[14] In addition, in Germany, the incidence of SLE in 2002 was 36.7 cases/100,000 individuals, with a female-to-male ratio of 4:1.[15] It is linked to a mortality risk approximately 2 – 5 times higher than the general population's.[16] Early mortality, defined as death occurring within 1 year of diagnosis, is believed to be primarily caused by severe disease activity.[17]

On the other hand, later mortality is more often attributed to difficulties arising from long-standing disease and the use of immunosuppressive medications.[18] Both infection and increased atherosclerosis contribute to late mortality. Although there have been many improvements in diagnosing and treating SLE and its related comorbidities, this disease continues to cause substantial illness and death.[19]

Substantial evidence indicates a significant relationship between SLE and a deficiency in complement C1q.[20] This deficiency contributes to the activation of $CD8^+$ T cells in the SLE model.[20] Autoantibody-producing B cells and self-reactive T cells are known to significantly contribute to the development and progression of autoimmune diseases, including SLE.[21] The diagnosis of SLE can be supported by laboratory testing, although it is initially based on clinical signs.[22] Initially, it is advisable to conduct a screening laboratory test. An elevated erythrocyte sedimentation rate (ESR) indicates active SLE, although C-reactive protein (CRP) levels are typically within the normal range or only slightly increased.[23] The complete blood count test can detect thrombocytopenia, leukopenia, lymphopenia, and specific hematological alterations, including autoimmune hemolytic anemia (AIHA). Renal parameters should include serum creatinine measurements, urine function evaluation, and urinary sediment examination.[24] Antinuclear antibodies (ANA),[25] anti-double-stranded DNA (anti-dsDNA) antibodies,[26] anti-Sm antibodies,[27] and levels of C3 and C4[28] should be identified as indicators of SLE. The evaluation of SLE involves precise diagnosis, continuous monitoring of disease activity, assessment of long-term damage and morbidity, and determination of the patient's overall health condition.[29]

This paper will review SLE in-depth, including its epidemiological rate and pathogenesis. Furthermore, it will discuss its manifestation features and the diagnosis and treatment options.

2. SLE mortality rate and (Epidemiology in KSA)

SLE is a complex autoimmune condition that affects multiple organ systems and is more prevalent in women, with a ratio of 9 females to 1 male. The disease often manifests during childbearing age and presents a significant public health issue due to its chronic nature and potential to cause considerable organ damage and increased mortality. Globally, the prevalence of SLE varies significantly based on geographic and ethnic factors, ranging from 20 to 150 cases/100,000 population. In North America and Europe, the prevalence is generally higher, typically within the range of 20 – 70 cases/100,000. In contrast, Asian and African populations are believed to have even greater incidence rates.

In Saudi Arabia, the exact prevalence of SLE is less well-documented compared to other regions. However, recent studies indicate a rising trend in the diagnosis of autoimmune diseases, including SLE. While the specific prevalence of SLE in Saudi Arabia is not fully established, the general burden of chronic autoimmune and inflammatory diseases in the country mirrors global trends. A regional study conducted at King Khalid University Hospital in Riyadh reported that the incidence of SLE in the Saudi population was estimated at 19.28/100,000 people,[30] with a higher frequency among younger women.

Mortality rates linked to SLE are significantly affected by the progression of the disease and its complications, especially concerning renal, cardiovascular, and infectious causes. In Saudi Arabia, while mortality data specifically linked to SLE is sparse, international studies suggest

that SLE patients have a 2 to 3 times higher risk of death compared to the general population, with cardiovascular disease (CVD) and lupus nephritis being primary contributors to mortality. Lupus nephritis, a major complication of SLE that affects the kidneys, is particularly common in Middle Eastern populations, including Saudi Arabia. Studies show that 30% to 60% of SLE patients in the region may develop nephritis, which significantly worsens long-term outcomes.[31]

CVD is a significant cause of death among SLE patients. In Saudi Arabia, where the overall burden of CVD is already high – with 37% of all deaths from non-communicable diseases linked to cardiovascular complications,[32] SLE patients face an increased risk. A global study found that individuals with SLE are 10 times more likely to suffer from premature atherosclerosis, heart attacks, and strokes compared to the general population. This risk is exacerbated by the high prevalence of associated conditions, such as hypertension, diabetes, and obesity within the Saudi population.

Because of its long-term impacts, SLE is considered a significant obstacle to achieving optimal health care standards. According to the World Health Organization, stroke mortality rates in the Kingdom of Saudi Arabia range from 55 to 95/100,000, whereas ischemic heart disease mortality rates range from 191 to 541/100,000.[33] While SLE may not be included in these figures, they do indicate a troubling trend in both SLE-related and non-SLE public health disorders, which significantly elevate the overall level of illness in the community.

Another factor contributing to SLE-related mortality in Saudi Arabia is the relatively late diagnosis and limited access to specialized care. Early intervention and comprehensive disease management are critical for improving outcomes; however, many patients may present with advanced disease due to delays in diagnosis, particularly in rural areas where healthcare resources are scarcer. The severity of the issue in the kingdom is further compounded by the high prevalence of obesity and low levels of physical activity, which are major risk factors for the SLE.[34]

3. Pathogenesis of SLE

SLE is a complex autoimmune disease characterized by the abnormal production of autoantibodies that target nuclear antigens. This results in widespread tissue inflammation and damage, often affecting multiple organs. While the exact cause of SLE remains not fully understood, its development involves a complex interaction between genetic factors, environmental triggers, hormonal influences, and dysregulation of the immune system. Genetically, susceptibility to SLE is significantly influenced by polymorphisms in key immune regulatory genes, particularly within the human leukocyte antigen (HLA) region, including HLA-DR2 and HLA-DR3, which are critically involved in antigen presentation. Mutations in genes encoding complement components (*e.g.*, C1q, C2, and C4) that are essential for the clearance of immune complexes and apoptotic cells further contribute to a pathogenic milieu.[35] In addition, non-HLA genes also play a critical role in disrupting immune tolerance and promoting autoimmunity in SLE. For example, genes involved in toll-like receptor (TLR) signaling pathways, such as *TLR7* and *TLR9*, as well as genes regulating B-cell receptor signaling, such as *BLK* and *BANK1*, contribute to the breakdown of immune regulation.[36] This genetic predisposition is exacerbated by environmental triggers, with ultraviolet (UV) radiation being a prominent factor that induces cell damage and the release of nuclear antigens, facilitating autoantibody production.[37] Infections, particularly with Epstein-Barr virus (EBV), have also been linked to SLE pathogenesis. Studies suggest that molecular mimicry – where EBV antigens resemble the body's own nuclear antigens – may lead to the production of harmful autoantibodies.[38] In addition, hormonal influences, especially estrogen, help explain why SLE is more common in women. Estrogen is believed to enhance B-cell survival, increase autoantibody production, and promote the expression of pro-inflammatory cytokines, all of which exacerbate the autoimmune response.[39] Together, these genetic, environmental, and hormonal factors create a perfect storm that drives the development and progression of SLE.

A major breakdown in immune regulation is central to the pathogenesis of SLE, leading to the production of a wide range of autoantibodies, particularly ANAs. These antibodies target components of the cell nucleus, such as dsDNA, histones, and ribonucleoproteins. This aberrant antibody production is precipitated by defective clearance of apoptotic cells and immune complexes, resulting in the persistent presence of nuclear antigens in the extracellular milieu. Dendritic cells play a key role in this regard by picking up these antigens and presenting them to T-cells, which then activate and help autoreactive B-cells.[40] This chain of events leads to the formation of germinal centers in secondary lymphoid organs, where B-cells undergo somatic hypermutation and class-switch recombination, ultimately churning out high-affinity autoantibodies. A critical part of this process involves TLRs, especially TLR7 and TLR9, which are activated by nucleic acids. This triggers signaling pathways, such as nuclear factor kappa B and interferon regulatory factors, leading to the production of type I interferons (IFNs).[41] Type I IFNs, particularly IFN-α, are

central to SLE. They help autoreactive B-cells survive, promote monocytes to differentiate into dendritic cells, and boost the expression of MHC class II molecules, which ramps up antigen presentation.[42] The increased activity of IFN-inducible genes, known as the "IFN signature," is a hallmark of SLE and is closely tied to disease severity.[43]

In addition to B-cell dysregulation, T-cell abnormalities are also critical in the pathogenesis of SLE. Regulatory T cells (Tregs), which normally keep autoimmune responses in check, are often reduced in number or do not function appropriately in SLE patients.[44] Making matters worse, there is an increase in T-helper 17 (Th17) cells, which produce the inflammatory cytokine interleukin (IL)-17. This contributes to the chronic inflammation that is a hallmark of SLE.[45] The imbalance between Tregs and Th17 cells further disrupts the body's ability to maintain self-tolerance, allowing the autoimmune response to continue unabated. Furthermore, the chronic activation of the immune system in SLE leads to widespread tissue damage and organ dysfunction, with the kidneys, skin, joints, and central nervous system being particularly susceptible. Advances in understanding the underlying mechanisms of SLE have paved the way for targeted therapies to modulate the immune response, such as B-cell depletion strategies and IFN inhibitors. However, the heterogeneous nature of the disease poses ongoing challenges in developing universally effective treatments.[46] The pathogenesis of SLE, therefore, represents a complex interplay of genetic, environmental, hormonal, and immunological factors, each contributing to the initiation and perpetuation of the autoimmune process.

4. The clinical manifestations of SLE

Fatigue, fever, and weight loss are common in SLE. Fatigue affects 80 – 100% of patients and is often associated with depression, sleep disturbances, and fibromyalgia.[47] Fever occurs in over 50% of patients, but it is usually challenging to distinguish lupus-related fever from other causes, such as infection or drug reactions. Lupus-related fever typically responds to non-steroidal anti-inflammatory drugs, acetaminophen, or glucocorticoids, whereas fever due to infection may not.[48] Weight changes are frequent and may result from SLE itself or its treatment; for example, glucocorticoid use may lead to weight gain, while decreased appetite can cause weight loss (Figure 1).

4.1. Arthritis and arthralgias

Over 90% of SLE patients experience arthritis or arthralgias. The arthritis is often migratory, polyarticular, and symmetrical, affecting multiple joints without causing joint erosion or deformity, unlike rheumatoid arthritis.[49]

4.2. Mucocutaneous involvement

Skin and mucous membrane lesions are common. The facial "butterfly rash," a malar rash over the cheeks and nose, is a hallmark of SLE and is often triggered by sun exposure. Some patients may develop discoid lesions, which can lead to scarring. Photosensitivity is a frequent characteristic. Oral and nasal ulcers are usually painless, and non-scarring alopecia is common.[50]

4.3. Cardiac and vascular involvement

Pericarditis is a common cardiac manifestation of SLE, affecting about 25% of patients. Other cardiac issues include myocarditis, an increased risk of coronary artery disease, and the potential for valvular disease due to Libman-Sacks endocarditis.[50] Raynaud phenomenon occurs in up to 50% of patients, presenting as cold-induced acral pallor followed by cyanosis.[51] Vasculitis occurs in 11 – 36% of patients, often manifesting as cutaneous lesions, although larger vessels can also be involved.[52]

4.4. Thromboembolic disease

Thromboembolic events, including arterial and venous thrombi, complicate SLE, especially in patients with antiphospholipid antibodies. In one study, 11% of patients experienced arterial and 5% experienced venous events over a median follow-up of 6.3 years.[53]

4.5. Kidney involvement

Lupus nephritis occurs in about 50% of patients and is a significant cause of morbidity and mortality. It can present as asymptomatic hematuria or more severe conditions, such as nephrotic syndrome and rapidly progressive glomerulonephritis.[54]

4.6. Gastrointestinal involvement

Gastrointestinal symptoms occur in 40% of patients and are often caused by medications or infections. Other SLE-related gastrointestinal issues can include esophagitis, pancreatitis, and mesenteric vasculitis.[55]

4.7. Pulmonary involvement

Pulmonary manifestations include pleuritis, pneumonitis, interstitial lung disease, and pulmonary hypertension. Immunosuppressive therapy increases the risk of pulmonary infections.[56]

4.8. Neurologic and neuropsychiatric involvement

Neurologic and psychiatric manifestations are diverse, ranging from seizures and strokes to cognitive dysfunction and psychosis. Antiphospholipid antibodies and lupus anticoagulants can increase the risk of thromboembolic events, leading to neurologic complications.[56]

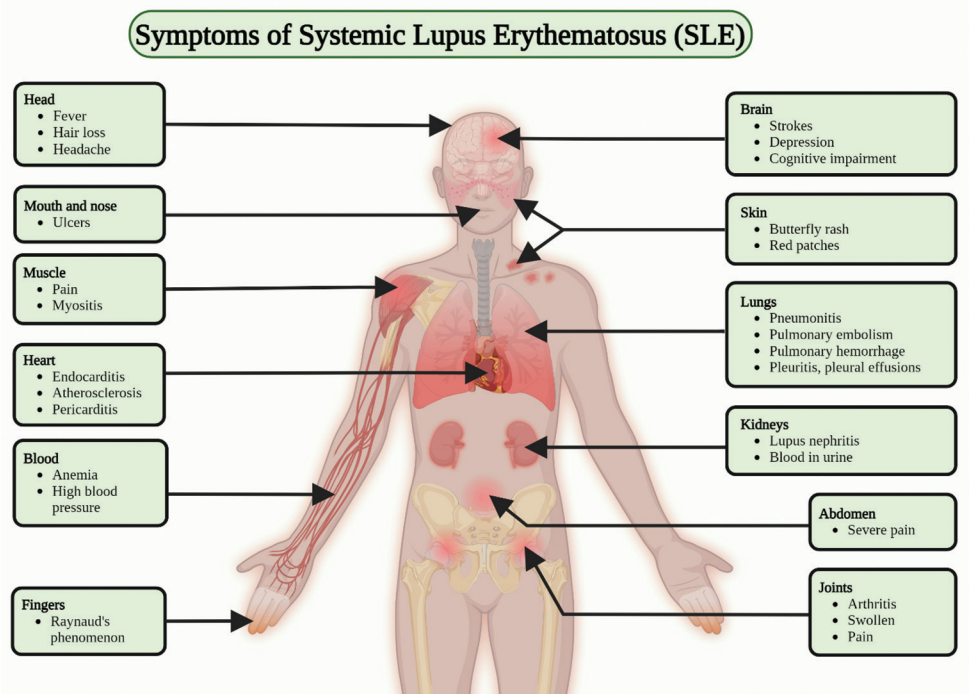

Figure 1. Symptoms of systemic lupus erythematosus. The disease exhibits a broad range of recognized clinical symptoms. The primary symptoms encompass fever, malaise, arthralgia, myalgia, headache, and diminished appetite and weight. The most prevalent symptoms in new instances or recurring active systemic lupus erythematosus include nonspecific fatigue, fever, arthralgia, and weight fluctuations. These symptoms may resemble other autoimmune disorders, viral diseases, and endocrine dysfunctions.

4.9. Hematologic abnormalities

SLE commonly affects all blood cell lines. Anemia due to chronic disease is common among SLE patients. Leukopenia, particularly lymphopenia, occurs in about 50% of patients and correlates with active disease.[57] Thrombocytopenia, though less common, can be severe and may require treatment. Lymph node enlargement and splenomegaly may also occur in association with active disease.

4.10. Ophthalmologic involvement

Keratoconjunctivitis sicca, often related to secondary Sjögren's syndrome, is SLE's most common eye manifestation.[58] Retinal vasculopathy can present as cotton wool spots. Other ophthalmologic manifestations include optic neuropathy, episcleritis, and glaucoma, which can be related to corticosteroid use.

4.11. Other conditions and complications

Hereditary angioedema and other complement deficiencies, such as C1, C2, and C4 deficiencies, can be associated with SLE.[59] Antiphospholipid syndrome is present in 40% of patients with SLE but does not always progress to the full syndrome.[60] SLE patients also have a higher prevalence of fibromyalgia, osteonecrosis, and osteoporosis.[61] SLE is also associated with an increased prevalence of autoimmune thyroid disease, such as Hashimoto's thyroiditis, and can co-occur with other autoimmune diseases, such as myasthenia gravis. A familial predisposition to autoimmune diseases is often observed in SLE patients.[62]

5. Diagnosis of SLE

Diagnosing SLE is a complex process that relies on a combination of clinical and laboratory criteria.[63] The clinical manifestations will cover the clinical criteria, and in this section, we will describe the intricate laboratory tests used to diagnose SLE. Around 99 % of individuals diagnosed with SLE have an increased ANA titer, which indicates the presence of autoimmunity.[64] Although several laboratory abnormalities are associated with this condition, the non-specific positive ANA can be detected in 5 – 20% of the general population.[65]

It is essential to note that many individuals can exhibit an initial negative ANA titer during the disease. This underscores the fact that the ANA test alone cannot diagnose SLE. A study conducted with 15 worldwide laboratories revealed that ANA tests provide positive results in a significant portion of individuals in the general population when diluted at 1:40, and in a smaller but still

notable percentage when diluted at 1:160.[66] The prevalence of positive ANA tests remained consistent across all age groups up to 60 years, the maximum age considered in the study.[66] If SLE is not present, the most frequent cause for a positive ANA test is the existence of another connective tissue disease such as Sjögren's syndrome (affecting 68% of patients), scleroderma (40 – 75% prevalence), rheumatoid arthritis (25 – 50% prevalence), and juvenile rheumatoid arthritis (16% prevalence). In addition, ANA testing may also be positive in individuals diagnosed with fibromyalgia.[67]

Anti-dsDNA antibodies (70 – 98% prevalence) are detectable in patients with positive ANA and a homogeneous fluorescence pattern.[68] The outcomes of the enzyme-linked immunosorbent assay require validation using radioimmunoassay (RIA) or the *Crithidia luciliae* immunofluorescence test.[69] Moreover, anti-Sm antibodies are specific indicators for SLE, with a prevalence between 14% and 40%.[70] In addition to causing venous and arterial thromboses and recurrent fetal loss, antiphospholipid antibodies can also be detected in 50% of lupus cases.[71] Evaluation is conducted by identifying antibodies to cardiolipin or beta-2 glycoprotein 1, or by the presence of a lupus anticoagulant, indicated by extended clotting times that remain uncorrected *in vitro* by mixing investigations.[72] Furthermore, C3 and C4 must be evaluated as indicators of complement intake or deficiency.[73] The evolution of SLE is characterized by exacerbations and remissions. Nonetheless, the ANA titer does not correlate with disease activity. Conversely, complement factor levels typically decrease concurrently with an elevation in anti-dsDNA antibodies, often happening months before disease onset. Consequently, it is essential to routinely monitor the progression of the disease, particularly regarding renal involvement.[74]

A screening laboratory test is recommended for the diagnosis of SLE. A high ESR indicates active SLE, but CRP levels are often normal or only slightly elevated.[75] A complete blood count analysis may reveal thrombocytopenia, leukopenia, and lymphopenia, along with features of AIHA. Renal function test criteria should include serum creatinine, urine analysis, and sediment examination.[76]

6. Management of SLE

6.1. Photoprotection

Exposure to UV light can exacerbate systemic manifestations of SLE. Patients are advised to avoid direct or reflected sunlight and other sources of UV light, such as fluorescent and halogen lights.[77] Sunscreens with both UV-A and UV-B protection and SPF ≥55 are recommended.

6.2. Hydroxychloroquine

Hydroxychloroquine is recommended for all patients with SLE. The typical dose is 5 mg/kg/day, with a maximum of 400 mg daily. It can be administered once or twice daily. Hydroxychloroquine has been sh

own to reduce overall mortality and improve survival.[78] Studies also indicate a reduction in disease flares, with one trial showing a flare rate of 73% in patients on placebo versus 35% in those continuing hydroxychloroquine.[79] Benefits extend to reduced symptoms, such as fatigue and joint pain, and it lowers the risk of thrombotic events, organ damage, and cancer.[80] Hydroxychloroquine is generally well tolerated, though rare side effects include retinopathy and QTc interval prolongation, especially in patients on other QT-prolonging drugs.[80]

6.3. Escalation of therapy

Moderate disease involves significant but non-organ-threatening manifestations such as fatigue, rashes, or hematologic issues. Hydroxychloroquine and short-term prednisone (5 – 15 mg/day) are often prescribed. Immunosuppressants, such as azathioprine, methotrexate, or mycophenolate mofetil may be added for patients who require more aggressive treatment.[81]

Organ-threatening SLE, such as lupus nephritis or central nervous system involvement, requires aggressive treatment. Patients are treated with high doses of glucocorticoids (oral prednisone 1–2 mg/kg/day or intravenous methylprednisolone 0.5 – 1 g/day for 3 days). Immunosuppressants, such as mycophenolate, cyclophosphamide, or rituximab are often added as glucocorticoid-sparing agents. Depending on the treatment, hospitalization may be required.[81]

6.4. Anifrolumab

Anifrolumab is a monoclonal antibody targeting the type I IFN receptor and is approved for patients with moderate to severe SLE, excluding those with severe lupus nephritis or neuropsychiatric SLE. It blocks cytokines, such as IFN-α, which are elevated in many patients with SLE. Anifrolumab shows particular promise in treating skin and joint manifestations.[82]

6.5. Belimumab

Belimumab, a monoclonal antibody that inhibits B cell activation by blocking the BLyS protein, is combined with other therapies. It typically takes 3 – 6 months to take full effect, so it is often combined with faster-acting medications, such as methotrexate in severe cases. Belimumab is FDA-approved and is a component of some regimens for lupus nephritis. A meta-analysis of six trials confirmed its efficacy for SLE.[83]

6.6. Rituximab

Rituximab, a B-cell-depleting antibody, is used in patients who have not responded to standard treatments. While its role remains uncertain, observational studies suggest it is effective for treating SLE and lupus nephritis.[84]

6.7. Investigational approaches

The investigational approach involves cellular therapies such as atacicept, anti-IL-6 receptor inhibitors, iberdomide, low-dose IL-2, obinutuzumab, daratumumab, anti-CD40 monoclonal antibody, litifilimab, and teclistamab. Details on ongoing clinical trials for SLE treatments in the US are available at www.clinicaltrials.gov.

7. Conclusion and future perspectives

SLE is a complex autoimmune disorder with significant global health implications. Its multifactorial etiology, involving genetic, environmental, and hormonal factors, leads to immune dysregulation and widespread organ damage. Despite advancements in understanding its pathogenesis, early diagnosis and effective management remain critical for improving patient outcomes. Although mortality rates have declined over the years, SLE continues to contribute to higher morbidity and mortality, particularly due to complications such as lupus nephritis and CVD. In regions, such as Saudi Arabia, where healthcare disparities and delayed diagnoses are common, SLE presents a substantial public health challenge.

The future of SLE management appears promising, with ongoing research exploring novel therapies, including cytokine inhibitors, cellular therapies, and personalized medicine approaches. Advances in biomarker discovery and the integration of artificial intelligence in disease monitoring have the potential to enhance early diagnosis and improve treatment precision. In addition, addressing gaps in healthcare access, particularly in underserved populations, will be crucial for improving global outcomes. Collaborative efforts among researchers, clinicians, and policymakers are essential for advancing SLE care, reducing its burden, and ultimately enhancing the quality of life for patients worldwide.

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Conflict of interest

The authors declare that they have no competing interests.

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Conceptualization: Abdurahman Alloghbi, Fahad S. Alshehri
Writing – original draft: All authors
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