10.48047/jocaaa.2024.33.06.148

Current and Emerging Strategies in the Management of Systemic Lupus Erythematosus: An Integrative Review

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Received: 13 March 2024, **Accepted:** 17 April 2024, **Published:** 20 May 2024

ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a prototypic chronic autoimmune disease characterized by immune dysregulation, multiorgan involvement, and heterogeneous clinical manifestations. Despite major advances in our understanding of its pathogenesis, the management of SLE remains challenging due to its relapsing–remitting course, unpredictable flares, and variable long-term outcomes. Corticosteroids, antimalarials, and immunosuppressants have long served as the foundation of therapy, yet their toxicities and incomplete disease control underscore the need for safer and more targeted treatments. The therapeutic landscape has expanded significantly over the past decade with the approval of biologics such as belimumab and anifrolumab, which specifically target B-cell survival and type I interferon pathways. These agents have shifted the paradigm toward mechanism-driven treatment and offer steroid-sparing benefits in selected patients. Meanwhile, conventional agents such as mycophenolate mofetil and cyclophosphamide remain indispensable, particularly in severe manifestations like lupus nephritis. The challenge now lies in integrating new therapies with established regimens to optimize outcomes while minimizing cumulative damage. Management also requires a tailored approach to organ involvement. Advances in lupus nephritis treatment emphasize combination regimens and early intervention to preserve renal function. Neuropsychiatric and cutaneous manifestations demand individualized strategies, often necessitating both systemic and local therapies. Beyond pharmacological interventions, lifestyle optimization, vaccination, and psychosocial support form critical adjuncts to improve quality of life and reduce comorbidity burden.

Personalized medicine is emerging as a cornerstone in SLE care, with increasing emphasis on biomarkers, pharmacogenomics, and precision approaches that may predict treatment response and disease trajectory. Despite these advances, unmet needs persist, including limited access to novel drugs, gaps in clinical trial inclusivity, and the lack of robust predictors of long-term outcomes. This review provides an integrative overview of current and emerging strategies in the management of SLE, highlighting conventional therapies, biologics, organ-specific care, glucocorticoid minimization, and non-pharmacological interventions. It further explores the evolving role of personalized medicine and identifies ongoing challenges that shape the future direction of SLE management. Together, these insights underscore the importance of individualized, evidence-based, and holistic approaches in improving patient outcomes.

10.48047/jocaaa.2024.33.06.148

Keywords: Emerging Strategies, Management, Systemic Lupus Erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by the production of autoantibodies, immune complex deposition, and widespread inflammation. The global prevalence of SLE ranges from 20 to 150 cases per 100,000 population, with higher incidence in women and certain ethnic groups, particularly those of African, Asian, and Hispanic descent [1]. The disease exhibits a heterogeneous clinical spectrum, affecting organs such as the kidneys, skin, central nervous system, cardiovascular system, and hematological compartments. This heterogeneity complicates both diagnosis and management, demanding a nuanced and individualized therapeutic approach.

Over the past several decades, significant progress has been made in understanding the immunopathogenesis of SLE, leading to the development of new diagnostic tools and therapeutic agents. Historically, treatment relied heavily on corticosteroids and broad-spectrum immunosuppressants, which remain essential but are associated with substantial toxicity and long-term damage [2]. With the advent of biologics and targeted therapies, clinicians now have access to more refined strategies that address specific immunological pathways, representing a paradigm shift in disease management.

Despite these advances, challenges remain. Many patients continue to experience flares, progressive organ damage, and treatment-related complications, highlighting the limitations of current strategies [3]. Furthermore, disparities in access to novel treatments, the unpredictable disease course, and the lack of reliable biomarkers for predicting therapeutic response remain critical gaps in care. These issues underscore the need for integrative approaches that combine established therapies with novel agents while incorporating non-pharmacological strategies to optimize outcomes.

The aim of this review is to provide a comprehensive and integrative overview of current and emerging strategies for managing SLE. It explores the role of conventional agents, biologics, and precision medicine while highlighting organ-specific approaches, glucocorticoid minimization, and supportive measures. By addressing both established and novel interventions, this review seeks to illuminate current best practices, identify persisting challenges, and propose directions for future research and clinical application. In doing so, it emphasizes the importance of individualized, evidence-based, and holistic management in improving the lives of patients living with SLE [4].

Conventional Management Strategies

Corticosteroids

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Corticosteroids have long been the cornerstone of SLE management due to their potent anti-inflammatory and immunosuppressive effects. They are effective in rapidly controlling disease activity, particularly during acute flares, and are often used as bridging therapy while other immunosuppressants or biologics take effect [5]. However, prolonged use is associated with significant adverse effects, including osteoporosis, diabetes, hypertension, cardiovascular disease, and increased infection risk. Moreover, long-term glucocorticoid exposure is a key contributor to irreversible organ damage in SLE patients, prompting a strong emphasis on steroid-sparing regimens in modern practice [6]. Strategies such as early tapering, the use of pulsed intravenous methylprednisolone for severe flares, and the combination with immunosuppressants or biologics aim to minimize toxicity while maintaining disease control [7].

Antimalarials

Hydroxychloroquine (HCQ) is a cornerstone of therapy for virtually all patients with SLE, unless contraindicated. Its benefits extend beyond disease activity control, including reduction in flare frequency, prevention of thrombotic events, and improvement in long-term survival [8]. HCQ also exerts favorable effects on lipid profiles and glucose metabolism, further contributing to cardiovascular risk reduction in SLE [9]. The 2019 EULAR recommendations strongly endorse HCQ for all patients, with dose adjustments based on weight to mitigate the risk of retinal toxicity [10]. Long-term adherence is critical, yet challenging, underscoring the importance of patient education and monitoring. Regular ophthalmologic screening is essential to detect early retinopathy, especially in patients with prolonged exposure.

Conventional Immunosuppressants

Immunosuppressants remain indispensable in managing moderate to severe SLE, particularly in organ-threatening disease. Azathioprine, methotrexate, mycophenolate mofetil (MMF), and cyclophosphamide represent the mainstays in this category, each with distinct indications and toxicity profiles. Azathioprine is frequently used for maintenance therapy, particularly in patients aiming for steroid-sparing regimens, while methotrexate is most effective in musculoskeletal and cutaneous manifestations [11]. MMF has become a preferred option in lupus nephritis due to its efficacy and favorable tolerability compared to cyclophosphamide, although the latter retains a role in severe or refractory cases [12]. Treatment selection is often guided by disease phenotype, severity, comorbidities, and patient preference, reflecting the heterogeneity of SLE presentations [13].

While these conventional therapies remain fundamental, their limitations—including incomplete disease control, cumulative toxicity, and heterogeneity in treatment response—have driven the development of biologic and targeted therapies. The integration of these novel agents with traditional approaches marks a critical evolution in SLE management.

Biologic and Targeted Therapies

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B-cell Targeted Therapies

B-cell hyperactivity and autoantibody production are central to SLE pathogenesis, making B-cell directed therapies a major focus of drug development. Belimumab, a monoclonal antibody targeting B-lymphocyte stimulator (BLyS), was the first biologic approved for SLE and has demonstrated efficacy in reducing disease activity, lowering flare rates, and achieving glucocorticoid-sparing effects [14]. Clinical trials such as BLISS-52 and BLISS-76 established its role in active, autoantibody-positive SLE, and subsequent studies have expanded its use to lupus nephritis [15]. Rituximab, a CD20 monoclonal antibody, depletes B cells and has been widely used off-label in refractory SLE despite mixed results in randomized controlled trials [16]. Nevertheless, real-world evidence supports its utility in severe disease, particularly lupus nephritis and neuropsychiatric involvement. Newer B-cell targeting agents, such as obinutuzumab and ocrelizumab, are under investigation with promising preliminary outcomes [17].

T-cell Modulation Strategies

T-cell dysfunction contributes to immune dysregulation in SLE by providing abnormal help to autoreactive B cells. Abatacept, a fusion protein that inhibits T-cell costimulation by binding to CD80/CD86, has been evaluated in clinical trials with modest benefits in selected patient populations [18]. While it has not achieved regulatory approval for SLE, it remains an option in refractory cases, especially for arthritis and musculoskeletal manifestations. Other approaches targeting T-cell signaling pathways are in development, including low-dose interleukin-2 therapy aimed at restoring regulatory T-cell function [19].

Emerging Biologics and Targeted Therapies

The approval of anifrolumab, a monoclonal antibody against the type I interferon receptor, marks a major milestone in SLE therapy. Interferon pathway activation is a hallmark of SLE, and inhibition with anifrolumab has been shown to improve global disease activity, cutaneous manifestations, and reduce flare frequency in clinical trials such as TULIP-1 and TULIP-2 [20]. Anifrolumab also demonstrates a steroid-sparing effect, aligning with modern therapeutic goals. Other novel targets include Janus kinase (JAK) inhibitors, which interfere with cytokine signaling and have shown efficacy in early trials, though concerns remain regarding infection risk [21]. Therapies directed against plasmacytoid dendritic cells, complement components, and other cytokines are also being explored, representing the next wave of targeted interventions [22].

The integration of biologics and targeted therapies into standard practice represents a paradigm shift in SLE management. Their judicious use, often in combination with conventional therapies, provides opportunities to enhance disease control, minimize glucocorticoid exposure, and improve long-term outcomes. However, challenges such as high cost, limited access, and variability in patient response necessitate ongoing research and real-world data to refine their use.

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Management of Organ-Specific Involvement

Lupus nephritis (LN) — induction and maintenance.

Renal involvement is one of the strongest determinants of long-term outcome in SLE, and timely, protocolized therapy is essential to preserve kidney function and limit cumulative damage. For proliferative LN (class III/IV with or without class V), induction traditionally relies on mycophenolate mofetil (MMF) or cyclophosphamide alongside glucocorticoids, with MMF favored in many populations due to comparable efficacy and a more favorable safety profile; cyclophosphamide retains value in rapidly progressive or refractory disease and in certain ethnic subgroups. After induction, maintenance with MMF or azathioprine reduces relapse risk, and early, structured steroid tapering is prioritized to minimize toxicity. Treatment selection should weight histology, chronicity index, comorbidities, fertility plans, and adherence considerations, while embedding strict blood pressure and renin–angiotensin–aldosterone system control, proteinuria targets, and hydroxychloroquine in the background regimen. Consensus statements emphasize treat-to-target concepts (e.g., ≥50% proteinuria reduction by 6 months and <0.7–0.8 g/day by 12 months) as pragmatic milestones for decision-making. [23,24,25]

LN — incorporating calcineurin inhibitors and novel add-on biologics.

Calcineurin inhibitors (CNIs) have re-emerged as key partners for MMF, leveraging complementary mechanisms to accelerate proteinuria reduction. Randomized data support “multitarget” induction (MMF + tacrolimus + steroids) as an alternative to cyclophosphamide in selected patients, particularly those with nephrotic-range proteinuria, while careful monitoring for hypertension, nephrotoxicity, and glycemic effects is required. Voclosporin, a next-generation CNI with more predictable pharmacokinetics, improved complete renal response rates when added to MMF and low-dose steroids and maintained efficacy over longer-term extension, offering a practical, steroid-sparing intensification route. In parallel, add-on belimumab to standard therapy has demonstrated superior renal outcomes and fewer flares, supporting early integration in patients with persistent serologic and clinical activity. Collectively, these data support a tiered approach: optimize MMF + glucocorticoids, consider CNI or belimumab intensification for suboptimal responders by 3–6 months, and reserve switch strategies for refractory trajectories. [26,27,15,28]

Neuropsychiatric SLE (NPSLE).

NPSLE encompasses a broad spectrum—from inflammatory (e.g., optic neuritis, acute confusional state) to thrombotic/ischemic phenotypes (often antiphospholipid-mediated)—demanding meticulous attribution and targeted therapy. For inflammatory syndromes, high-dose glucocorticoids with adjunct

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cyclophosphamide are commonly employed, with rituximab considered in refractory cases; supportive measures (antiepileptics, migraine prophylaxis, rehabilitation) are integral. When an ischemic mechanism is suspected or antiphospholipid syndrome (APS) is present, anticoagulation and antiplatelet strategies take precedence, layered atop background SLE control. Evidence remains heterogeneous and largely observational; thus, management is guided by EULAR frameworks emphasizing early evaluation for competing etiologies (infection, metabolic derangements, drug effects), MRI and CSF when indicated, and strict vascular risk reduction. Regular reassessment is critical, as both undertreatment and overtreatment (e.g., prolonged high-dose steroids without objective inflammation) can harm outcomes. [29,10,31]

Cutaneous lupus erythematosus (CLE).

Cutaneous disease is both prevalent and prognostically informative, with activity often mirroring systemic inflammation and adherence. Foundational measures—rigorous photoprotection, smoking cessation, and universal hydroxychloroquine with weight-based dosing—reduce flares and improve lesion control. Topical strategies include class-appropriate corticosteroids and calcineurin inhibitors for sensitive areas, with intralesional steroids for hypertrophic plaques. Systemic escalation (methotrexate, MMF, dapsone) is reserved for recalcitrant disease; thalidomide/lenalidomide can be highly effective but require stringent risk mitigation for neuropathy and thromboembolism. Among biologics, anifrolumab has demonstrated consistent improvements in cutaneous endpoints across phase 3 trials and is a compelling option in patients with prominent skin activity and systemic disease, while plasmacytoid dendritic-cell–directed therapy represents a future avenue. Structured assessment with validated tools (e.g., CLASI) helps standardize response and informs tapering. [32,20,22,33]

Cardiovascular and hematological manifestations

Cardiovascular disease (CVD) is a leading cause of late morbidity in SLE, driven by chronic inflammation, steroid exposure, renal involvement, and traditional risk factors. Management hinges on aggressive risk modification (blood pressure, lipids, glycemia), judicious glucocorticoid minimization, sustained hydroxychloroquine (which favorably modulates thrombosis risk and lipids), and statins according to general population thresholds, with a lower trigger in high-risk LN or APS. Hematologic involvement spans autoimmune hemolytic anemia and immune thrombocytopenia to thrombotic microangiopathy; first-line therapy typically includes short courses of glucocorticoids ± IVIG for severe cytopenias, with rituximab favored as a steroid-sparing option and thrombopoietin receptor agonists considered in refractory thrombocytopenia. APS mandates long-term anticoagulation after thrombosis and careful avoidance of high-dose estrogen; in arterial events or “triple-positive” profiles, vitamin K antagonists remain standard. Regular surveillance for drug-induced cytopenias and infection prophylaxis completes a holistic safety strategy. [,37,38]

Glucocorticoid Minimization and Damage Prevention

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Glucocorticoids have been indispensable in controlling acute inflammation and flares in SLE, but their long-term use remains one of the strongest drivers of cumulative organ damage. Chronic exposure to even moderate daily doses (≥7.5 mg prednisone equivalent) is linked to osteoporosis, avascular necrosis, cataracts, cardiovascular disease, infections, and metabolic syndrome [39]. Consequently, modern management emphasizes minimizing cumulative glucocorticoid burden while maintaining adequate disease control. The treat-to-target paradigm advocates early tapering to the lowest effective dose, ideally ≤5 mg/day, and discontinuation in stable remission when possible [40].

Pulse intravenous methylprednisolone is increasingly favored for severe flares as it provides rapid disease suppression with less long-term toxicity compared to high-dose oral regimens. Tapering strategies should be individualized based on flare severity, organ involvement, and background immunosuppression, but consensus guidelines recommend that tapering begin promptly once disease control is achieved [41]. Early initiation of immunosuppressants such as MMF or azathioprine, and biologics like belimumab or anifrolumab, can facilitate steroid-sparing and maintain remission.

Preventive measures to mitigate glucocorticoid-related damage are equally critical. These include bone protection strategies (calcium, vitamin D, bisphosphonates in high-risk patients), cardiovascular risk assessment and management, weight-bearing exercise, and vaccination to reduce infection risk [42]. Regular screening for complications such as osteoporosis, cataracts, and metabolic syndrome should be integrated into long-term care. Importantly, patient education regarding the risks of prolonged steroid use enhances adherence to tapering strategies and promotes engagement with adjunctive therapies.

Ultimately, glucocorticoid minimization reflects a central therapeutic goal in SLE: controlling disease activity without sacrificing long-term safety. Emerging biologics and combination regimens have made this increasingly feasible, but sustained vigilance and structured monitoring are necessary to prevent irreversible steroid-related morbidity. By aligning treatment with treat-to-target strategies and employing proactive preventive measures, clinicians can significantly reduce long-term organ damage and improve quality of life for patients with SLE [43].

Personalized and Precision Medicine Approaches

Treat-to-target, state definitions, and activity indexing.

Personalization in SLE begins with standardized targets and reliable measurement tools that allow therapy to be tailored to the individual disease trajectory. Low disease activity state (LLDAS) and DORIS remission have emerged as pragmatic, clinically meaningful endpoints associated with reduced flares and organ damage, enabling stepwise intensification or de-escalation based on whether patients meet these states over time. Alongside global indices such as SLEDAI-2K and organ-specific systems like BILAG, these targets provide a common language for clinicians and patients to co-navigate treatment decisions. Embedding LLDAS/DORIS into routine visits supports earlier tapering of

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glucocorticoids and more timely addition of steroid-sparing agents when targets are missed, thereby operationalizing precision care around outcomes that matter. [44–46]

T

herapeutic drug monitoring (TDM) and adherence-aware dosing.

Interpatient pharmacokinetic variability and nonadherence can masquerade as refractory disease. Hydroxychloroquine (HCQ) whole-blood level monitoring has repeatedly linked subtherapeutic levels with higher flare risk, while steady-state targets (commonly ~500–1000 ng/mL in many laboratories) correlate with improved outcomes and fewer discontinuations. Incorporating TDM allows clinicians to distinguish undertreatment from true nonresponse, optimize dosing in patients with high BMI or drug–drug interactions, and support shared decision-making about risk–benefit trade-offs when retinal toxicity concerns arise. In parallel, periodic TDM can reveal silent nonadherence—a modifiable driver of apparent treatment failure—redirecting the plan toward education, reminders, and simplified regimens rather than unnecessary escalation. [47,48]

Biomarker-guided biologic selection.

Molecular stratification is increasingly actionable in SLE. A high type I interferon (IFN) gene signature enriches for clinical response to anifrolumab, aligning mechanism with phenotype and offering a data-informed rationale for agent selection in patients with prominent mucocutaneous or serologically active disease. Conversely, B-cell pathway activity—reflected in elevated BAFF/BLyS and autoantibody profiles—has been associated in exploratory analyses with favorable belimumab responses, supporting pathway-concordant choices in seropositive, flare-prone patients. While no single biomarker is yet definitive, converging serologic and transcriptomic cues can tilt probability toward one targeted therapy over another and should be integrated with organ involvement, comorbidities, and patient preferences. [49,50]

Complement activation products and renal precision monitoring.

Traditional complement measures (C3/C4) and anti-dsDNA remain useful but imperfect for real-time disease biology. Cell-bound complement activation products (CB-CAPs) and anti-C1q offer greater specificity for active immune complex disease in some cohorts, while urinary biomarkers—MCP-1, NGAL, TWEAK, and sCD163 among others—enhance detection of subclinical renal inflammation and predict impending lupus nephritis (LN) flares. Serial panels that combine proteinuria trajectories with urinary chemokines and sediment activity can refine the timing of biopsy, guide intensification (e.g., adding a calcineurin inhibitor or belimumab), and inform tapering once biomarkers normalize, thereby reducing both missed activity and overtreatment. [51–53]

Pharmacogenomics and dose individualization.

Pharmacogenetic guidance is most mature for thiopurines: TPMT and NUDT15 variants predict intolerance and myelotoxicity with azathioprine, enabling pre-emptive dose adjustments or alternative

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choice (e.g., MMF) in poor metabolizers. Emerging data suggest roles for drug transporters and metabolizing enzymes affecting calcineurin inhibitors and antimalarials, though clinical implementation remains limited. As broader panels and rapid genotyping become more accessible, integrating pharmacogenomics with TDM (for HCQ, CNIs) offers a two-pronged precision strategy—anticipating toxicity risk upfront and titrating exposure in real time to reach the therapeutic window without excess harm. [54]

Conclusion

The management of systemic lupus erythematosus has evolved substantially over the past decades, moving from an era dominated by broad immunosuppression and glucocorticoids to one increasingly shaped by biologics, targeted therapies, and personalized medicine. Conventional agents remain indispensable, particularly in organ-threatening disease, but the emphasis today lies in minimizing cumulative steroid toxicity, preventing long-term damage, and tailoring regimens to individual disease phenotypes. The approval of therapies such as belimumab, anifrolumab, and voclosporin underscores a growing arsenal of mechanism-based interventions that align more closely with disease biology and facilitate steroid-sparing strategies.

Equally important are the integrative aspects of care: early recognition and targeted management of organ involvement, proactive cardiovascular and infection risk mitigation, and incorporation of lifestyle measures, vaccination, and psychosocial support. Precision approaches—leveraging biomarkers, therapeutic drug monitoring, and emerging multi-omic profiling—offer new avenues to match therapies with patient-specific immunologic signatures and treatment trajectories.

Despite these advances, challenges persist. Not all patients respond adequately to available therapies, access to novel agents is uneven, and robust predictors of long-term outcomes remain elusive. The complexity of SLE continues to demand individualized care plans, multidisciplinary collaboration, and sustained engagement between patients and clinicians. Future directions will hinge on integrating biomarker-driven approaches into clinical practice, expanding access to innovative treatments, and refining treat-to-target frameworks to further reduce disease burden and improve survival.

In summary, contemporary SLE management represents a dynamic interplay between conventional and emerging therapies, preventive strategies, and personalized care. By continuing to bridge scientific discovery with clinical pragmatism, the goal of sustained remission with minimal treatment-related harm becomes increasingly attainable for patients living with this complex disease.

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