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Review article

Targeted Horizons in Systemic Lupus Erythematosus (SLE): A Comprehensive Review of Passive Immunotherapy from Monoclonal Antibodies to Anti-Idiotype Networks

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Abstract

Systemic lupus erythematosus (SLE) is a hetegeneous autoimmune disease driven by dysregulated B-cell activation, autoantibody production, and type I interferon signalling. For decades, treatment relied on non-specific immunosuppressants and corticosteroids, which carry substantial toxicity and often fail to control disease. The past two decades have seen a paradigm shift with the emergence of passive immunotherapies that precisely target pathogenic pathways. This review provides a comprehensive overview of passive immunotherapy for SLE, covering monoclonal antibodies targeting B cells (rituximab, obinutuzumab, belimumab), cytokine pathways (anifrolumab), co-stimulatory molecules, and emerging cellular therapies including CAR-T cells. Recent network meta-analyses show that telitacicept (odds ratio [OR] 5.2 for SRI-4 response), anifrolumab (OR 1.6 for BICLA), and deucravacitinib (OR 1.6 for BICLA) are superior to standard therapy in moderate-to-severe SLE. The Phase III TULIP-SC trial of subcutaneous anifrolumab achieved a 56.2% BICLA response rate vs. 37.1% for placebo (p=0.0002), with 29.0% attaining DORIS remission. The REGENCY Phase III trial of obinutuzumab in proliferative lupus nephritis demonstrated a complete renal response rate of 46.4% vs. 33.1% (p=0.02). A distinctive emerging frontier is the revival of anti-idiotype antibody therapy—rooted in Jerne's network theory—which aims to neutralise pathogenic autoantibodies or selectively eliminate autoreactive B-cell clones, as supported by murine models and natural anti-idiotypes in IVIg. Despite these advances, disease heterogeneity and the lack of standardised definitions for refractory SLE remain major challenges. CAR-T therapy has shown encouraging early remission rates in refractory SLE, though long-term safety and durability are uncertain. This review synthesises mechanisms, clinical evidence, safety profiles, guideline recommendations, and future directions, highlighting the potential of precision immunotherapies—including anti-idiotype strategies—to achieve sustained remission in SLE.

Keywords:
systemic lupus erythematosus, passive immunotherapy, monoclonal antibodies, anti-idiotype antibodies, B-cell depletion, anifrolumab, belimumab, obinutuzumab, CAR-T therapy, type I interferon, autoimmune disease, precision medicine.

Introduction

Systemic lupus erythematosus is a chronic, multisystem autoimmune disorder characterised by loss of self-tolerance, immune complex deposition, and progressive organ damage (Pan et al., 2020). The disease manifests through non-specific symptoms such as fever, fatigue and arthralgia, with the skin and kidneys frequently affected (Huang, 2023). SLE predominantly affects women and follows a relapsing-remitting pattern (Pan et al., 2020). Despite improvements in supportive care and the introduction of targeted biologics, a subset of patients remains unresponsive to conventional immunosuppressants, experiencing persistent disease activity, cumulative organ damage and reduced quality of life (Mastalerz et al., 2025).

For many years, the European Alliance of Associations for Rheumatology (EULAR) recommended only two biological agents for SLE: belimumab and rituximab (Fanouriakis et al., 2024). However, the therapeutic landscape has expanded significantly, with anifrolumab (an interferon receptor inhibitor) appearing in new SLE treatment guidelines in 2023 (Fanouriakis et al., 2024). Several other biological agents targeting different cells or cytokines are being evaluated in Phase II and Phase III clinical trials, and experimental therapies such as chimeric antigen receptor T-cell therapy or stem cell transplantation appear promising for severe forms of SLE (Tanaka, 2025).

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This review aims to synthesise current knowledge on passive immunotherapy for SLE—defined as the administration of exogenous antibodies or antibody-derived products to modulate immune responses (Casadevall et al., 2015)—covering mechanisms of action, clinical evidence, safety considerations, guideline recommendations and future directions. Particular attention is given to the emerging revival of anti-idiotype antibody strategies as a modern, network-based therapeutic approach (Murphy et al., 2025).

1. Historical Context: From Serum Therapy to Monoclonal Antibodies

The concept of passive antibody administration has a long history. In the 19th century, polyclonal antibodies from xenographic sources were used to treat infectious diseases such as diphtheria (Casadevall et al., 2015). Emil von Behring was awarded the first Nobel Prize in Physiology or Medicine in 1901 for his discovery of serum therapy for diphtheria (Casadevall et al., 2015). These empirical approaches provided the foundation for understanding humoral immunity and the chemical properties of antibodies (Pelletier & Mukhtar, 2023).

The late 20th century brought the development of monoclonal antibody technology, which resulted in many products to treat autoimmune and allergic diseases (Pelletier & Mukhtar, 2023). Early monoclonal antibodies were of xenographic source and were fraught with problems of immunogenicity; these forms did not gain favour until chimerisation took place in the mid-1990s (Pelletier & Mukhtar, 2023). Further development of humanised and then fully human monoclonal antibodies has led to an evolution of therapies for oncologic, inflammatory, autoimmune and other diseases (Huang, 2023). This historical progression set the stage for the application of passive immunotherapy to SLE (Guo et al., 2026).

2. Immunopathology of SLE: Rationale for Passive Immunotherapy

2.1 Dysregulated Immune Response

Dysregulated immune response plays a critical role in SLE, encompassing both innate and adaptive immunity (Pan et al., 2020). Breakdown of self-tolerance is the main pathogenesis of SLE, with the innate and adaptive immune networks interlinked through cytokines, complement, immune complexes and intracellular signalling kinases (Guo et al., 2026).

2.2 Central Role of B Cells

B-cell tolerance and production of autoantibodies are critical mechanisms that drive SLE pathophysiology (Parodis et al., 2023). Excessive proliferation and activation of autoreactive B cells, which drive the production of multiple autoantibodies, constitute a critical mechanism in the pathogenesis of SLE (B cell-targeted therapies, 2025). Activation of B cells through T–B-cell interaction plays a central role in the disease process (Pan et al., 2020).

2.3 Type I Interferon Pathway

SLE is mainly driven by dysregulated B-cell activation and type I interferon (IFN-I) signalling (Guo et al., 2026). The type I interferon pathway has emerged as a key therapeutic target, with elevated IFN signatures correlating with disease activity (Mastalerz et al., 2025).

2.4 T-Cell Abnormalities

Dysregulated T-cell responses also contribute to SLE pathogenesis (Pan et al., 2020). Therapeutic strategies for autoimmune diseases have historically been based on glucocorticoids and immunosuppressive agents that broadly suppress immune responses (Huang, 2023). Novel treatment approaches targeting T-cell signalling pathways are under active investigation (Tanaka, 2025).

3. Types of Passive Immunotherapy for SLE

3.1 B-Cell-Targeted Therapies

B-cell-targeted therapies represent a major category of passive immunotherapy for SLE, including agents that deplete B cells (anti-CD20 antibodies) and those that modulate B-cell survival and activation (BAFF/APRIL antagonists) (B cell-targeted therapies, 2025).

3.1.1 Rituximab

Rituximab is a chimeric anti-CD20 monoclonal antibody that depletes CD20-positive B cells (B cell-targeted therapies, 2025). It has been used off-label in SLE for years. However, the original B-cell depleting clinical trials—EXPLORER (systemic SLE) and LUNAR (lupus nephritis)—failed to achieve statistical significance (B cell-targeted therapies, 2025). Subsequent investigations suggested that failure to attain clinical response was related to inadequate B-cell depletion in tissues: while B cells were depleted in peripheral blood, they remained present in lymph nodes harvested at surgery (Anti-CD20 therapy, 2025). Despite these trial failures, rituximab remains recommended for organ-threatening and refractory disease in the 2023 EULAR guidelines (Fanouriakis et al., 2024).

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3.1.2 Obinutuzumab

Obinutuzumab is a humanised, type II anti-CD20 monoclonal antibody with distinct properties rendering it capable of superior B-cell killing compared to rituximab (Anti-CD20 therapy, 2025). The NOBILITY Phase II trial in proliferative lupus nephritis tested the hypothesis that enhanced B-cell depletion would increase the rate of complete renal response (Anti-CD20 therapy, 2025). This was followed by the Phase III REGENCY study, which demonstrated superiority of obinutuzumab plus standard of care compared to standard of care alone, with complete renal response rates of 46.4 % versus 33.1 %, respectively ($p = 0.02$) (Anti-CD20 therapy, 2025). Robust B-cell depletion with obinutuzumab was responsible for the attainment of significant effect sizes observed in both trials (Anti-CD20 therapy, 2025).

3.1.3 Belimumab

Belimumab is a fully human monoclonal antibody that inhibits B-cell activating factor, thereby reducing B-cell survival and autoantibody production (B cell-targeted therapies, 2025). It was the first biologic approved specifically for SLE and remains a cornerstone of targeted therapy (Fanouriakis et al., 2024). The 2023 EULAR recommendations include belimumab among the biological agents to be considered for prompt initiation to control disease and facilitate glucocorticoid tapering (Fanouriakis et al., 2024).

3.2 Targeting Cytokine Pathways

3.2.1 Anifrolumab (Type I Interferon Receptor Inhibition)

Anifrolumab is a monoclonal antibody that blocks the type I interferon receptor (Mastalerz et al., 2025). In 2023, anifrolumab appeared in new SLE treatment guidelines (Fanouriakis et al., 2024). The Phase III TULIP-SC trial investigated the efficacy and safety of subcutaneous anifrolumab in patients with moderately to severely active, autoantibody-positive SLE receiving standard therapy (AstraZeneca, 2026). The trial met its primary endpoint: 56.2 % of patients receiving anifrolumab achieved a reduction in disease activity at week 52 versus 37.1 % receiving placebo, as measured by the British Isles Lupus Assessment Group-based Composite Lupus Assessment (difference = 19.1 %, 95 % CI 9.0–29.2 %; $p = 0.0002$) (AstraZeneca, 2026). In pre-specified secondary and exploratory endpoints, 29.0 % of patients taking anifrolumab achieved DORIS remission and 40.1 % attained low-level disease activity (AstraZeneca, 2026). The safety profile was consistent with the known clinical profile of intravenous anifrolumab, with the frequency of overall adverse events balanced between groups (AstraZeneca, 2026). Subcutaneous anifrolumab is approved in the European Union and is under regulatory review in other countries (AstraZeneca, 2026).

A network meta-analysis confirmed that anifrolumab exhibited significant BICLA response in moderate-to-severe SLE patients (OR 1.6, 95 % CI 1.3–2.0) (Efficacy and Safety of Biologics for SLE, 2025). For patients with elevated baseline IFN signatures, anti-type I interferon biologics such as anifrolumab and sifalimumab are recommended to maximise clinical benefits (Mastalerz et al., 2025).

3.3 Co-stimulatory Blockade

Therapies targeting co-stimulatory molecules aim to disrupt T-cell–B-cell interactions (B cell-targeted therapies, 2025). Iscalimab, a novel anti-CD40 monoclonal antibody, has shown efficacy in lupus nephritis by reducing proteinuria at 24 weeks (Tanaka, 2025). Treatments targeting B cells and co-stimulatory molecules are expected to be particularly effective given the central role of T-B-cell interaction in pathogenesis (Pan et al., 2020).

3.4 Anti-Idiotype Antibody Therapy: A Modern Revival of Jerne's Network Theory

An intriguing and conceptually elegant approach that has recently regained attention is the use of anti-idiotype antibodies (Murphy et al., 2025). The theoretical foundation was laid in 1973 when Niels Jerne proposed the Network Theory, envisioning the immune system as a functional network of antibodies (idiotypes) and anti-idiotypic antibodies that are made in response to the inherent immunogenicity of immunoglobulin variable chains (Murphy et al., 2025). In 1974, anti-idiotypic responses were observed, providing proof of the network concept (Murphy et al., 2025). The theory posits that the immune system is intricately regulated to achieve tolerance to "self," and that the vast repertoire of antibodies can reciprocally recognise each other, forming a self-regulating circuit (Murphy et al., 2025).

In the context of SLE, where pathology is often driven by a small, highly specific population of "rogue" B cells that produce harmful autoantibodies, anti-idiotype strategies offer a precision approach (Krysov, 2026). These antibodies are designed to bind and neutralise autoantibodies or to eliminate the specific B-cell population that produces them (Krysov, 2026). One of the most studied examples is found in intravenous immunoglobulin (IVIg) preparations. Natural anti-idiotypic antibodies within IVIg can neutralise pathogenic autoantibodies in

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diseases such as SLE, antiphospholipid syndrome and pemphigus vulgaris (Danieli et al., 2025). The anti-idiotypic antibodies in IVIg activate the inhibitory FcγRIIb receptor, leading to off-signalling on B cells and suppression of autoantibody production (Human immunoglobulin therapy, 2026).

Experimental evidence in murine models of SLE has been particularly compelling. Shoenfeld et al. (2002) affinity-purified specific natural polyclonal anti-double-stranded DNA anti-idiotypic antibodies from commercial IVIg (IVIg-ID) and tested them in NZB/W F1 mice. Treatment with concentrated specific anti-double-stranded DNA anti-idiotypic antibodies was more effective in suppressing the humoral reaction and clinical signs of SLE than native IVIg (Shoenfeld et al., 2002). IVIg-ID-treated mice showed a significant decline in anti-double-stranded DNA antibody titres, reduced proteinuria, and a longer survival time (Shoenfeld et al., 2002). Immunohistology revealed only mesangial IgG deposits in the IVIg-ID-treated group, whereas control and IVIg-treated mice showed both mesangial and capillary wall deposits (Shoenfeld et al., 2002).

Further refinements have employed peptide mimetics of anti-double-stranded DNA idiotypes. Blank et al. (2005) introduced a lupus-specific IVIg subfraction prepared by affinity purification on synthetic peptide columns (psIVIG). These psIVIG preparations inhibited the binding of anti-double-stranded DNA antibodies from 12 lupus patients to double-stranded DNA by 15–46 % for individual peptides and up to 87–94 % for a cocktail (Blank et al., 2005). In NZB/W F1 mice, psIVIG improved circulating anti-double-stranded DNA antibodies, leukopenia, proteinuria and immunoglobulin deposits in the kidneys (Blank et al., 2005). Importantly, these effects were achieved at 200-times lower concentrations than regular IVIg (Blank et al., 2005).

Despite these promising preclinical results, clinical translation has faced challenges. The initial decline in popularity of anti-idiotype approaches was partly due to the clinical failure of early anti-idiotypic antibodies as therapeutics, which led to scepticism regarding the physiological relevance of the network phenomenon (Murphy et al., 2025). However, the network theory has never been disproven, and modern evidence continues to support its validity (Murphy et al., 2025). The variable outcomes of IVIg treatment in SLE—ranging from resolution of proteinuria to worsening nephritis—may be related to the variable enrichment of different lots of IVIg in suppressive anti-pathogenic idiotype antibodies (Pathogenic anti-DNA idiotype-reactive IgG, 1994).

Looking forward, the future utility of anti-idiotype therapy may involve cocktails of different monoclonal anti-idiotypic antibodies (Murphy et al., 2025). Studies are focusing on how the network theory involves the generation of potential “antigen mirror” effects and how the network ultimately regulates both B-cell and T-cell responses over time (Murphy et al., 2025). Engineered anti-idiotypic antibodies conjugated to immunotoxins (e.g., saporin) have shown specific potential in selectively eliminating pathogenic idiotype-positive B cells while sparing the normal B-cell repertoire (Suppression of experimental SLE, 1994). These modern incarnations of anti-idiotype therapy, combined with advances in monoclonal antibody engineering and peptide chemistry, are breathing new life into Jerne’s half-century-old network concept as a viable precision immunotherapy for SLE (Krysov, 2026; Murphy et al., 2025).

3.5 Emerging B-Cell Depletion Approaches

Various other B-cell depletion approaches are under investigation for SLE, including chimeric antigen receptor T-cell therapy, T-cell-engaging therapy, and monoclonal antibodies directed against CD19, BAFF receptor or B-cell maturation antigen (Chimeric Antigen Receptor T Cell Therapy, 2025; B cell-targeted therapies, 2025).

4. Clinical Trial Evidence

4.1 Network Meta-Analysis Findings

A comprehensive Bayesian network meta-analysis including 29 randomised controlled trials with a total of 13,712 patients compared the efficacy and safety of biologics for SLE (Efficacy and Safety of Biologics for SLE, 2025). Key findings are summarised in **Table 1**.

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Table 1. Efficacy of biologics compared to standard therapy in moderate-to-severe SLE patients (data from Efficacy and Safety of Biologics for SLE, 2025)

Biologic Agent	Primary Efficacy Outcome	Odds Ratio (95 % CI)
Telitacicept	SRI-4 response	5.2 (1.4–20.0)
Anifrolumab	BICLA response	1.6 (1.3–2.0)
Deucravacitinib	BICLA response	1.6 (1.0–2.5)

Regarding safety, no significant statistical differences were observed among the various treatment options (Efficacy and Safety of Biologics for SLE, 2025). Cluster analysis revealed that deucravacitinib exhibited the best efficacy-safety profile. Telitacicept showed the most pronounced improvement in SRI-4 response but was associated with higher rates of adverse events and serious adverse events, whereas anifrolumab and deucravacitinib displayed advantages in reducing serious adverse events (Efficacy and Safety of Biologics for SLE, 2025).

4.2 Head-to-Head Comparisons

A systematic review and meta-analysis using indirect comparisons compared telitacicept and belimumab for SLE treatment, searching six databases for randomised controlled trials published up to November 2025 (Xing et al., 2024). These analyses provide urgently needed evidence for comparing current and emerging SLE biologics (Xing et al., 2024).

4.3 Emerging CAR-T Therapy

CAR-T therapy, a revolutionary modality in oncology, is now emerging as a promising approach in severe autoimmune diseases including SLE (Chimeric Antigen Receptor T Cell Therapy, 2025). By redirecting autologous T cells to target B-cell antigens such as CD19 or BCMA, CAR-T therapy enables deep and sustained B-cell depletion, potentially resetting immune tolerance (Chimeric Antigen Receptor T Cell Therapy, 2025). Early case series have reported encouraging remission rates and serologic improvements in refractory SLE (Chimeric Antigen Receptor T Cell Therapy, 2025).

One example is IMPT-514, a bispecific chimeric antigen receptor targeting CD19 and CD20, currently in Phase I/II clinical evaluation for active, refractory lupus nephritis and SLE (Chimeric Antigen Receptor T Cell Therapy, 2025). IMPT-514 treatment consists of a single infusion of CAR-transduced autologous T cells administered intravenously after a lymphodepleting therapy regimen (Chimeric Antigen Receptor T Cell Therapy, 2025). The long-term durability, relapse risk, safety profile and cost-effectiveness of CAR-T therapy in autoimmune disease remain uncertain and require confirmation in larger, controlled trials (Chimeric Antigen Receptor T Cell Therapy, 2025).

5. Safety Considerations

5.1 General Safety Profile of Biologics

The network meta-analysis indicated that there were no significant statistical differences in adverse events and serious adverse events among various biologic treatment options for SLE (Efficacy and Safety of Biologics for SLE, 2025). However, telitacicept was associated with higher rates of adverse events and serious adverse events compared to other agents (Efficacy and Safety of Biologics for SLE, 2025).

5.2 Infection Risk

Immunosuppression-related infections remain a concern with passive immunotherapy (2025 ACR Guideline, 2025). The 2025 ACR guidelines include a Good Clinical Practice Statement that all people with SLE should receive screening, monitoring and management for comorbid conditions, including infection (2025 ACR Guideline, 2025). The EULAR recommendations similarly emphasise preventative measures for infections (Fanouriakis et al., 2024).

5.3 Long-Term Safety

The long-term safety profile of newer agents, particularly CAR-T therapy, remains uncertain and requires confirmation in larger, controlled trials with extended follow-up (Chimeric Antigen Receptor T Cell Therapy, 2025).

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6. Clinical Practice Guidelines

6.1 EULAR 2023 Recommendations

The EULAR Task Force agreed on five overarching principles and 13 recommendations concerning the use of hydroxychloroquine, glucocorticoids, immunosuppressive drugs (methotrexate, mycophenolate, azathioprine, cyclophosphamide), calcineurin inhibitors (cyclosporine, tacrolimus, voclosporin), and biologics (belimumab, anifrolumab, rituximab) (Fanouriakis et al., 2024). Key recommendations include:

- Hydroxychloroquine is recommended for all patients with lupus at a target dose of 5 mg/kg real body weight per day (Fanouriakis et al., 2024).
- Prompt initiation of immunosuppressive drugs and/or biological agents (anifrolumab, belimumab) should be considered to control disease and facilitate glucocorticoid tapering/discontinuation (Fanouriakis et al., 2024).
- Cyclophosphamide and rituximab should be considered in organ-threatening and refractory disease, respectively (Fanouriakis et al., 2024).
- For active lupus nephritis, add-on therapy with belimumab or calcineurin inhibitors should be considered (Fanouriakis et al., 2024).

6.2 American college of Rheumatology (ACR) 2025 Guidelines

The ACR 2025 SLE treatment guidelines emphasise universal use of hydroxychloroquine, minimising glucocorticoid exposure, and early introduction of conventional and/or biologic immunosuppressive therapies (2025 ACR Guideline, 2025). The guidelines shift care to organ-specific approaches, prioritising organ threat and disease intensity over a one-size-fits-all immunosuppressive approach (2025 ACR Guideline, 2025). Recommendations were rated by consensus as being either Strong or Conditional, though the level of evidence for nearly all recommendations is either very low or low (2025 ACR Guideline, 2025).

6.3 Treat-to-Target Strategies

Both EULAR and ACR guidelines emphasise treat-to-target strategies centred on clinical remission and low disease activity as primary goals (Fanouriakis et al., 2024; 2025 ACR Guideline, 2025). Recently revised treatment recommendations now emphasise DORIS remission attainment as the primary goal of care and strongly encourage tapering toward oral corticosteroid discontinuation to minimise long-term exposure (Fanouriakis et al., 2024).

7. Challenges and Limitations

7.1 Disease Heterogeneity

The heterogeneity of SLE is a crucial aspect contributing to the failure of large clinical trials for new targeted therapies (Guo et al., 2026). The complexity of SLE immunopathogenesis and disease heterogeneity present significant challenges in the development of effective immunological therapies (Huang, 2023).

7.2 Refractory Disease

There is no universally accepted definition for refractory SLE (Mastalerz et al., 2025). Most studies define refractoriness pragmatically as failure to achieve sustained disease control despite at least two standard immunosuppressants or biologics at adequate dose and duration (Mastalerz et al., 2025). This heterogeneity complicates comparison across studies and emphasises the need for standardised response definitions in future clinical trials (Mastalerz et al., 2025).

7.3 Trial Design

The reliance on indirect comparisons in network meta-analyses necessitates cautious interpretation of findings (Efficacy and Safety of Biologics for SLE, 2025). Further research should prioritise direct head-to-head trials to validate the efficacy and safety profiles of biologics (Xing et al., 2024).

7.4 Access and Cost

The real-world scalability, accessibility and translational windows of emerging therapies over the next 5 to 10 years remain important considerations (Guo et al., 2026).

8. Future Directions

8.1 Precision Immunotherapy

Converging advances in human immunology, molecular medicine and cell engineering are enabling a paradigm shift towards mechanism-based precision therapies (Guo et al., 2026). Key therapeutic domains include:

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1. **Selective targeting of immune-cell surface antigens and costimulatory pathways** – BAFF/APRIL antagonism and CD19-directed CAR-T strategies that deplete or recalibrate autoreactive B-cell compartments (B cell-targeted therapies, 2025; Chimeric Antigen Receptor T Cell Therapy, 2025).
2. **Modulation of proinflammatory cytokine networks and intracellular signalling cascades** – including IFN-I pathway blockade and pharmacologic inhibition of JAK/STAT and mTOR axes (Mastalerz et al., 2025; Tanaka, 2025).
3. **Next-generation, autoantibody-focused approaches** – such as mimetic peptides, CAAR-T cells, and antigen-specific Tregs that aim to confine immune intervention to pathogenic antigenic circuits while minimising systemic immunosuppression (Guo et al., 2026).

8.2 CAR-T Therapy Expansion

One of the most disruptive developments presented at EULAR 2025 was the emergence of cell therapies as a treatment strategy in autoimmune disease (Chimeric Antigen Receptor T Cell Therapy, 2025). Historically reserved for oncology, CAR-T technology is now being explored as a curative modality in conditions like lupus and myositis (Chimeric Antigen Receptor T Cell Therapy, 2025). Researchers have succeeded in achieving long-term remission in patients with severe, long-standing SLE with the help of CAR-T cells targeting the B-cell compartment (Chimeric Antigen Receptor T Cell Therapy, 2025).

8.3 Oral Targeted Agents

The only available oral treatments for SLE are largely limited to antimalarials, corticosteroids and voclosporin (Mastalerz et al., 2025). Emerging oral agents such as enpatoran (TLR7/8 inhibitor) and deucravacitinib (TYK2 inhibitor) represent potential new therapeutic classes for SLE (Efficacy and Safety of Biologics for SLE, 2025; Tanaka, 2025).

8.4 Artificial Intelligence in Immunotherapy Development

The emerging role of artificial intelligence and machine learning in addressing inter-patient heterogeneity—ranging from multi-omic molecular endotyping and predictive therapeutic modelling to the computational design of next-generation antibodies and CARs—may accelerate progress towards mechanism-guided, individualised and durable disease control and remission in SLE (Guo et al., 2026).

Conclusion

Passive immunotherapy has transformed the treatment landscape of systemic lupus erythematosus over the past two decades (Huang, 2023; Guo et al., 2026). From the early disappointments of rituximab trials to the regulatory approvals of belimumab and anifrolumab, and now to the promising frontier of CAR-T therapy and the revival of anti-idiotype network strategies, the field has made remarkable progress (B cell-targeted therapies, 2025; Chimeric Antigen Receptor T Cell Therapy, 2025; Murphy et al., 2025). The recent Phase III TULIP-SC trial demonstrating efficacy of subcutaneous anifrolumab with DORIS remission rates of 29.0 % and the REGENCY study showing superiority of obinutuzumab in lupus nephritis represent major advances (AstraZeneca, 2026; Anti-CD20 therapy, 2025). Network meta-analyses have quantified the superior efficacy of agents such as telitacicept (OR 5.2 for SRI-4), anifrolumab (OR 1.6 for BICLA) and deucravacitinib (OR 1.6 for BICLA) compared to standard therapy (Efficacy and Safety of Biologics for SLE, 2025).

However, significant challenges remain. Disease heterogeneity continues to complicate clinical trial design and patient selection (Guo et al., 2026). The lack of universally accepted definitions for refractory disease and response endpoints hampers cross-study comparisons (Mastalerz et al., 2025). Long-term safety data, particularly for cellular therapies, are still emerging (Chimeric Antigen Receptor T Cell Therapy, 2025). Access to these often costly biologics remains limited in many healthcare systems (Guo et al., 2026).

The future of SLE treatment lies in personalised, targeted therapies that minimise side effects and improve patient outcomes (Guo et al., 2026). Synergising mechanistic breakthroughs in immunology, molecular medicine and computational biology may accelerate progress toward mechanism-guided, individualised and durable disease control and remission in SLE (Guo et al., 2026). As therapeutic options continue to expand, the goal of achieving sustained remission without chronic immunosuppression—once a distant hope—is moving closer to clinical reality (Tanaka, 2025). Anti-idiotype strategies, built upon Jerne's network theory, exemplify the potential of harnessing natural immune regulatory circuits to restore self-tolerance with unprecedented specificity (Murphy et al., 2025; Krysov, 2026).

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No original datasets were generated for this review article. All cited data and findings are available within the original research publications referenced in the manuscript, accessible via the provided Digital Object Identifiers (DOIs) or through respective journal platforms.

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