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Systemic Lupus Erythematosus: New Diagnostic and Therapeutic Approaches

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Abstract

Systemic lupus erythematosus (SLE) is a devastating autoimmune disease that can result in substantial morbidity and mortality. Diagnosis and treatment of SLE are clinical challenges. Patient presentation and response to therapy are heterogeneous because of the complex immune dysregulation that results in SLE disease pathogenesis. An intricate interplay between genetic risk and skewing of adaptive and innate immune system responses leads to overproduction of type I interferons and other cytokines, complement activation, immune-complex deposition, and ultimately inflammation and tissue damage. Here, we review the classification criteria as well as standard and emerging diagnostic tools available to identify patients with SLE. We then focus on medical management, including novel therapeutics, nonpharmacologic interventions, and comorbidity management.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease with a varying clinical course and prognosis. Signs and symptoms of SLE can be subtle or robust, affect a single organ system or several, and change over time, making it a difficult disease to diagnose. Typical manifestations include skin rashes, including the malar "butterfly rash," arthritis, pleurisy and serositis, alopecia, and lupus nephritis. Frustratingly for clinicians and patients alike, response to treatment can be variable and difficult to predict. This clinical heterogeneity likely stems from the complex immune dysregulation that results in SLE disease pathogenesis. On a cellular level, this process is driven by interactions between the adaptive and innate immune systems that lead to upregulation of cytokines, complement activation, immune-complex deposition, and ultimately inflammation and tissue damage (1). In this article, we review the classification criteria and diagnostic tools available and then focus on medical management, including standard and novel therapeutics, nonpharmacologic interventions, and comorbidity management.

DIAGNOSTICS

Early diagnosis of SLE is crucial to prevent flares and resultant tissue damage. Importantly, the road to SLE starts before clinical disease. Autoantibodies have been found in serum of SLE patients approximately 3–9 years prior to diagnosis (2). Antinuclear antibody (ANA), anti-Ro, anti-La, and antiphospholipid antibodies are the earliest present in serum, and accrual of new autoantibody subtypes typically stops after disease onset (2).

Corrigendum >

ANA testing is now widely available, and this has improved the lag time to diagnosis of SLE; however, there is still considerable delay to diagnosis. A UK study found that in the 5 years prior to diagnosis, patients with SLE saw their primary care provider twice as many times as patients without SLE for symptoms including arthritis, rash, fatigue, serositis, fever, and others (3). Delays in diagnosis may contribute to racial disparities in disease outcome, as Black and Hispanic patients frequently present with more severe manifestations at the time of diagnosis (4).

Autoantibody Testing

ANAs are a group of autoantibodies that bind to various nuclear and cytoplasmic antigens (5). ANA is a sensitive biomarker for evaluation of suspected ANA-associated rheumatic diseases, most commonly SLE, and ANA detection is usually a requirement for entering into clinical trials for SLE (6). It is not useful for monitoring of disease activity (7). There are three primary assays for ANA testing: enzyme immunoassay, multiplex immunoassay, and indirect immunofluorescence assay on HEp-2 cells, the latter being the gold standard (6, 7).

Up to 25% of healthy patients can be ANA positive, limiting the screening test's specificity (8, 9). Most patients who are ANA positive never develop rheumatic disease (6). ANA positivity is more common among females and certain ethnic and racial groups, including African Americans (8, 10). Many healthy individuals with positive ANA have antibodies directed at the dense fine speckles 70 (DFS70) antigen (11), and anti-DFS70 antibodies are exceedingly rare in patients with suspected ANA-associated rheumatic diseases (12).

The extractable nuclear antigen panel tests for specific autoantibodies that react with components of the cell nucleus, revealing 2–11 different autoantibodies that have diagnostic and prognostic implications (5). Separate from extractable nuclear antigen testing, anti-dsDNA (double-stranded DNA) testing is highly specific for SLE, and antibody levels correlate with disease activity, particularly lupus nephritis (reviewed in 13). The European Autoimmunity Standardization Initiative has standardized morphologic features of various patterns (7) that have specific antigen and disease correlates (14) (**Table 1**).

Table 1 Outline of antinuclear antibody patterns and associated disease manifestations

Antinuclear antibody pattern	Associated antigen targets	Clinical disease correlate
Homogeneous	dsDNA, histones, chromatin	SLE, drug-induced SLE, JIA, chronic autoimmune hepatitis
Dense fine speckled	DFS70	Healthy and other non-SARD conditions
Centromere	CENP-B (centromere)	Limited cutaneous SSc, PBC
Fine speckled	SS-A/Ro, SS-B/La, Mi-2, TIF1γ, Ku	SjS, SLE, SCLE, neonatal lupus erythematosus, congenital heart block, DM, SSc, SSc-AIM overlap
Coarse speckled	Sm, RNP, U1RNP, RNA-polymerase III	SLE, SSc, MCTD, SSc-AIM overlap, UCTD
Nucleolar	Th/To, PM/Scl, U3RNP, RNA-polymerase I	SSc, SSc-AIM overlap, Raynaud's, SjS, cancer

Abbreviations: AIM, autoimmune myositis; DM, dermatomyositis; JIA, juvenile idiopathic arthritis; MCTD, mixed connective tissue disease; PBC, primary biliary cirrhosis; SARD, systemic autoimmune rheumatic disease; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus; SjS, Sjogren's syndrome; SSc, scleroderma; UCTD, undifferentiated connective tissue disease.

2019 EULAR/ACR Classification Criteria

Prior to 2019, there were two major classification criteria for SLE: the 1997 American College of Rheumatology (ACR) criteria and the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria. In order to maintain the specificity of the 1997 ACR criteria but increase the sensitivity of the SLICC criteria, the 2019 European Alliance of Associations for Rheumatology (EULAR)/ACR classification criteria for SLE were developed for research purposes (15). ANA ≥ 1:80 had a 98% sensitivity rate for diagnosis of SLE and was added as an entry requirement for the criteria. Differential weighting of criteria on a points system was used with 10 points indicating classification of SLE. Additionally, the caveat that criteria are only to be counted toward SLE if no other explanation exists was included. The 2019 criteria have been validated in adult and pediatric populations with sensitivities of 92% and 89%, respectively (16, 17).

Cell-bound Complement Testing

The newly developed multianalyte assay panel, commercially called the AVISE test (Exogen Diagnostics), performs a two-tiered test that employs cell-bound complement activation products (CB-CAPs) as biomarkers for diagnosis and disease activity (18). The test measures autoantibodies, erythrocyte-bound C4d, and B cell–bound C4d to assist in diagnosing SLE (18). CB-CAPs have higher sensitivity than standard complement and anti-dsDNA measurements alone for adult and pediatric SLE (19, 20) and predict progression from probable SLE to classifiable SLE by ACR criteria (21). Additionally, abnormalities of CB-CAPs can predict higher SLE severity index scores in patients with otherwise normal complement (22). A recent study of 161 patients found that CB-CAPs testing increased physician confidence in SLE diagnosis and increased frequency of early treatment with hydroxychloroquine (HCQ) (18).

Interferon Testing

Type I and type II interferons are upregulated before classifiable SLE develops, although the data to support these findings are limited by small studies (23, 24). Functional assays for blood testing are not yet commercially available but may be soon. Interferon testing remains a valuable research tool but has not yet proven viable as a biomarker in clinical practice.

ESTABLISHED TREATMENTS

Standard-of-care treatment of all SLE patients utilizes antimalarial therapy, typically HCQ, unless there is a contraindication to this medication (25). Antimalarials work to reduce antigen loading in the lysosome and also inhibit interferon activation by nucleic acids (reviewed in 26). HCQ is generally well tolerated and has been shown to lower the risk of disease flares (27), improve life expectancy (28), decrease thrombosis risk (29), and have positive effects on skin disease (30) and musculoskeletal manifestations of SLE. Importantly, early use of HCQ may be beneficial as it can reverse inflammatory cytokine and interferon changes in patients with incomplete SLE (31, 32). Use of HCQ during pregnancy also lowers the risk of premature birth (33) and fetal heart block in anti-Ro-positive mothers (34). There are data to support the use of other antimalarial medications such as chloroquine and quinacrine in SLE, but a higher rate of retinal toxicity (for chloroquine) and difficulty with access (for quinacrine) limit their widespread use (25). Side effects of HCQ use can include gastrointestinal distress and, more rarely, retinal toxicity and cardiomyopathy. Retinal toxicity can be limited through proper dosing (goal of 5 mg/kg/day) and through annual screening after the first 5 years on HCQ using advanced techniques such as optical coherence tomography (35). Monitoring HCQ blood levels may also have utility to identify patients at higher risk of retinal toxicity (36).

Glucocorticoids are traditionally used as a fast-acting way to gain control over disease activity. Dosage depends on the severity of disease, with 5–10 mg prednisone equivalent usually sufficient for mild manifestations. More severe disease can require higher dosing: up to 0.5–1 mg/kg prednisone equivalent with or without initial pulse intravenous (i.v.) methylprednisolone (37) for lupus nephritis, severe hematologic involvement, or central nervous system disease. Limiting steroid dosing to only what is essential and tapering whenever possible are desirable, as steroid use correlates strongly with damage accumulation over time in patients (38, 39).

Beyond antimalarials, the choice of additional treatments for SLE patients depends on the disease manifestations of the patient. **Table 2** summarizes the 2019 EULAR recommendations for

Table 2 Summary of 2019 EULAR recommendations for management of SLE[a]

	Mild	Moderate	Severe	Lupus nephritis
Definition	Constitutional symptoms Mild arthritis Rash ≤9% BSA Platelets 50–100 × 10^3 mm^3 SLEDAI ≤ 6 BILAG C or ≤1 BILAG B manifestation	RA-like arthritis Rash 9–18% BSA Cutaneous vasculitis ≤18% BSA Platelets 20–50 × 10^3 mm^3 Serositis SLEDAI 7–12 ≥2 BILAG B manifestations	Major organ threatening disease (cerebritis, myelitis, pneumonitis, mesenteric vasculitis) Platelets <20 × 10^3 mm^3 TTP-like disease or acute hemophagocytic syndrome SLEDAI > 12 ≥1 BILAG A manifestation	Class III, IV, V
First-line treatment	HCQ GC Skin: topical GC, CNI	HCQ GC MTX AZA MMF CNI	HCQ GC MMF CYC	HCQ GC MMF CYC
Refractory disease treatment	MTX AZA	BEL Anifrolumab	Anifrolumab RTX	BEL CNI/VSC

[a]Table based on recommendations in Reference 25 and drug label indications.

Abbreviations: AZA, azathioprine; BEL, belimumab; BILAG, British Isles Lupus Assessment Group; BSA, body surface area; CNI, calcineurin inhibitors; CYC, cyclophosphamide; GC, glucocorticoids; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; TTP, thrombotic thrombocytopenic purpura; VSC, voclosporin.

management of SLE (25). No therapies are approved by the US Food and Drug Administration (FDA) specifically for cutaneous SLE indications, so management of skin disease is based on expert opinion. Therapies such as topical steroids and topical calcineurin inhibitors, dapsone, methotrexate, lenalidomide, or mycophenolate mofetil (MMF) can be used (40). For arthritis, methotrexate (41), leflunomide (42), and MMF (43) may all offer benefit and allow for steroid dose reduction. Methotrexate has also been shown to generally ameliorate global SLE disease activity (41). Azathioprine is often used to reduce global SLE disease activity as well (25). Cyclophosphamide (CYC) therapy is usually reserved for organ-threatening manifestations such as central nervous system involvement or lupus nephritis.

Prior to recent advances (see below), lupus nephritis therapy had remained unchanged for a decade. The mainstay was CYC, used orally in the 1970s and then primarily through i.v. pulse therapy (0.5–1.0 g/m^2) in the 1980s (44). A second protocol for CYC dosing, termed Euro-lupus, in which the patient receives six 500 mg i.v. CYC doses 2 weeks apart, was shown to be equally effective in achieving renal remission compared to higher-dose pulse CYC (45) and now is the preferred initial choice for CYC use in most patients. After trials were criticized for providing data on only European (predominantly Caucasian) patients, subsequent trials using Euro-lupus dosing have also shown equal response rates in patients of color (46). A study completed in 2009 demonstrated that a target dose of 3 g/day MMF and i.v. pulse CYC achieved equal efficacy in terms of renal response rate, with no differences in adverse events (47). Thus, MMF has also become a standard option for lupus nephritis therapy.

While monotherapy with MMF or CYC is still considered standard of care, options for dual therapy and targeted therapies have recently been FDA approved (**Figure 1**). Belimumab (BEL) (see below for details) in combination with MMF or CYC may increase the chance of a partial or complete renal response over MMF or CYC alone (48) and is now FDA approved for this indication. In addition, use of a calcineurin inhibitor in combination with MMF may provide better renal response rates. This has been shown for tacrolimus (49) and also voclosporin (VSC), which received FDA labeling for lupus nephritis in 2021 (50) (see below). Tacrolimus may also have benefit in lupus nephritis as a monotherapy, but further studies need to be completed before this is implemented as standard practice (51).

Recent Therapeutic Advances

Belimumab. BEL is a recombinant, fully human monoclonal antibody (mAb) that blocks the binding of soluble B lymphocyte stimulator to its receptor on B cells, thus decreasing B cell survival, differentiation, and activation. It was the first biologic to be FDA approved for SLE and is available as an i.v. infusion or a subcutaneous injection.

Four large double-blinded phase III randomized controlled trials (RCTs) demonstrated efficacy of BEL (52–55) in patients with active disease on background standard-of-care therapy. Improvements included response on composite indices, reduction of flares, and reduction of steroid exposure (52–54). A recent review also found efficacy of BEL and no indication of increased harm in treated patients (56), and a 6-year follow-up study of Belimumab in Subjects with Systemic Lupus Erythematosus (BLISS-76) patients found long-term, meaningful improvements in fatigue and health-related quality-of-life outcomes among BEL-treated patients (57). One caveat is that patients with organ-threatening disease were excluded from the trials.

More recently, BEL was evaluated for treatment of lupus nephritis in a phase III double-blinded RCT, which showed improved primary efficacy renal response and complete renal response at week 104 in BEL-treated patients compared to placebo and lower risk of renal-related event or death in the BEL group (58).

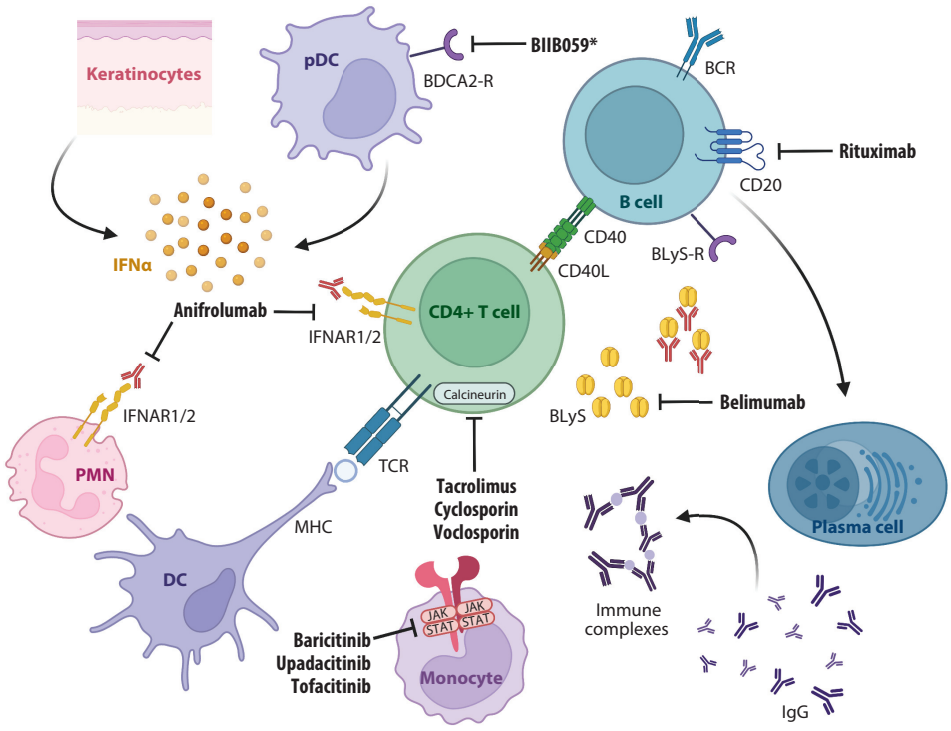

Figure 1

Summary of specific targets of recently approved and investigational SLE therapeutics. Abbreviations: BCR, B cell receptor; BDCA2, blood dendritic cell antigen 2; BDCA2-R, BDCA2 receptor; BLyS, B lymphocyte stimulator; BLyS-R, BLyS receptor; DC, dendritic cell; IFNα, interferon α; IFNAR1/2, interferon α receptor 1/2; IgG, immunoglobulin G; MHC, major histocompatability complex; pDC, plasmacytoid dendritic cell; PMN, polymorphonuclear cell; SLE, systemic lupus erythematosus; TCR, T cell receptor. *Identifies investigational product. Figure adapted from images created with BioRender.com.

Rituximab. Rituximab (RTX) is a chimeric mAb that targets CD20, a transmembrane protein on all B cells except pro-B cells and plasma cells, which results in cytotoxicity and B cell depletion. Several case series and retrospective studies have shown improvement in SLE parameters, including lupus nephritis, with RTX treatment (59, 60). RTX efficacy was studied in nonrenal SLE with moderate to severe disease activity on standard-of-care background therapy, but the study did not meet its primary or secondary endpoints (61). Subgroup analysis did show higher rates of major and partial clinical responses among African American and Hispanic patients than in the trial as a whole. Subsequently, the phase III RCT LUNAR set out to study RTX in SLE patients with class III or IV lupus nephritis (62). Although the study did not meet primary or secondary endpoints, there were more partial responders in the RTX-treated group than in the placebo group (31% versus 15%), and no patients required CYC rescue therapy in the RTX group (compared to 8 patients in the placebo group). Despite the failure of RTX to show efficacy in RCT data, clinicians still use it, particularly in refractory patients or SLE-associated hematologic disease, often with excellent results.

Anifrolumab. Anifrolumab is a human mAb targeting the type I interferon receptor subunit 1 that inhibits signaling of all type I interferons and is given by i.v. infusion (63). It received FDA approval

for treatment of SLE in 2021. A phase II RCT found that anifrolumab reduced disease activity in patients with moderate to severe SLE (64); however, the first phase III RCT, TULIP-1, missed the primary endpoint of SLE responder index-4 (65). Several secondary endpoints, including the British Isles Lupus Assessment Group–based Composite Lupus Assessment (BICLA), showed favorable response. Subsequently, a second phase III RCT, TULIP-2, was pursued with BICLA as the primary endpoint (66). This study showed significant reduction in disease activity in patients with moderate to severe SLE (66). Pooled data from TULIP-1 and TULIP-2 showed reduction in flares, including those arising from steroid taper (67). Anifrolumab will likely be a useful tool in the SLE treatment armamentarium for patients with moderate to severe disease activity, especially in the skin, who are unable to tolerate or do not respond to conventional therapies; however, real-world efficacy data are pending.

Voclosporin. VSC is an oral calcineurin inhibitor in the same drug class as tacrolimus and cyclosporin. VSC was approved in January 2021 by the FDA for treatment of active lupus nephritis in combination with background immunosuppressive agents (68). Two pivotal RCTs have shown improved renal response rate and reduced proteinuria when VSC was combined with MMF and steroids, compared to MMF and steroids alone (50, 69). Preliminary interim data from a 2-year extension study have shown sustained reductions in proteinuria and no change in renal function after up to 30 months VSC exposure (70); additional data will be published at the conclusion of the study.

Emerging therapies. Ongoing research is examining novel interventions to benefit SLE patients. Inhibition of various immune-related kinases, including JAK1 and TYK2, has shown promise, and larger RCTs are ongoing (71). Blockade of specific cell types like plasmacytoid dendritic cells has also shown early promise (72). Studies are investigating strategies to increase regulatory T cells through use of low-dose IL-2 and IL-2-like molecules (reviewed in 73). There is great hope that the next 10–20 years of research will be transformative for SLE management as new pathologic pathways are discovered and therapies developed.

NONPHARMACOLOGIC INTERVENTIONS

Vitamin D Supplementation

Vitamin D deficiency and insufficiency are prevalent among SLE patients and associated with sun avoidance (74). Vitamin D deficiency is correlated with higher disease activity, higher levels of fatigue, and increased risk of thrombosis in SLE patients (74–80). In lupus nephritis, vitamin D supplementation may reduce proteinuria and slow kidney damage progression (79). The recommended target level of 25(OH) vitamin D is 40 ng/mL, as higher levels did not show added therapeutic benefit (79). Vitamin D supplementation is well tolerated (76), and levels should be routinely tested to ensure absorption (81).

Dietary Modifications

Dysbiosis of the gut microbiome in SLE likely has a role in disease generation and activity but needs further research. Several studies comparing diverse SLE human populations to healthy controls have shown a decreased ratio of Firmicutes to Bacteroidetes (82, 83), and several studies using lupus-prone mice have shown that dysbiosis or particular skewing of commensal organisms worsens autoimmune manifestations (84, 85). In one study, antibiotic-induced changes in gut microbiota resulted in decreased systemic autoimmunity and improved renal pathology in the murine lupus model (86).

Despite this evidence of dysbiosis in SLE, the interactions of diet and microbiome require further study to justify evidence-based recommendations on factors like probiotics and diet for SLE patients. Further, while there is no agreed-upon "lupus diet," several dietary modifications may have beneficial effects. In one cross-sectional study, a Mediterranean diet decreased disease severity and cardiovascular risk in SLE patients (87). It has also been noted that higher dietary intake of omega-3 fatty acids and lower omega-6:omega-3 ratios were favorably associated with patient-reported outcomes in SLE and sleep quality (88).

Avoiding Ultraviolet Light

Ultraviolet (UV) light exposure can induce flares of both systemic and cutaneous SLE (89, 90). Although the exact mechanisms of UV-induced autoimmunity remain poorly understood, evidence suggests that generation of reactive oxygen species, increased DNA damage, increased antigen exposure, production of inflammatory mediators including type I interferons, and increased inflammatory cell recruitment are involved (91). Protection from UV exposure with broad-spectrum sunscreens is strongly recommended (92); sun protection factor (SPF) 30 or higher improves protection. Other methods of photoprotection include shade seeking, sun avoidance, hats, sunglasses, long sleeves, and long pants (93). Education regarding photoprotection should be emphasized.

Limiting Glucocorticoid Exposure

Glucocorticoids provide rapid suppression of the immune system in SLE flares but cause toxicity (94). The goal for glucocorticoid use is to reduce the dose to $\leq$7.5 mg daily as quickly as possible and maintain the lowest dose necessary (25). Short-term glucocorticoid complications include obesity, hypertension, type 2 diabetes, susceptibility to infection, and irreversible damage including avascular necrosis and stroke (94). Long-term consequences include cataracts, osteoporotic fractures, and cardiovascular disease (94). Damage accrual is dependent on time and dose (95, 96). One SLE cohort study found that 80% of organ damage was possibly or definitely related to glucocorticoid exposure over the 15-year study period (96).

Recent trials have suggested that limiting cumulative glucocorticoid exposure may not negatively affect outcomes. In a pilot study, 50 patients with active lupus nephritis were given RTX and MMF, two doses of i.v. methylprednisolone 500 mg, and no oral steroids (RITUXILUP). After 12 months, 53% achieved complete remission, which is comparable to the results of prior studies with conventional oral steroid use (97). The recent phase III RCT of VSC used starting doses of prednisone 25 mg/day, suggesting that efficacy is not harmed by lower-dose steroid regimens (50). Further randomized trials are needed to determine if low-dose steroid regimens are as effective as conventional therapy.

Comorbidity Management

Cardiovascular disease and infections account for the majority of SLE-associated mortality (98). Cardiovascular risk factors, including hypertension and type 2 diabetes, are more common among SLE patients, and resistant hypertension is nearly twice as likely in SLE patients compared to controls (99). Health maintenance examination and prevention of complications related to SLE disease and treatment are essential in providing quality care. Management includes maintaining up-to-date vaccination status; routine age-appropriate malignancy screening; hypertension, diabetes, and hyperlipidemia screening and management; and education regarding self-management strategies and healthy lifestyle.

CONCLUSION

SLE is a multifactorial autoimmune disease that can affect nearly every organ in the body. In the past 50 years, we have moved from chronic steroids and high-dose chemotherapeutic regimens to targeted biologic therapy. Disease control and mortality from SLE have improved over the years (100), but there is still work to be done. Healthcare disparities, systemic racism (101), and lack of efficient and affordable access to newer medications (102) all contribute to suboptimal outcomes in SLE patients. Effective management strategies will need to synergize precision therapies and social determinants of health to make the greatest impact on patients' lives.

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