Biological Therapies in Systemic Lupus Erythematosus: Current Evidence, Emerging Targets, and Future Directions

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Abstract

Background: Systemic lupus erythematosus (SLE) is a complex multisystem autoimmune disease frequently encountered in internal medicine, characterized by dysregulated innate and adaptive immune responses leading to widespread tissue injury. Despite advances in conventional immunosuppressive therapy, many patients experience relapses, treatment resistance, or drug-related toxicity. The heterogeneity of SLE across organ systems — renal, hematologic, neuropsychiatric, and cardiovascular — poses major therapeutic challenges in daily medical practice. In recent years, biologic agents have emerged as promising targeted options, addressing the underlying immune mechanisms while potentially reducing corticosteroid exposure and improving quality of life.

Aim:

This review aims to provide an evidence-based and clinically oriented synthesis of biological therapies in SLE, focusing on their immunologic rationale, therapeutic efficacy, safety, and practical relevance within internal medicine. It examines approved and emerging biologic agents, explores their organ-specific implications, and highlights how these targeted therapies are reshaping management paradigms for internists caring for patients with systemic disease.

Conclusion:

Biological therapies have transformed the therapeutic landscape of SLE, moving from empirical immunosuppression toward precision medicine grounded in immune-pathogenic mechanisms. Agents such as belimumab and anifrolumab have demonstrated consistent benefits in reducing disease activity and steroid dependence, while newer molecules targeting B cells, cytokine pathways, and co-stimulatory signals show encouraging results in clinical trials. For internal medicine practitioners, familiarity with these agents—along with vigilant monitoring for infection risk, vaccination strategies, and long-term safety—has become essential. Ongoing research into biomarkers, patient stratification, and combination strategies promises to refine biologic use further, bridging immunopathogenesis with individualized clinical care. Understanding these therapies in the context of systemic organ involvement is crucial for optimizing outcomes and guiding the future of multidisciplinary SLE management.

Keywords: *Biological Therapies, Systemic Lupus Erythematosus, Future Directions*

Introduction

Clinical Burden and Relevance in Internal Medicine

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disorder characterized by loss of immune tolerance, production of autoantibodies, and widespread inflammation leading to tissue and organ damage. Within internal medicine, SLE represents a prototypic systemic disease requiring broad clinical insight due to its protean manifestations involving renal, hematologic, cardiovascular, pulmonary, and neuropsychiatric systems. The disease primarily affects women of reproductive age but carries lifelong morbidity and premature mortality. Despite improved survival rates over the past decades, patients continue to experience substantial disease burden driven by relapses, cumulative organ damage, and treatment-related complications, particularly from chronic corticosteroid use [1].

Limitations of Conventional Therapies

Conventional therapy for SLE relies on glucocorticoids, antimalarials such as hydroxychloroquine, and nonspecific immunosuppressants including azathioprine, mycophenolate mofetil, methotrexate, and cyclophosphamide. Although these agents suppress inflammation and prevent flares, they act broadly on immune cells without targeting specific pathogenic mechanisms. This lack of precision often results in inadequate disease control and significant adverse effects, such as infections, metabolic disorders, bone loss, and cardiovascular risk. Additionally, a subset of patients remains refractory or develops dependence on corticosteroids, leading to long-term complications and diminished quality of life. The need for safer, more selective treatments that modulate the immune response without global suppression has become increasingly apparent [2].

Biologic Therapy — A New Era in SLE Treatment

Biological agents have revolutionized therapeutic strategies in autoimmune diseases by specifically targeting key molecules involved in immune dysregulation. In SLE, the development of biologics has been guided by deeper insights into disease immunopathogenesis, particularly the roles of B cells, T-cell co-stimulation, and cytokine networks such as type I interferons. Agents like **belimumab**, a monoclonal antibody targeting B-lymphocyte stimulator (BLyS), and **anifrolumab**, which inhibits the type I interferon receptor, have demonstrated significant clinical efficacy and steroid-sparing potential. Their introduction has shifted the management paradigm toward mechanism-based and individualized therapy, allowing better disease control and improved safety profiles compared with conventional agents [3].

Aim and Scope of the Review

This review aims to provide an evidence-based synthesis of biological therapies in SLE from the internal medicine perspective. It focuses on the immunologic rationale, clinical efficacy, and safety of approved and emerging biologics while integrating their relevance across systemic organ manifestations. The review also addresses practical considerations such as patient selection, monitoring, infection risk, and integration of biologic therapy into multidisciplinary care models frequently encountered in internal medicine practice. By bridging mechanistic understanding with clinical application, this work intends to assist clinicians in translating recent advances into effective patient-centered care [4].

Research Gap and Future Directions

Despite growing evidence and regulatory approvals, the clinical uptake of biologic therapies in SLE remains limited outside rheumatology specialty settings. The heterogeneity of disease phenotypes, variable therapeutic response, and absence of validated biomarkers for predicting treatment success continue to challenge routine clinical use. Moreover, the long-term safety of biologic combinations and their optimal integration with conventional immunosuppressive therapy remain under investigation. These gaps underscore the need for further translational research, real-world data, and interdisciplinary collaboration to optimize biologic utilization across the spectrum of internal medicine [5].

Pathophysiology of Systemic Lupus Erythematosus — Basis for Targeted Biological Therapy

Overview of Immune Dysregulation in SLE

The pathophysiology of systemic lupus erythematosus (SLE) is defined by a profound loss of immune self-tolerance resulting in the activation of autoreactive lymphocytes and production of pathogenic autoantibodies. These autoantibodies form immune complexes that deposit in tissues, triggering complement activation and inflammation. The immune response involves both innate and adaptive components, including dendritic cells, B cells, T cells, and a range of cytokines that perpetuate chronic immune activation. From an internal medicine standpoint, this immune dysregulation manifests clinically as multi-organ injury, with nephritis, cytopenias, and vasculitis representing key features of systemic involvement [6].

Role of B Cells in Disease Pathogenesis

B cells play a central role in SLE by producing autoantibodies directed against nuclear and cytoplasmic antigens such as double-stranded DNA, Smith antigen, and ribonucleoproteins. Beyond antibody production, B cells act as antigen-presenting cells and secrete proinflammatory cytokines, thereby amplifying immune responses. Elevated levels of B-lymphocyte stimulator (BLyS), also known as BAFF (B-cell activating factor), support the survival of autoreactive B cells and correlate with disease activity. This pivotal role has made the BLyS pathway a prime therapeutic target, leading to the development of **belimumab**, the first approved biologic agent for SLE. By inhibiting BLyS, belimumab reduces the survival of autoreactive B cells and mitigates autoantibody-mediated damage [7].

T-Cell Dysfunction and Co-stimulatory Signaling

T cells contribute to lupus pathogenesis through aberrant activation, defective regulatory function, and enhanced help to B cells. Disrupted T-cell receptor signaling, increased expression of co-stimulatory molecules such as CD40L, and altered cytokine profiles lead to sustained autoimmunity. The imbalance between effector T helper (Th) subsets and regulatory T cells (Tregs) promotes chronic inflammation and tissue injury. Therapeutic strategies targeting T-cell co-stimulation, such as **abatacept**, aim to restore immune homeostasis by blocking CD80/CD86–CD28 interactions, thereby limiting T-cell activation and downstream autoantibody production [8].

Type I Interferon Pathway Activation

The type I interferon (IFN) signaling pathway has emerged as a hallmark of SLE pathogenesis. Plasmacytoid dendritic cells produce excessive interferon-alpha in response to nucleic acid-containing immune complexes, leading to upregulation of interferon-stimulated genes that sustain immune activation. This “interferon signature” is observed in the majority of SLE patients and correlates with disease activity, especially in those with cutaneous and hematologic manifestations. Targeting the type I IFN receptor with **anifrolumab** has demonstrated significant clinical efficacy, underscoring the translational relevance of this pathway. Inhibition of interferon signaling interrupts the vicious cycle of immune activation and inflammation, marking a pivotal step toward disease-specific intervention [9].

Cytokine Networks and Innate Immune Activation

Cytokines such as interleukin (IL)-6, IL-10, and IL-17, along with tumor necrosis factor-alpha (TNF-α), play critical roles in amplifying the inflammatory cascade in SLE. Dysregulated cytokine production enhances B-cell differentiation, T-cell activation, and neutrophil extracellular trap (NET) formation, all of which contribute to organ damage. Therapies targeting these cytokines are under investigation, with IL-6 blockade showing promise in early trials. Understanding the complexity of cytokine interactions provides a foundation for novel biologics that modulate these upstream inflammatory signals rather than broad immunosuppression [10].

Complement Activation and Immune Complex Deposition

Complement activation is a central pathogenic mechanism in SLE, particularly in lupus nephritis.

Immune complexes formed by autoantibodies and nuclear antigens activate the classical complement pathway, leading to inflammation and tissue damage. Deficiencies in early complement components (C1q, C4) paradoxically predispose to SLE due to impaired clearance of apoptotic cells. Therapies that modulate complement activation, such as C5 inhibitors, are being explored as adjunctive approaches to mitigate end-organ injury in severe cases. Understanding complement biology bridges the gap between immune dysfunction and the systemic manifestations of lupus encountered in internal medicine [11].

Rationale for Targeted Biological Therapy

The expanding knowledge of lupus immunopathogenesis has shifted therapeutic strategies from nonspecific suppression toward selective immune modulation. Biologic agents provide an opportunity to disrupt disease-driving pathways with greater precision, reducing collateral immunosuppression. By targeting B-cell activation, co-stimulation, and cytokine signaling, biologics aim to restore immune equilibrium rather than simply dampen inflammation. For internists managing complex lupus cases, this mechanistic understanding underpins the rational selection of biologic agents based on organ involvement, serologic profiles, and disease phenotype [12].

Rationale for Biologic Therapy in SLE from an Internal Medicine Perspective

Bridging Pathophysiology and Clinical Practice

For the internist managing systemic lupus erythematosus (SLE), understanding the immunologic foundation of the disease is crucial to selecting appropriate therapy. Conventional treatments such as glucocorticoids and cytotoxic agents act broadly across immune pathways, providing rapid control but at the cost of cumulative toxicity. In contrast, biologic therapies are designed to modulate discrete immunologic checkpoints implicated in lupus pathogenesis. Their selective action allows clinicians to target specific drivers of disease activity, offering a balance between efficacy and safety that aligns with the principles of precision medicine. The integration of biologic agents into the internal medicine framework reflects the transition from empiric therapy to mechanism-guided intervention [13].

Reducing Corticosteroid Dependence and Long-Term Toxicity

One of the most compelling rationales for introducing biologic therapy is the potential to minimize corticosteroid exposure, a major determinant of long-term morbidity in SLE. Chronic steroid use is associated with hypertension, diabetes, osteonecrosis, infections, and accelerated atherosclerosis—complications frequently managed in internal medicine. Biologic agents such as belimumab and anifrolumab have demonstrated steroid-sparing effects in randomized controlled trials, achieving sustained disease control while allowing for dose reduction or discontinuation of prednisone. This shift toward targeted therapy thus addresses not only disease activity but also the metabolic and systemic sequelae that complicate lupus care in general medical practice [14].

Improving Disease Control in Refractory and Multisystem Disease

A subset of SLE patients exhibit partial or poor response to standard immunosuppressive regimens. These refractory cases, often characterized by persistent serologic activity, lupus nephritis, or hematologic manifestations, pose significant therapeutic challenges. Biologic agents offer new avenues for these patients by specifically targeting the immunologic pathways responsible for treatment resistance. Belimumab has demonstrated benefit in refractory lupus and nephritis, while anifrolumab has shown efficacy in cutaneous and systemic disease subtypes. For internists, these developments expand therapeutic possibilities, particularly for patients with multi-organ involvement requiring coordinated care across specialties [15].

Enhancing Safety Through Targeted Modulation

Broad immunosuppressive therapies impair host defense mechanisms, predisposing patients to infections and malignancy. Biologic agents, by contrast, act at defined immunologic checkpoints, limiting collateral suppression of protective immunity. For example, blocking BLyS or the type I interferon receptor does not generally induce severe lymphopenia or bone marrow suppression. Nonetheless, vigilance remains essential, as biologics can still increase susceptibility to specific infections, particularly viral reactivation and opportunistic pathogens. The internist's role includes

monitoring for early infection signs, ensuring appropriate vaccination, and balancing therapeutic benefits against risks in patients with comorbid conditions [16].

The biologic era has ushered in a broader paradigm of personalized medicine in systemic autoimmune disease. By linking disease phenotype, serologic profile, and immunologic signature to specific therapeutic targets, clinicians can tailor treatment more effectively. This is particularly relevant to internal medicine, where patients often present with overlapping syndromes or atypical systemic manifestations. Biomarkers such as elevated BLyS levels, interferon gene expression signatures, or autoantibody patterns may eventually guide biologic selection. The integration of such markers into clinical decision-making represents an evolving frontier in SLE care that aligns with internal medicine's focus on individualized and evidence-based management [17].

For internists, biologic therapy requires not only pharmacologic understanding but also coordinated multidisciplinary management. Regular monitoring for infection, organ function, and immunologic markers is essential. Biologic treatment plans should be individualized based on disease activity indices, organ involvement, and prior treatment exposure. As more biologic options become available, internal medicine physicians must remain conversant with efficacy data, mechanisms, and safety profiles to appropriately co-manage patients alongside rheumatologists, nephrologists, and dermatologists. This collaboration ensures optimal disease control while addressing systemic and metabolic complications frequently seen in hospital and outpatient settings [18].

B-Cell–Targeted Therapies

B cells play a pivotal role in the pathogenesis of systemic lupus erythematosus (SLE) through autoantibody production, antigen presentation, and cytokine secretion. These functions contribute to the chronic activation of both innate and adaptive immunity, perpetuating inflammation and tissue injury. Given their central role, B cells represent one of the earliest and most rational therapeutic targets for biologic intervention. The goal of B-cell–directed therapy is to attenuate the autoimmune cascade while preserving sufficient immune competence to prevent infection.

Belimumab, a fully human monoclonal antibody targeting B-lymphocyte stimulator (BLyS, also known as BAFF), was the first biologic agent approved for SLE. By binding soluble BLyS, belimumab inhibits its interaction with B-cell receptors, leading to decreased survival of autoreactive B cells and reduced autoantibody formation. The pivotal BLISS-52 and BLISS-76 trials demonstrated significant improvement in disease activity indices, reduced flare rates, and steroid-sparing effects compared with standard therapy. Subsequent studies confirmed its safety and benefit across diverse populations and organ systems, including lupus nephritis, for which belimumab gained regulatory approval in 2020. For internists, belimumab offers a viable option in patients with moderate to severe disease unresponsive to conventional agents, particularly those with renal or musculoskeletal involvement who require long-term immunosuppression minimization [19].

Rituximab, a chimeric monoclonal antibody targeting CD20 on pre-B and mature B lymphocytes, induces B-cell depletion through complement-mediated and antibody-dependent cytotoxicity. Although two major phase III trials (EXPLORER and LUNAR) did not meet their primary endpoints, extensive real-world experience and open-label studies have established rituximab as a valuable option for refractory SLE, particularly in severe lupus nephritis, hematologic cytopenias, and neuropsychiatric disease. Its utility in internal medicine is underscored by its efficacy in multi-organ disease and in patients requiring hospitalization for severe flares. Despite its broad immunologic effects, rituximab remains generally well-tolerated when used with appropriate infection prophylaxis and monitoring for hypogammaglobulinemia [20].

Beyond belimumab and rituximab, several novel anti–B-cell strategies are under active investigation. Agents such as **obinutuzumab**, a humanized anti-CD20 antibody with enhanced B-cell–depleting capacity, have shown encouraging results in refractory lupus nephritis. Other approaches target B-cell survival factors or plasma cell differentiation through inhibition of BAFF receptor signaling and CD19-mediated pathways. These emerging biologics may provide alternatives for patients with incomplete

responses or relapsing disease despite conventional and first-line biologic therapy. From an internal medicine perspective, understanding these therapies facilitates individualized care, especially for patients managed across multiple specialties where disease manifestations overlap [21].

The evolution of B-cell–targeted therapy in SLE exemplifies the translation of immunopathogenic insight into clinical application. By modulating rather than abolishing B-cell activity, biologic agents have achieved meaningful reductions in disease activity and corticosteroid burden while maintaining acceptable safety profiles. Ongoing clinical trials continue to refine the optimal timing, combination strategies, and biomarkers predicting response, reinforcing the centrality of B-cell modulation in the modern therapeutic algorithm of SLE. For internists, these advances not only expand treatment options but also underscore the need for multidisciplinary coordination and vigilant long-term follow-up [22].

Cytokine Inhibitors and Interferon Pathway Blockade

Cytokine dysregulation represents a fundamental feature of systemic lupus erythematosus (SLE), orchestrating the interaction between innate and adaptive immune responses. Among these cytokines, type I interferons, interleukins (ILs), and tumor necrosis factor (TNF) play pivotal roles in amplifying inflammation and sustaining autoimmunity. The therapeutic targeting of cytokine pathways has therefore become a cornerstone of biologic development in SLE, offering more precise immunomodulation than traditional immunosuppressive agents. For internists, the advent of cytokine inhibitors has expanded the treatment landscape, particularly for patients with severe systemic disease or intolerance to standard therapy.

The **type I interferon (IFN) pathway** has emerged as the most validated cytokine target in lupus. Excessive production of IFN-α by plasmacytoid dendritic cells drives the expression of interferon-stimulated genes that perpetuate B-cell activation and tissue inflammation. **Anifrolumab**, a fully human monoclonal antibody directed against the type I interferon receptor subunit 1 (IFNAR1), effectively blocks signaling from all type I interferons. The phase III TULIP-1 and TULIP-2 trials demonstrated that anifrolumab significantly improved global disease activity, reduced flares, and enabled steroid tapering compared with placebo. Improvements were particularly notable in mucocutaneous and musculoskeletal domains, with acceptable safety profiles dominated by mild viral infections such as herpes zoster. The approval of anifrolumab marked a major step toward cytokine-based therapy in SLE, confirming the clinical relevance of the interferon signature long recognized in pathophysiologic studies [23].

Beyond interferon blockade, **interleukin-6 (IL-6)** and **interleukin-12/23** pathways are under active exploration as potential therapeutic targets. IL-6 promotes B-cell differentiation, antibody production, and acute-phase response, linking immune activation to systemic inflammation and endothelial dysfunction. Trials with IL-6 receptor inhibitors such as **tocilizumab** have demonstrated modest improvements in arthritis and serologic activity, though infectious complications and limited durability of response have tempered enthusiasm. Nevertheless, IL-6 inhibition remains a rational approach for patients with inflammatory features overlapping with other autoimmune conditions, a common clinical scenario in internal medicine [24].

The **IL-12/23 axis**, involving Th1 and Th17 differentiation, has also been implicated in lupus pathogenesis, particularly in cutaneous and renal disease. **Ustekinumab**, a monoclonal antibody blocking the shared p40 subunit of IL-12 and IL-23, has shown encouraging results in early trials, leading to reductions in disease activity scores and improved skin manifestations. However, larger studies are required to confirm its efficacy and define its role relative to other biologic agents. These findings underscore the diversity of cytokine-mediated pathways in lupus and highlight the potential for combination or sequential biologic therapy in refractory disease [25].

Emerging cytokine targets include **interleukin-17 (IL-17)** and **B-cell–activating cytokine BAFF**, both of which bridge innate and adaptive immunity. IL-17 contributes to neutrophil recruitment and tissue inflammation, while BAFF amplifies B-cell survival and antibody production. Dual blockade of BAFF and APRIL (A Proliferation-Inducing Ligand) is under investigation with agents such as **telitacicept**,

which may achieve deeper modulation of the B-cell axis and greater disease control. These biologics represent the next generation of cytokine-focused therapy aiming to provide broader yet more physiologic immune regulation [26].

From the internal medicine perspective, cytokine inhibition holds particular promise for patients with diffuse systemic involvement, refractory cutaneous disease, or steroid dependence. The availability of anifrolumab and ongoing evaluation of IL-targeted therapies offer opportunities for individualized treatment, especially in patients with comorbidities limiting traditional immunosuppression. Close monitoring for infections, vaccination before therapy initiation, and multidisciplinary coordination remain essential to maximize safety and efficacy. As understanding of cytokine networks deepens, their targeted blockade is expected to integrate increasingly into the standard of care for systemic lupus erythematosus [27].

Cellular and Co-stimulatory Modulation Therapies

Aberrant T-cell activation plays a central role in the immunopathogenesis of systemic lupus erythematosus (SLE), contributing to autoantibody production, cytokine release, and loss of self-tolerance. Therapeutic strategies directed toward modulating T-cell signaling and co-stimulation aim to restore immune homeostasis without inducing broad immunosuppression. From an internal medicine standpoint, these therapies hold promise for improving disease control in patients with refractory systemic involvement and for reducing corticosteroid burden in those requiring long-term immunomodulation.

One of the best-characterized agents in this class is **abatacept**, a fusion protein composed of the extracellular domain of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) linked to an IgG1 Fc fragment. Abatacept inhibits T-cell activation by blocking the interaction between CD80/CD86 on antigen-presenting cells and CD28 on T cells. Although early randomized controlled trials did not meet their primary endpoints, post-hoc analyses and real-world studies have demonstrated abatacept's benefit in specific lupus subsets, including musculoskeletal and serositis-dominant disease. Its mechanism offers a more physiologic approach to immune regulation, particularly valuable for internal medicine physicians managing patients with overlapping autoimmune features such as rheumatoid-like arthritis or mixed connective tissue disease [28].

Another emerging approach involves **low-dose interleukin-2 (IL-2)** therapy, which selectively expands and activates regulatory T cells (Tregs) while suppressing effector T-cell and Th17 responses. In SLE, defective Treg function contributes to the persistence of autoimmunity; restoring this regulatory network may re-establish tolerance. Clinical studies using intermittent low-dose IL-2 have reported improvements in global disease activity, serologic parameters, and reduction in corticosteroid requirement with an excellent safety profile. This therapy is particularly appealing for internists, as it offers immune restoration rather than suppression and may be beneficial in patients at risk for infection or metabolic complications from standard therapies [29].

Efforts to further modulate T-cell activation include investigational agents targeting **CD40–CD40L** and **ICOS–ICOSL** co-stimulatory pathways, which mediate B-cell help and antibody class switching. Monoclonal antibodies such as **dapirolizumab pegol** (anti-CD40L) have demonstrated promising reductions in disease activity and flare frequency in phase II trials, with acceptable tolerability. These agents may become valuable tools for managing patients with systemic disease unresponsive to B-cell or cytokine-targeted therapies. Their integration into clinical practice will depend on long-term safety data and identification of biomarkers predicting response [30].

Beyond these biologic agents, strategies to re-balance immune cell networks through **cellular therapies** are under early investigation. These include adoptive transfer of autologous regulatory T cells and mesenchymal stem cell therapy, both of which aim to restore tolerance and suppress inflammatory circuits. While still experimental, such approaches represent the frontier of biologic modulation, aligning with internal medicine's growing focus on personalized and regenerative immune therapy [31].

Overall, T-cell and co-stimulatory modulation therapies provide a complementary dimension to B-cell

and cytokine blockade in SLE management. For internists, understanding their mechanisms and clinical applicability is essential for comprehensive care of patients with complex autoimmune disease. These agents embody the principle of immune recalibration rather than suppression, offering durable control with reduced systemic toxicity—a crucial goal in the long-term management of lupus patients across diverse organ systems [32].

Organ-Specific Considerations

Systemic lupus erythematosus (SLE) exhibits remarkable heterogeneity in organ involvement, often necessitating coordinated management across multiple subspecialties within internal medicine. Biological therapies have shown varying efficacy across organ systems, reflecting both differential immunopathology and distinct tissue responses to immune modulation. Understanding these nuances allows internists to tailor treatment based on disease phenotype, severity, and comorbidities, optimizing outcomes while minimizing systemic toxicity.

Lupus Nephritis

Renal involvement remains one of the most serious manifestations of SLE, occurring in up to 50% of patients and contributing significantly to long-term morbidity and mortality. Conventional therapies such as corticosteroids and cytotoxic agents have improved survival but remain limited by toxicity and incomplete renal response. The addition of biologic therapy has markedly advanced management. **Belimumab** demonstrated efficacy in lupus nephritis in the BLISS-LN trial, where its combination with standard immunosuppression significantly increased renal response rates and reduced proteinuria. Similarly, **rituximab** and **obinutuzumab** have shown benefit in refractory cases, providing alternative B-cell–directed strategies for patients with persistent disease activity. **Anifrolumab** also shows potential renal benefit, with post-hoc analyses suggesting improved renal parameters in interferon-high subsets. For internists, biologic therapy now represents an essential consideration in the long-term renal protection of lupus patients, particularly those at risk for progression to chronic kidney disease [33].

Hematologic Manifestations

Hematologic abnormalities such as autoimmune hemolytic anemia, thrombocytopenia, and leukopenia are common and may be severe in SLE. These complications are frequently encountered in internal medicine practice, often requiring hospitalization and multidisciplinary input. While corticosteroids remain first-line therapy, biologic agents—particularly **rituximab**—have demonstrated high efficacy in refractory cytopenias by depleting autoreactive B cells. Rituximab-induced remission in lupus-associated thrombocytopenia and autoimmune hemolytic anemia has been reported in multiple observational studies, often achieving durable responses. Belimumab has also shown modest benefit in reducing serologic activity and stabilizing blood counts. The use of biologics in hematologic lupus provides an opportunity to reduce steroid exposure and maintain hematologic stability, especially in patients with comorbid cardiovascular or metabolic disease [34].

Neuropsychiatric Lupus

Central nervous system involvement in SLE encompasses a broad spectrum ranging from cognitive dysfunction and seizures to psychosis and cerebrovascular disease. The pathogenesis is multifactorial, involving autoantibody-mediated neuronal injury, microvascular inflammation, and cytokine dysregulation. Biologic therapy for neuropsychiatric lupus remains an area of emerging research. **Rituximab** has shown benefit in case series for refractory neuropsychiatric manifestations, improving cognitive and seizure outcomes. Experimental models suggest that interferon blockade with **anifrolumab** may mitigate neuroinflammation by dampening microglial activation. While data remain limited, these agents provide mechanistic rationale for targeting immune-driven neurotoxicity. For internal medicine physicians managing hospitalized or complex lupus patients, early recognition and targeted biologic intervention may prevent irreversible neurological damage [35].

Cardiovascular and Pulmonary Involvement

Patients with SLE have an increased risk of premature atherosclerosis, myocarditis, and pulmonary hypertension, largely driven by chronic inflammation and vascular dysfunction. Cytokine modulation,

particularly through **anifrolumab** and IL-6 blockade, offers potential vascular benefit by reducing endothelial activation and systemic inflammation. Preliminary evidence suggests improvement in surrogate markers of vascular function and reduction in cardiovascular risk factors with biologic therapy. Pulmonary manifestations such as interstitial lung disease and pleuritis may also respond to B-cell and cytokine-targeted approaches. From an internal medicine viewpoint, integrating biologics into care may reduce the burden of inflammatory comorbidities, aligning lupus management with cardiometabolic prevention strategies [36].

Multisystem and Hospital-Based Care

Internists often coordinate the care of lupus patients during acute hospitalizations for flare management, infections, or organ complications. In this context, familiarity with biologic mechanisms, dosing schedules, and infection prophylaxis is essential. Biologic therapy may be initiated or continued in inpatient settings for severe flare control, particularly in nephritis or hematologic crises. Close communication with rheumatology and nephrology is vital to optimize immunomodulatory strategies and prevent adverse outcomes. The integration of biologics into systemic lupus management has therefore redefined the internal medicine role—transforming it from crisis-based intervention to longitudinal, precision-guided care [37].

Safety, Monitoring, and Practical Considerations

The integration of biologic therapies into the management of systemic lupus erythematosus (SLE) has transformed therapeutic outcomes but also introduced new safety and monitoring challenges. For internists, awareness of the unique risk profile and monitoring requirements of biologic agents is essential for ensuring safe and effective long-term treatment. Unlike traditional immunosuppressants, biologics target specific components of the immune response, which modifies the pattern of adverse events and infection susceptibility. Vigilant pre-treatment evaluation, ongoing monitoring, and coordination with specialty care are key aspects of optimal management.

Infection remains the most significant risk associated with biologic therapy. The inhibition of B-cell or cytokine pathways can predispose to both common and opportunistic infections, although the risk varies depending on the mechanism of action. **Rituximab**, through prolonged B-cell depletion, increases susceptibility to bacterial infections, reactivation of hepatitis B, and rarely, progressive multifocal leukoencephalopathy. **Anifrolumab** has been associated with an increased incidence of mild to moderate herpes zoster and upper respiratory tract infections due to altered antiviral defense linked to interferon blockade. **Belimumab**, though generally well tolerated, may increase infection risk in patients with high baseline disease activity or concomitant immunosuppression. Internists should ensure comprehensive infection screening prior to biologic initiation, including hepatitis B and C serology, tuberculosis testing, and HIV screening, as well as regular clinical surveillance during therapy [38].

Vaccination strategies form a cornerstone of biologic safety management. Live vaccines should be avoided during treatment and for at least one dosing cycle before therapy initiation. Inactivated vaccines, including influenza, pneumococcal, and COVID-19 vaccines, should be administered prior to or early in biologic therapy to maximize immune response. The efficacy of vaccination may be attenuated under B-cell–depleting agents such as rituximab; therefore, immunization should ideally occur at least four weeks before infusion. Internists play a pivotal role in coordinating these preventive measures and counseling patients on infection risk mitigation, particularly for those requiring travel or prolonged hospitalization [39].

Monitoring parameters vary according to the biologic class but generally include regular assessment of complete blood count, renal and hepatic function, and immunoglobulin levels. **Rituximab** necessitates periodic monitoring of serum immunoglobulins and B-cell counts to guide re-treatment timing and detect hypogammaglobulinemia. **Belimumab** and **anifrolumab** require monitoring for emerging infections and signs of hypersensitivity, which, though rare, can occur during infusion or early treatment phases. Baseline and follow-up assessments of disease activity using validated indices such as SLEDAI or BILAG are essential for gauging therapeutic efficacy. Integration of these parameters into electronic

medical records can enhance multidisciplinary communication and prevent adverse outcomes [40].

The potential association between biologic therapy and malignancy remains an area of ongoing investigation. Long-term data suggest that the overall risk of malignancy with B-cell–targeted agents and interferon blockade is not significantly elevated compared with the background lupus population. However, internists should maintain vigilance, particularly for lymphoproliferative disorders in patients with prolonged immunosuppression or prior exposure to cytotoxic agents. Routine cancer screening in accordance with general population guidelines remains appropriate, with additional attention to cervical, breast, and hematologic surveillance in high-risk groups [41].

In the inpatient setting, management of biologic-treated lupus patients requires a nuanced approach. During severe infections, major surgery, or sepsis, temporary suspension of biologic therapy is recommended until the patient stabilizes. Internists should also be alert to delayed infusion reactions and rare hypersensitivity syndromes that may mimic lupus flare. Conversely, distinguishing infection from disease activity remains a recurrent diagnostic challenge, demanding a multidisciplinary approach that combines clinical, serologic, and imaging data. Coordination between internal medicine, rheumatology, nephrology, and infectious disease specialists ensures timely diagnosis and continuity of biologic therapy once infection is controlled [42].

Finally, patient education and shared decision-making are integral to safe biologic use. Internists must discuss therapy expectations, adherence, infection precautions, and reproductive considerations. Women of childbearing potential require counseling regarding pregnancy planning, as safety data for biologics in pregnancy are evolving. Belimumab and anifrolumab should be used with caution, whereas rituximab may be considered in select cases after risk-benefit evaluation. Regular follow-up and adherence to standardized safety protocols enable early detection of complications and reinforce patient confidence in therapy [43].

Emerging Targets and Future Directions

The therapeutic landscape of systemic lupus erythematosus (SLE) continues to evolve rapidly as novel biologic targets are identified through advances in molecular immunology and translational research. Despite the approval of belimumab and anifrolumab, a substantial proportion of patients continue to experience active disease or organ damage progression, underscoring the need for additional therapeutic options. Emerging biologic agents and precision medicine strategies are now aiming to address these unmet needs by refining immune modulation, enhancing response prediction, and personalizing treatment.

Recent attention has focused on **dual-target biologics** that simultaneously modulate overlapping immune pathways. **Telitacicept**, a recombinant fusion protein inhibiting both B-cell–activating factor (BAFF) and a proliferation-inducing ligand (APRIL), has demonstrated superior suppression of autoantibody production compared with single-pathway blockade. Phase II and III trials report significant reductions in disease activity and corticosteroid requirements, suggesting potential as a next-generation biologic for SLE. Similarly, **dapirolizumab pegol**, targeting CD40 ligand (CD40L), has shown encouraging results in phase II studies, reducing flare rates and improving serologic markers. These dual or co-stimulatory approaches reflect an emerging paradigm in lupus therapy—addressing the redundancy and complexity of immune signaling that often underlies treatment resistance [44].

Parallel to biologic innovation, **bispecific antibodies** and **fusion molecules** are under development to modulate multiple immune pathways concurrently. Agents combining interferon and B-cell blockade, or coupling cytokine inhibition with complement modulation, are in early clinical testing. These engineered molecules aim to optimize efficacy while maintaining manageable safety profiles. For internists, such therapies promise broader disease coverage and may simplify complex polypharmacy regimens in patients with multisystem involvement.

Another key frontier is **biomarker-guided therapy**, which seeks to personalize biologic selection based on immune signatures. High baseline expression of interferon-stimulated genes has been shown to predict better response to **anifrolumab**, while elevated BAFF levels may identify patients who respond

optimally to **belimumab** or **telitacicept**. Integration of gene-expression profiling, proteomic panels, and serologic markers into clinical practice could enable internists and rheumatologists to tailor therapy dynamically, improving efficacy and reducing unnecessary exposure to biologics. Incorporating biomarker-driven algorithms into electronic medical records and multidisciplinary care pathways will be a crucial step toward practical implementation of precision medicine in lupus [45].

The exploration of **novel immune targets** continues to expand. Therapies directed against plasmacytoid dendritic cells (pDCs), such as **vibostolimab** and **CD123-targeting antibodies**, aim to suppress upstream interferon production, potentially improving outcomes in interferon-high lupus phenotypes. **Complement inhibitors**, including **eculizumab** and C5a receptor antagonists, are also under study for refractory lupus nephritis and vasculitis-dominant presentations. Meanwhile, **Janus kinase (JAK) inhibitors**, though not strictly biologics, represent small-molecule modulators of intracellular cytokine signaling that may complement biologic therapy. The convergence of biologics and targeted small molecules may ultimately redefine lupus treatment, offering combination or sequential strategies that mirror oncology-style precision therapeutics [46].

Equally important are innovations in **drug delivery and patient accessibility**. The development of subcutaneous formulations of biologics such as belimumab and anifrolumab enhances convenience and adherence, facilitating use in outpatient internal medicine settings. Biosimilars are expected to improve global accessibility and reduce healthcare costs, broadening biologic availability in resource-limited regions where lupus burden remains high. These trends underscore the growing role of internists in managing biologic therapy across diverse healthcare environments [47].

Looking forward, the integration of **multi-omics data**, artificial intelligence, and real-world evidence is expected to accelerate the transition toward personalized lupus care. Predictive modeling based on genomic and clinical data could identify optimal biologic combinations or sequencing strategies for individual patients. As biologic therapy becomes increasingly precise, internists will play a pivotal role in early identification, monitoring, and holistic management of lupus patients across the continuum of care—from inpatient stabilization to long-term follow-up. This multidisciplinary, data-driven approach promises to transform lupus from a chronic relapsing disease into a manageable condition with improved survival and quality of life [48].

Conclusion

The advent of biologic therapy has reshaped the therapeutic paradigm of systemic lupus erythematosus (SLE), offering targeted immune modulation grounded in an improved understanding of disease pathophysiology. For internal medicine practitioners, who often serve as the first line of diagnosis and long-term coordinators of care, the emergence of these therapies represents both an opportunity and a responsibility—to translate mechanistic insight into clinical application while maintaining vigilance for safety and systemic comorbidities.

Biologic agents such as **belimumab** and **anifrolumab** have provided tangible benefits by reducing disease activity, enabling corticosteroid tapering, and improving quality of life for patients with moderate to severe SLE. Their success validates the strategy of pathway-specific immunomodulation, confirming that precise interference with key immune mediators—B-cell survival factors and type I interferon signaling—can produce meaningful clinical outcomes. In refractory or organ-threatening disease, **rituximab**, **obinutuzumab**, and other B-cell–depleting agents continue to play a pivotal role, particularly for lupus nephritis and hematologic manifestations. Collectively, these biologics have bridged the gap between empirical immunosuppression and mechanism-based, evidence-guided therapy.

From the internal medicine perspective, biologic therapy has redefined the management goals of lupus: not merely controlling flares, but achieving sustained remission, preventing organ damage, and minimizing treatment toxicity. This shift requires a holistic and multidisciplinary approach that integrates rheumatology, nephrology, hematology, infectious disease, and primary care expertise. The internist's role extends beyond prescription to encompass **long-term monitoring, infection prevention,**

vaccination planning, comorbidity management, and patient education, ensuring that biologic therapy is delivered safely and effectively across diverse healthcare settings.

The future of lupus care lies in **precision and personalization**. Advances in genomics, proteomics, and immune phenotyping will enable stratification of patients according to molecular signatures, guiding biologic selection and dosing. The development of dual-target and bispecific antibodies, as well as integration of biologics with small-molecule inhibitors, promises to expand treatment horizons. Internists will increasingly rely on biomarkers and digital health tools to monitor response and adjust therapy dynamically, ushering in a new era of data-driven autoimmune care.

Ultimately, biologic therapy represents not an endpoint but a pivotal milestone in the evolving management of SLE. As scientific discovery continues to unravel the complex immune networks driving lupus, the challenge for internal medicine will be to ensure equitable access, rational use, and multidisciplinary stewardship of these advanced treatments. By combining mechanistic understanding with clinical judgment, internists can lead the transition toward a future where lupus is managed with precision, safety, and sustained remission as realistic and achievable goals.

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