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NEW THERAPEUTIC STRATEGIES IN SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

BACKGROUND

Systemic lupus erythematosus is a clinically heterogeneous autoimmune disease with an unpredictable course, recurrent flares, and risk of progressive organ damage. Despite the availability of clinical guidelines and established therapies, treatment outcomes remain variable, and many patients do not achieve sustained disease control. The growing understanding of immunopathogenic mechanisms, including B cell dysregulation, interferon signaling, and intracellular pathways, has led to the development of targeted and mechanism oriented therapies. However, the comparability of clinical evidence is limited due to heterogeneity in study populations, outcome measures, and study designs.

AIM

To present and systematize existing and emerging treatment strategies for systemic lupus erythematosus with analysis of their mechanisms of action, clinical efficacy, and safety.

METHODS

A structured narrative review was conducted using PubMed, Scopus, and Google Scholar for publications from 2015 to 2025. The selection included international clinical guidelines, systematic reviews, meta-analyses, and original clinical studies. Articles were limited to English and Polish. A total of 100 records were identified, of which 45 were included after screening and eligibility assessment based on predefined criteria.

RESULTS

Therapeutic strategies in systemic lupus erythematosus can be classified according to key immunopathogenic targets, including B cell survival and differentiation, type I interferon signaling, T cell activation, and intracellular kinase pathways. Belimumab and anifrolumab represent established targeted therapies with demonstrated efficacy in reducing disease activity and enabling glucocorticoid dose reduction. Rituximab is used in refractory disease, primarily based on observational evidence. In lupus nephritis, voclosporin improves renal outcomes as part of combination therapy. Emerging agents, including obinutuzumab, telitacicept, and TYK2 inhibitors, expand mechanism-based approaches, while CAR T cell therapy represents a novel strategy with potential for durable remission. Clinical efficacy is moderate and varies depending on disease phenotype and background therapy. Safety profiles differ across therapeutic classes, with risks including infections, infusion reactions, and organ specific adverse effects. Long term safety and durability of response remain insufficiently defined for newer therapies.

CONCLUSIONS

Current evidence supports a transition toward mechanism based and personalized treatment strategies in systemic lupus erythematosus. Targeted therapies improve disease control and allow reduction of glucocorticoid exposure, but their comparative effectiveness and long-term safety remain uncertain. Further studies with standardized endpoints, longer follow up, and direct comparative designs are required to define optimal therapeutic sequencing and patient selection.

Keywords: systemic lupus erythematosus, lupus nephritis, immunopathogenesis, targeted therapy, biologic therapy, B cell therapy, interferon pathway, JAK STAT pathway, TYK2 inhibitors, belimumab, anifrolumab, rituximab, CAR T cell therapy, efficacy, safety

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune inflammatory disease characterized by a wide range of clinical manifestations and a relapsing-remitting course [1]. This clinical variability makes both diagnosis and individualized treatment particularly challenging. Although the cause of SLE remains unknown, genetic factors are strongly implicated, as highlighted by the recent description of a gain-of-function pathogenic variant in the TLR7 gene in affected patients, along with environmental factors such as radiation, sun, tobacco, etc., and hormonal influences [2]. The prevalence of SLE varies considerably between ethnic groups. In the adult group, it is estimated to range from 30 to 210 cases per 100,000 individuals [3,4]. The disease most commonly occurs between the ages of 15 and 45, and affects women approximately nine times more often than men [3,10,11].

The core feature of the disease is the persistent production of autoantibodies and immune complex deposition resulting from a sustained breakdown of immune tolerance, the survival and activation of autoreactive lymphocytes [5]. Consequently, this leads to the dysfunction and destruction of multiple organs [10,12].

As noted above, the wide range of clinical manifestations in SLE is one of the main challenges in diagnosing and treating this disease. The characteristic malar rash across the cheeks and nose, discoid rash, photosensitivity, oral ulcers, arthritis, and hematological abnormalities are examples of typical clinical symptoms [3,6]. Systemic polyarthritis is a common symptom of musculoskeletal involvement, frequently accompanied by morning stiffness. Serositis can occur in the form of pleuritis or pericarditis, while neuropsychiatric involvement may present with seizures or psychotic symptoms. Leukopenia and thrombocytopenia are common hematological abnormalities. A major repercussion is renal involvement (lupus nephritis), which is usually indicated by persistent protein or cellular casts in the urine. Kidney damage results from the accumulation of immune complexes, often containing anti-dsDNA and anti-nucleosome antibodies, which initially localize in the subendothelial and mesangial regions before progressing to the basement membrane and subepithelial compartments [3,6].

The heterogeneous manifestations of SLE led to the development of the classification criteria formed by the American College of Rheumatology (ACR) and the Systemic Lupus International Collaborating Clinics (SLICC) to aid in diagnosis and research [6,7]. Treatment of SLE usually involves a multi-drug regimen [8,9].

Relevance: systemic lupus erythematosus remains a clinically heterogeneous disease with an unpredictable course, frequent flares, and a risk of progressive organ damage. Despite the availability of clinical guidelines and accumulated evidence, limitations in the comparability of study results persist due to heterogeneity of patient populations, differences in clinical trial design, and a lack of long term follow up. In particular, variability exists in inclusion criteria, baseline disease activity, spectrum of organ involvement, assessment tools such as SLEDAI and BILAG, background therapy including glucocorticoid and immunosuppressant use, endpoints, and response criteria. These factors hinder direct comparison of results and their interpretation in clinical practice, which justifies the need for a comprehensive

analysis of current and emerging therapeutic approaches targeting key immunopathogenic pathways.

Scientific novelty: the study provides a structured synthesis of current and emerging therapeutic strategies with a focus on their mechanisms of action, clinical efficacy, and safety, including biologic agents, small molecules, and cell based therapies. The review allows alignment of major therapeutic approaches within a pathogenetic framework and helps to clarify their place in contemporary clinical practice, although it remains predominantly descriptive and does not include a formal comparative analysis.

AIM: To present existing and emerging treatment strategies for systemic lupus erythematosus with analysis of their mechanisms of action, clinical efficacy, and safety.

Objectives:

1. To summarize data on targeted therapies used in systemic lupus erythematosus.
2. To describe the mechanisms of action of key biological agents and small molecules.
3. To analyse their clinical efficacy and safety profile.
4. To review emerging and investigational therapeutic approaches, including cell based therapies.

2. METHODOLOGY

This narrative review was planned as a structured narrative review with transparent search and selection procedures. A comprehensive literature search was conducted in PubMed, Scopus, and Google Scholar, covering publications from 2015 to 2025, to capture contemporary evidence on new and emerging treatment methods in systemic lupus erythematosus, including therapies used in lupus nephritis. In addition, selected earlier landmark publications were included when necessary to describe key immunopathogenic mechanisms and the rationale behind emerging target therapies.

Primary search terms included "systemic lupus erythematosus", "SLE", "emerging treatment methods", "lupus nephritis", as well as therapy focused keywords such as "targeted therapy", "biologic antibodies", "B cell directed therapies", "belimumab", alongside outcome related terms such as "disease activity", "glucocorticoid sparing effect", "renal response". Only full text articles were considered eligible.

To ensure a high standard of clinical relevance, inclusion was restricted to international clinical guidelines, peer reviewed systematic reviews, meta-analyses, and original research, including randomized controlled trials, prospective and retrospective cohort studies, and case series with clinically interpretable outcomes. Studies were included if they enrolled human subjects with systemic lupus erythematosus, reported clearly defined clinical endpoints, and provided sufficient methodological detail, defined as a description of study design, patient characteristics, intervention, and outcome measures. Quantitative thresholds included a minimum sample size of 20 patients for original studies and a minimum follow up period of 12 weeks for interventional studies where applicable.

Exclusion criteria included opinion articles, narrative commentaries, conference abstracts without accessible full text, duplicate records, studies lacking clearly defined outcomes, studies with insufficient methodological transparency, and reports with sample size below 20 patients unless addressing rare or highly specific clinical scenarios.

The search was limited to articles published in English and Polish.

The study selection process was performed in several stages. After removal of duplicates, titles and abstracts were screened for relevance to the topic. Full text assessment was then conducted to confirm eligibility according to predefined criteria.

The initial search identified 100 records. After screening and eligibility assessment, 45 sources were included in the final analysis.

The methodological quality of included studies was assessed descriptively according to study design, with priority given to randomized controlled trials, systematic reviews, and meta analyses. Observational studies were evaluated based on clarity of population definition, consistency of outcome reporting, and adequacy of follow up. Studies with a high risk of bias, defined by unclear methodology or incomplete outcome reporting, were considered with caution in the interpretation of results.

The review was conducted in accordance with the SANRA principles. The scientific relevance of the topic was defined through identification of current clinical challenges in SLE management. The literature search strategy was explicitly described with defined databases, time frame, and search terms. The referencing was performed using up to date and clinically relevant sources. Data presentation was structured according to key therapeutic mechanisms and clinical applications. The analysis was focused on critical interpretation of therapeutic strategies rather than simple

listing of studies. The manuscript structure followed a logical progression from pathogenesis to current and emerging therapies, ensuring coherence and clarity of the review. The aim was clearly formulated and consistently reflected in the selection and synthesis of the literature.

3. RESULTS

3.1. PATHOGENESIS

The pathogenesis of systemic lupus erythematosus is still unknown, even though it affects approximately 3.4 million people worldwide [10]. According to the latest data, about 400,000 people are diagnosed with it each year [10,11]. The onset of systemic lupus erythematosus is thought to result from complex interactions between genetic predispositions and environmental triggers, such as ultraviolet (UV) light, infections, and hormonal influences [12,13]. This leads to the creation of pathogenic autoantibodies that target nucleic acids and their binding proteins resulting in immune dysregulation. These antibodies combine with the innate and adaptive immune systems to form immune complexes in various tissues. Such accumulation leads to acute and chronic inflammation, eventually causing damage to affected organs [12]. Systemic lupus erythematosus pathogenesis is primarily driven by immune response dysregulation. The innate and adaptive immune systems are disrupted, which leads to the progression of the disease. Observed innate dysfunction includes impaired neutrophil phagocytic function, increased oxidative stress and accumulation of dendritic cells at sites of inflammation. In parallel, excessive T-cell and B-cell activation and impaired clearance of autoreactive B-cells are all components of adaptive immune response dysfunction [12,14]. This collectively leads to increased autoantibody production. In addition, patients with SLE often show increased serum levels of type I interferons (IFNs), which have been associated with greater disease activity and more severe clinical manifestations [15].

3.2. CURRENT TREATMENT METHODS

Current treatment of systemic lupus erythematosus includes a combination of antimalarial medication, glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), and conventional immunosuppressive agents. The choice of specific treatment strategy depends on the severity of the disease and organ involvement. While these strategies can considerably reduce disease activity, they are limited by incomplete disease control, potential for relapse, cumulative organ damage, and significant toxicity, especially with extended glucocorticoid exposure [8,12].

For milder cases, usually therapy includes NSAIDs, antimalarial agents, and low doses of glucocorticoids. Using antimalarial drugs has been proven to reduce constitutional symptoms of SLE, such as fever, fatigue, musculoskeletal and dermatological issues, while remaining a cornerstone for maintaining remission of the disease [16,17]. It has also been noticed that antimalarial drugs allow a lower dose of glucocorticoids and have positive effects on metabolism, specifically improved glycemic control and insulin sensitivity [17,18]. In more severe cases, a variety of glucocorticoids and immunosuppressive treatments are used. These include azathioprine, methotrexate, cyclophosphamide, and mycophenolate mofetil [19]. Methotrexate is frequently considered for articular and cutaneous manifestations to reduce steroid intake and decrease the overall activity of the disease [20]. Similarly, azathioprine shows positive effects in patients with arthritis and may mediate steroid-sparing effect [21]. Mycophenolate mofetil inhibits inosine monophosphate dehydrogenase and modulates dendritic cell subsets, thereby halting the progression of the autoimmune cascade [12,22]. It is widely used for both induction and maintenance therapy in lupus nephritis, with additional usage in selected extrarenal manifestations. Cyclophosphamide is typically used in severe cases of SLE, especially those in vital organs such as severe systemic vasculitis [8]. Given that, there has been a transition from broad immunosuppression towards more targeted, mechanism-driven therapies aimed at improving quality of life and achieving disease remission, with some biological medications already approved.

3.3. LATEST THERAPEUTIC ADVANCES

Recurring disease exacerbations, organ-specific complications, and the limited efficacy of conventional therapies, along with the side effects associated with commonly used immunosuppressive medications, have encouraged the development of targeted therapies for SLE. Current therapeutic strategies explore interventions aimed at distinct mechanisms of the disease pathogenesis, with particular focus on B-cell directed therapies, IFN, and agents blocking TNF-α [3,8]. Some of the biological medications have already been introduced with positive responses.

3.3.1 Belimumab

Belimumab is a fully human monoclonal antibody that targets BAFF/BLyS (also known as CD257), a cytokine from TNF-family that plays an important role in B-cell activation, survival, and differentiation [23,24]. Inhibition of BAFF leads to limited survival of autoreactive B cells, therefore lowers autoantibody production and helps in the modulation of the dysregulated immune response [23].

Randomized controlled trials have demonstrated that belimumab is associated with clinically relevant reduction in disease activity and decreased glucocorticoid requirements compared with placebo [25]. Modest improvements in health-related quality of life have been observed, though these did not reach thresholds considered clinically meaningful [25,26]. Clinical trial data suggest that belimumab is generally well tolerated and does not appear to increase the risk of serious infections, major adverse events or mortality rate compared to placebo [25,26]. Long-term observational data suggest sustained disease control and steroid-sparing effects, particularly in patients with predominant musculoskeletal and mucocutaneous manifestations [23,26].

Belimumab was first approved for adults with SLE in 2011 and later extended to include pediatric patients in 2019, making it the first biologic agent approved for systemic lupus erythematosus [24]. Current recommendations support its use in patients with active disease, particularly in cases without neuropsychiatric involvement [26]. Recent studies suggest that belimumab may also be beneficial as add-on therapy in lupus nephritis, as it has been associated with improved renal function, reduced proteinuria, and a lower risk of renal-related complications and mortality [23]. In addition, combination strategies targeting B-cell pathways, such as rituximab induction followed by belimumab, as well as the concurrent use of both agents, have shown promising results [24]. Ongoing investigations aim to refine the optimal positioning of belimumab within the SLE treatment algorithm, including its potential early use before conventional immunosuppressants, which may confer better outcomes and facilitate earlier glucocorticoid tapering [26].

3.3.2. Rituximab

Rituximab is an anti-CD20 monoclonal antibody that depletes B cells through antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), apoptosis induction and suppression of B-cell proliferation, while sparing plasma cells and hematopoietic stem cells [23]. Although not formally approved for SLE, rituximab is widely used off-label in clinical practice, particularly in patients with severe or refractory disease manifestations, including lupus nephritis and immune-mediated cytopenias [24]. Observational registry data indicate potential reduction in disease activity, flare frequencies and glucocorticoid use following rituximab treatment [10,24]. As it was mentioned before, clinical trials evaluating sequential or combination strategies with BAFF inhibition have suggested improved durability of clinical response in refractory SLE and lupus nephritis while establishing an acceptable risk profile [24]. Overall, these findings suggest that rituximab continues to play an important role in the management of this disease, especially in patients with severe manifestations that do not respond adequately to standard approved therapies.

3.3.3. Anifrolumab

Anifrolumab is a fully human monoclonal antibody that targets the type I interferon receptor subunit 1 (IFNAR1), thereby inhibiting signaling from all type I interferons (IFN) [23,27]. This mechanism is particularly relevant in SLE, as many patients demonstrate an increased interferon gene signature that has been linked to higher disease activity and more severe clinical presentations [23]. The clinical efficacy of anifrolumab was evaluated and demonstrated significant clinical superiority over placebo, particularly with respect to improvements in cutaneous and musculoskeletal symptoms [23,28]. Therapeutic response was more pronounced in patients with a high baseline interferon gene signature, supporting a biomarker-driven treatment approach [28,29]. Real-world evidence further supports these findings, indicating rapid clinical improvements allowing patients to reach a Lupus Low Disease Activity State (LLDAS) after six months of therapy [10,27]. Safety analyses revealed an incidence of herpes zoster and upper respiratory tract infections, although serious adverse events occurred at rates comparable to placebo, indicating an overall acceptable safety profile [27]. Based on these results, anifrolumab has been approved by the FDA and EMA for the treatment of adults with moderate to severe non-renal, non-neuropsychiatric SLE as add-on therapy to standard of care [10,23].

3.3.4. Voclosporin

Voclosporin is a next-generation calcineurin inhibitor that was approved as an add-on therapy for lupus nephritis. Although it is structurally related to cyclosporine, it was designed to offer more predictable pharmacokinetics and a potentially lower risk of nephrotoxicity compared with previous calcineurin inhibitors [23]. By inhibiting the calcineurin pathway, voclosporin suppresses T-cell activation and consequently reduces immune-mediated inflammation within the kidneys [10,23]. Clinical studies have shown that adding low doses of voclosporin to standard therapy leads to higher renal response rates compared with standard therapy alone [23]. Importantly, compared to traditional calcineurin inhibitors, voclosporin has shown favorable safety and efficacy profiles in phase II and III clinical trials, therefore supporting its role in long-term disease control [10,30]. Based on these findings, voclosporin has been approved for the treatment of active lupus nephritis and is incorporated into recent EULAR and KDIGO recommendations as an add-on therapy for lupus nephritis [21,31].

The currently used target therapies in systemic lupus erythematosus and lupus nephritis, together with their

mechanism of action, main indication, clinical benefits, and key safety considerations, are summarized in Table 1.

Table 1. Currently used targeted therapies in SLE and lupus nephritis.

Therapy (status)	Mechanism	Main indication	Clinical benefit	Key safety / monitoring
Belimumab (approved)	BAFF/BLyS inhibition	Active SLE; add on in LN	Reduced disease activity and steroid intake	Generally well tolerated; monitor infection risk [23-26]
Anifrolumab (approved)	IFNAR1 blockade (type I IFN)	Moderate–severe non renal, non neuropsychiatric SLE	Improves skin/ joint manifestations; higher LLDAS attainment	Herpes zoster/ URTI risk; vaccination and surveillance [28,29]
Voclosporin (approved in LN)	Calcineurin inhibition	Active lupus nephritis (add on)	Higher renal response within combination regimens	Monitor kidney function, BP, drug interactions [30,31]
Rituximab (off label)	Anti CD20 B cell depletion	Severe/refractory SLE; Selected cases of LN	May reduce activity/flares and steroid exposure	Infusion reactions; infection risk; vaccination timing [10,24]

Abbreviations: BAFF/BlyS, B cell activating factor; IFNAR1, type I interferon receptor subunit 1; LN, lupus nephritis; LLDAS, Lupus Low Disease Activity State; URTI, upper respiratory tract infection.

3.4. EVOLVING TARGET THERAPIES

Following the introduction of targeted biologic and small-molecule therapies into clinical practice, ongoing research in systemic lupus erythematosus has focused on expanding and refining mechanism-based therapeutic approaches. Advances in the understanding of SLE immunopathology have revealed additional molecular pathways and cellular interactions that contribute to the disease's heterogeneity and, in some cases, limited response to existing therapies [32]. As a result, new therapeutic strategies are being developed to target intracellular signaling cascades, co-stimulatory pathways, and other immune cell populations that are not adequately addressed by currently approved treatments [23]. This evolving therapeutic landscape reflects a shift towards precision-oriented interventions and combination strategies that may further improve long-term disease control for patients with SLE.

3.4.1. B-cell targeted therapies

Next-generation therapies directed at B-cells are designed to provide more sustained and effective suppression of autoreactive B-cell populations. Obinutuzumab, a type II anti-CD20 monoclonal antibody, has demonstrated enhanced B-cell depletion compared with rituximab through enhanced Fc gamma receptor-mediated mechanisms and stronger direct cytotoxic mechanisms [23,33]. In clinical trials, such as the phase II NOBILITY study in lupus nephritis, obinutuzumab added to standard therapy resulted in significantly higher complete renal response rates compared with placebo [23]. Its potential efficacy in patients with inadequate response to rituximab further supports its role as an alternative therapy in refractory SLE [23,33,34].

Telitacicept is a recombinant fusion protein that inhibits both BAFF and APRIL, cytokines critical for B-cell survival and differentiation, and offers more comprehensive suppression of pathogenic B-cell activity than BAFF inhibition alone [25]. It is currently being evaluated in clinical trials, with a phase III monotherapy study completed and published, showing significantly higher clinical responder rates compared to placebo, while other trials are still ongoing [23,35]. Another approach involves directly targeting the BAFF receptor with agents such as ianalumab, currently under

evaluation in randomized trials [12,36]. Overall, these therapies illustrate the continued progress in B-cell directed treatment strategies in SLE, with the aim of achieving more sustained control of autoreactive B-cells while minimizing systemic toxicity.

3.4.2. CO-STIMULATORY PATHWAYS

Modulating co-stimulatory signaling offers an additional mechanism to reduce autoreactive immune responses in SLE. Dapirolizumab pegol, PEGylated anti-CD40 ligand (CD40L), disrupts T-cell-dependent B-cell activation while avoiding the thromboembolic complications associated with previous anti-CD40L antibodies [23,37]. Ongoing phase III evaluation is underway to further evaluate its efficacy and long-term safety in moderate-to-severe SLE [33,37].

3.4.3. SMALL-MOLECULE THERAPIES TARGETING INTRACELLULAR SIGNALING

Alongside biologic agents, small-molecule therapies have emerged as an important area of investigation in SLE, with voclosporin already officially approved. The JAK-STAT pathway has gained considerable attention because of its key role in mediating cytokine and interferon signaling [12,23]. While findings from trials of JAK inhibitors have not been consistent, selective TYK2 inhibition appears to present encouraging results so far [27,33]. Deucravacitinib has demonstrated higher composite response rates compared with placebo, with an acceptable safety profile, supporting TYK2 inhibition as a promising small-molecule approach in SLE [23,33,38].

3.4.4. CYTOKINE-DIRECTED AND INTERFERON-PATHWAY MODULATORS

Research into therapies that target inflammatory cytokines continues to be an area of investigation in systemic lupus erythematosus. Agents that inhibit interleukin-6 (IL-6) signaling, such as tocilizumab and sirukumab, have shown some preliminary efficacy in reducing the disease activity in patients with mild to moderate SLE in early studies [39,40]. Similarly, blockade of interleukin-12 and interleukin-23 with Ustekinumab has demonstrated promising results in phase II studies. However, it did not meet phase III endpoints, therefore further development of the drug was ultimately discontinued [12,41]. Similarly, AMG 811, an anti-interferon-γ monoclonal antibody, has shown biomarker modulation with an acceptable safety profile, though clear clinical benefits have yet to be established [42].

Therapies aimed at the interferon pathway are increasingly recognized as a promising approach in the treatment of systemic lupus erythematosus. Litifilimab is a humanized IgG1 monoclonal antibody directed against dendritic cell antigen 2 (BDCA2), which results in reduced production of type I interferon by plasmacytoid dendritic cells [23]. Early trials have demonstrated a decrease in joint counts and cutaneous disease activity compared with placebo, although some secondary endpoints were less consistent [23,43]. E6742, an inhibitor of Toll-like receptors (TLR7/8), represents another investigational agent targeting upstream innate immune sensors that trigger type I interferon production and inflammatory cascades in SLE [27]. It aims to reduce the activation of plasmacytoid dendritic cells and subsequent interferon-driven pathology, offering a potentially complementary mechanism to direct interferon receptor blockade and remains under early clinical investigation [27,43].

3.4.5. CELL-BASED THERAPIES

Cell-based approaches are increasingly being explored as novel therapeutic options in the management of SLE. CD19-directed chimeric antigen receptor (CAR) T-cell therapy has shown profound and sustained clinical and serological remission in early clinical experiences involving patients with severe, refractory SLE [23,44]. Follow-up studies suggest durable remission accompanied by reconstruction of naive B-cell compartments, indicating potential restoration of immune tolerance [44,45]. Although these results are promising, additional controlled clinical trials are needed to define long-term safety, durability of response, and optimal patient selection [45].

Consistent with this evolving therapeutic landscape, selected emerging and investigational therapies targeting key immune pathways in SLE are summarized in Table 2, alongside with their stage of development and the main clinical signals reported so far.

Table 2. Selected emerging and investigational therapies targeting key immune pathways in SLE.

Agent / Strategy	Target pathway	Stage	Key signal reported	References
Obinutuzumab	Type II anti CD20 B cell depletion	Phase 3 (lupus nephritis)	Improved renal response when added to standard therapy	[34]

Telitacicept	Dual BAFF/ APRIL inhibition	Phase 3	Higher responder rates vs placebo in monotherapy trial	[35]
Dapirolizumab pegol	CD40L co stimulation blockade	Phase 2; Phase 3 ongoing	Clinical activity improvements in phase 2; long term data pending	[37]
Deucravacitinib	Selective TYK2 inhibition (JAK–STAT)	Phase 2	Higher composite response vs placebo with acceptable safety	[38]
Litifilimab	Anti BDCA2 (pDC), lowers type I IFN	Phase 2	Improved cutaneous activity and joint counts vs placebo	[43]
E6742	TLR7/8 inhibition (innate immune trigger)	Early clinical development	Mechanism based rationale; clinical benefit under investigation	[27,43]
Cytokine directed approaches	IL 6, IL 12/23, IFN γ blockade	Early studies / mixed results	Preliminary signals (IL 6); phase 3 failure (IL 12/23); biomarker modulation (IFN γ)	[39–42]
CAR T cell therapy	CD19 directed	Case series & phase 1	Deep remissions in highly refractory SLE; durability and safety under evaluation	[44,45]

Abbreviations: APRIL, a proliferation inducing ligand; pDC, plasmacytoid dendritic cell; TLR, Toll like receptor; TYK2, tyrosine kinase 2.

4. DISCUSSION

Managing systemic lupus erythematosus remains a challenge despite significant progress in treatment, mostly because the disease itself is unpredictable and biologically diverse. Two patients with the same diagnosis may present a completely different set of clinical manifestations. This diversity often leads to inconsistent responses to standard regimens and helps explain why a proportion of patients continue to experience flares, persistent activity, and organ damage. A major practical difficulty is that many effective regimens rely on glucocorticoids, which in long-term use lead to cumulative morbidity and organ damage, becoming an integral component of the overall disease burden rather than a transient adverse effect [9,12].

A central development highlighted in the review literature is the shift from broad immunosuppression toward targeted therapeutic strategies that offer the potential for improved efficacy and reduced toxicity compared with conventional treatments [6,12]. Recent research has concentrated on therapies that target specific immune pathways, particularly those involving B-cell regulation, interferon signaling, and co-stimulatory pathway blockade. This approach aligns with clinical priorities such as reducing flare frequency, maintaining low disease activity, and limiting cumulative toxicity [12,23].

In this context, approved biologic agents such as belimumab and anifrolumab represent clinically relevant examples of mechanism-based treatment. Belimumab has demonstrated significant improvements in reducing disease activity and facilitating glucocorticoid-sparing strategies, with an overall acceptable safety profile [23-26]. Anifrolumab has shown clinically significant benefits, particularly for cutaneous and musculoskeletal manifestations, and trial data support its long-term tolerability [28,29]. B-cell directed strategies remain crucial in modern management of this disease. Rituximab, while often used off-label, is frequently considered in refractory or severe manifestations, supported mainly by observational and registry-based evidence [10,24].

For severe organ involvement, particularly lupus nephritis, current management is increasingly based on combination regimens. Adding voclosporin, a next-generation calcineurin inhibitor, to standard background therapy has been associated with higher renal response rates in phase 3 trials. Long-term observations support its role as an adjunct strategy aimed at improving renal outcomes while enabling minimization of glucocorticoids. These findings are reflected in contemporary lupus nephritis guidance [30,31]. Emerging therapies, such as obinutuzumab, telitacicept, and small molecules targeting intracellular signaling pathways (e.g., JAK-STAT and TYK2) further illustrate how treatment is moving toward mechanism-based choices and, increasingly, toward combination regimens personalized to disease phenotype [34,35,38].

Novel cell-based therapies, particularly CD19-directed CAR T-cell strategies, represent a highly innovative direction for refractory SLE. Early clinical reports have shown promising potential in achieving durable remission in selected cases of refractory SLE [13,44,45]. However, these strategies remain investigational and require careful evaluation in controlled studies, along with longer follow-up periods to define durability, relapse patterns and overall safety [13,44].

It has to be taken into consideration that several factors limit how directly the available evidence can be translated into everyday practice. SLE is highly heterogeneous, and clinical trials differ in eligibility criteria, background immunosuppression, follow-up duration and outcome definitions, which complicates cross-trial interpretation [27,33]. In addition, many studies enroll selected populations that may not reflect real-world patients with different disease duration or extensive prior treatment exposure. Finally, long-term safety and durability data remain limited for several newer agents. These limitations underline the importance of continued research to clarify long-term safety and efficacy, refine patient selection and ensure that novel treatments become accessible to a broader population of patients with systemic lupus erythematosus.

Overall, the management of SLE is evolving toward more personalized, mechanism-driven strategies and rational combination approaches that may enable more sustained disease control with fewer side effects and better quality of life [23,24,27]. Ongoing progress will require stronger long-term safety and effectiveness evidence, improved patient stratification including biomarker-informed approaches where available, and clearer guidance on how new agents should be sequenced within treatment algorithms.

5. CONCLUSION

Targeted therapies in SLE can be grouped according to key mechanisms, including B cell modulation, type I interferon pathway inhibition, calcineurin dependent pathways, and intracellular signaling blockade. Belimumab and anifrolumab have the strongest evidence among approved agents for selected forms of active SLE, whereas rituximab is used in refractory or severe disease based mainly on observational data. In lupus nephritis, voclosporin is supported as part of combination therapy with improved renal outcomes in this specific setting.

Clinical efficacy varies across strategies and disease phenotypes. BLyS and interferon targeted therapies provide moderate and context dependent benefits in non renal disease, while rituximab is primarily applicable in refractory manifestations. Calcineurin based therapy is most justified in lupus nephritis and is not directly comparable to systemic biologic therapy outside renal involvement. Combination regimens are most relevant in organ threatening disease, particularly renal involvement.

Emerging therapies, including obinutuzumab, telitacicept, TYK2 inhibitors, and CAR T cell approaches, expand mechanism based strategies but remain supported mainly by early phase or limited data, and their role in routine practice is not yet defined.

Safety profiles differ by class and require context specific interpretation. Biologic therapies are associated with infections and infusion reactions, whereas calcineurin based treatment carries renal and metabolic risks. Long term safety of newer agents remains insufficiently characterized.

Overall, a mechanism based and phenotype oriented approach is supported, but direct comparison between strategies is limited by heterogeneity of available evidence. Further comparative studies with standardized endpoints and longer follow up are required to define optimal sequencing and patient selection.

DISCLOSURE

AUTHORS' CONTRIBUTIONS

All authors contributed substantially to the conception and design of the review, literature analysis and interpretation, drafting and critical revision of the manuscript, and approved the final version for publication.

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All authors have read and agreed with the published version of the manuscript.

USE OF AI

Artificial intelligence tools were used solely to assist with vocabulary refinement and language editing. All conceptual decisions, including study design, data interpretation, and final approval of the manuscript, were made independently by the authors to ensure the integrity and originality of the work.

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