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Review

Therapeutic Strategies Targeting Immune Dysregulation in Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease driven by loss of immune tolerance, dysregulated nucleic acid sensing and cytokine signaling, abnormal B- and T-cell activation, persistent autoantibody production, and impaired clearance of immune cells and debris. These interconnected abnormalities promote immune-complex formation, complement activation, and multiorgan tissue injury. Recent advances in biologics, small-molecule inhibitors, cellular therapies, and combination regimens reflect an ongoing transition from broad immunosuppression toward mechanism-based treatment. This review summarizes major immunopathogenic mechanisms of SLE and evaluates established and emerging targeted therapeutic strategies according to disease phenotype, trial maturity, efficacy, safety, and principal limitations. The strongest evidence supports type I interferon and B-cell survival blockade, B-cell depletion, and calcineurin–NFAT inhibition, represented by anifrolumab, belimumab, obinutuzumab, and voclosporin. Several Phase 3 programs are evaluating additional TLR, co-stimulatory, FcRn, JAK/TYK2, and B-cell-directed strategies, whereas CD38, BCMA, and cellular therapies remain less mature and require controlled confirmation. Because systemic SLE, lupus nephritis (LN), and cutaneous lupus use distinct populations and outcome measures, efficacy estimates should not be compared directly across phenotypes. Future progress will depend on biomarker-guided patient stratification, rational sequencing of therapy, and careful evaluation of long-term safety, durability, access, and affordability, which may support more personalized treatment in SLE and LN.

Keywords: autoimmune disease; cytokines; inflammation; lupus nephritis; mechanism-based therapy; systemic lupus erythematosus

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1. Introduction

The immune system maintains host defense and tissue homeostasis through tightly regulated innate and adaptive responses. Disruption of immune tolerance and regulatory networks can result in chronic inflammation, autoantibody production, immune-complex formation, and progressive tissue damage. Accordingly, autoimmune diseases constitute a growing global health burden and frequently show marked female predominance [1–3].

Systemic lupus erythematosus (SLE) is a highly female-biased and heterogeneous systemic autoimmune disease, with female-to-male incidence and prevalence rate ratios of 5.8 and 8.5, respectively [4]. It is characterized by loss of immune tolerance, autoantibody production, immune-complex deposition, complement activation, and inflammation-mediated multiple organ injury, including the joints, kidneys, nervous system, lungs, vasculature, and skin [5]. Defective clearance of apoptotic cells and immune debris increases exposure to self-derived nucleic acids, activating innate immune-sensing pathways and type I interferon (IFN-I) responses. These signals promote pathogenic T- and B-cell activation, plasma-cell differentiation, autoantibody production, and tissue injury, thereby sustaining chronic autoimmune inflammation [6,7]. Persistent autoreactive B cells and long-lived plasma cells further sustain chronic disease activity. Lupus nephritis (LN), which affects approximately 40% of SLE patients, remains a major cause of morbidity, mortality, irreversible organ damage, and long-term treatment burden [8].

Advances in understanding these interconnected mechanisms have shifted SLE treatment from broad immunosuppression toward more selective, durable, and mechanism-based therapy. Current approaches target innate immune sensing, cytokines and their receptors, pathogenic immune cells, intracellular signaling pathways, and long-lived plasma cells. Clinical success with IFN-I and B-cell survival blockade, B-cell depletion, and calcineurin inhibition, together with emerging cellular therapies, illustrates this therapeutic transition [6,7,9].

This review summarizes major immunopathogenic mechanisms of SLE, including genetic susceptibility, excessive immune activation, cytokine dysregulation, and impaired clearance of immune cells and debris. It further evaluates established and emerging targeted therapies according to molecular mechanism, disease phenotype, development phase, efficacy, safety, and major limitations, with emphasis on clinically mature therapies and on the appropriate interpretation of early-stage evidence. Therapies are discussed by disease phenotype (systemic SLE, lupus nephritis, and cutaneous disease), and each is labeled with its level of evidence, from peer-reviewed Phase 3 trials to early-phase, uncontrolled, or registry-only data. We also discuss safety, monitoring, cost, and access, which determine whether trial results translate into clinical benefit.

2. Immunopathogenesis of SLE

SLE results from mutually reinforcing defects in immune tolerance, nucleic acid sensing, cytokine regulation, and clearance of self-antigens. These abnormalities sustain autoantibody production, immune-complex deposition, complement activation, and organ damage.

2.1. Overactivation of Immune Responses

A central feature of SLE is breakdown of B- and T-cell tolerance, leading to autoantibody production and immune complex deposition in the kidneys, skin, joints, and central nervous system. With CD40L–CD40 signaling and follicular helper T (Tfh)-cell support, B cells undergo germinal-center maturation, class switching, and differentiation into memory B cells and plasma cells [10].

Self-derived nucleic acids activate innate sensing pathways, including endosomal toll-like receptor (TLR), cGAS–STING, and RIG-I–MAVS pathways, inducing IFN-I, particularly IFN-α and IFN-β [11]. Persistent TLR7–IFN-I signaling enhances dendritic-cell antigen presentation, pathogenic T-cell polarization, B-cell differentiation, and autoantibody production [12]. Nucleic acid-containing immune complexes further induce IFN-I and promote autoreactive lymphocyte activation, establishing a self-amplifying loop (Figure 1).

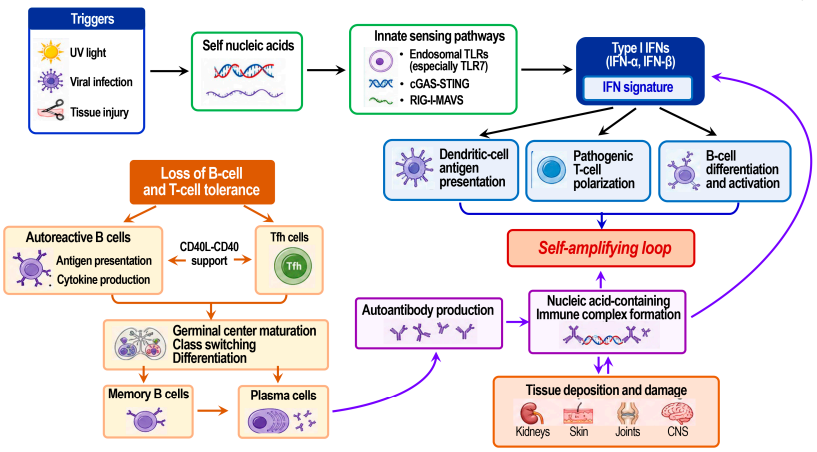


Figure 1. Overactivation of immune responses in SLE. Self-derived nucleic acids activate endosomal TLRs, cGAS–STING, and RIG-I–MAVS. These pathways induce IFN-I, promoting dendritic-cell antigen presentation, pathogenic T-cell polarization, and B-cell activation. Loss of B- and T-cell tolerance, supported by Tfh cells and CD40L–CD40 signaling, promotes germinal-center maturation, class switching, memory B-cell and plasma-cell differentiation, autoantibody production, and immune-complex formation. Immune complex deposition damages target organs and further stimulates innate sensors, sustaining inflammation via a self-amplifying loop. The different colors of the arrows and frames in this figure are used solely to group related elements and distinguish them from surrounding elements. Abbreviations: cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; CNS, central nervous system; IFN-I, type I interferons; RIG-I-MAVS, retinoic acid-inducible gene I-mitochondrial antiviral-signaling protein; SLE, systemic lupus erythematosus; Tfh, follicular helper T cell; TLR, toll-like receptor; UV, ultraviolet.

2.2. Cytokine Dysregulation

Cytokine dysregulation shapes both disease activity and therapeutic response. In SLE, $CD4^+$ T-cell subsets, including helper T cells (Th1, Th2, Th17, Tfh, Tph) and regulatory T cells (Tfr and Treg), generate inflammatory or regulatory cytokines that determine B-cell activation, tissue inflammation, and immune homeostasis [13,14]. In particular, enhanced Th17 activity and defective Treg function are associated with disease activity. Their contrasting metabolic programs—glycolysis in Th17 cells and oxidative metabolism in Tregs—further connect immunometabolic imbalance with persistent inflammation [15]. Cytokine dysregulation is not only a consequence of autoimmunity but also a determinant of phenotype, progression, and treatment response (Figure 2).

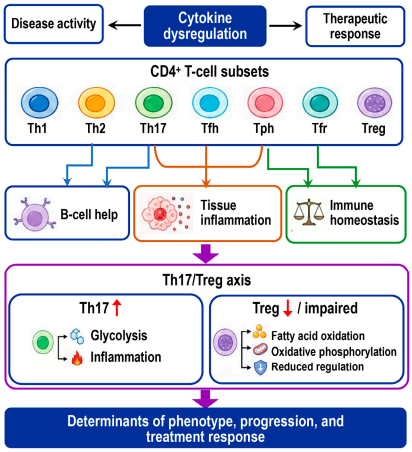


Figure 2. Cytokine dysregulation in SLE. $CD4^+$ T-cell subsets and the Th17/Treg metabolic balance regulate B-cell help, tissue inflammation, and immune homeostasis, thereby shaping disease

phenotype, progression, and treatment response. The different colors of the arrows and frames in this figure are used solely to group related elements and distinguish them from surrounding elements. Abbreviations: Th1/2/17, helper T 1/2/17 cell; Tph, peripheral helper T cell; Tfr, follicular regulatory T cell; Treg, regulatory T cell. For abbreviations not defined here, refer to the preceding figure or the Abbreviations section at the end of the manuscript.

2.3. Impaired Clearance of Immune Cells and Debris

Defective removal of autoreactive lymphocytes, apoptotic debris, neutrophil extracellular traps (NETs), and immune complexes prolongs exposure to nuclear antigens. These materials activate fragment crystallizable (Fc) receptors and endosomal TLRs, thereby sustaining IFN-driven immune responses [16,17]. Complement is protective when facilitating debris clearance but pathogenic when excessively activated in immune-complex-mediated tissue injury, particularly LN [18]. Macrophage dysfunction further impairs clearance and promotes autoreactive T-cell responses [19]. Thus, defective clearance links self-antigen persistence to nucleic acid sensing and chronic inflammation (Figure 3).

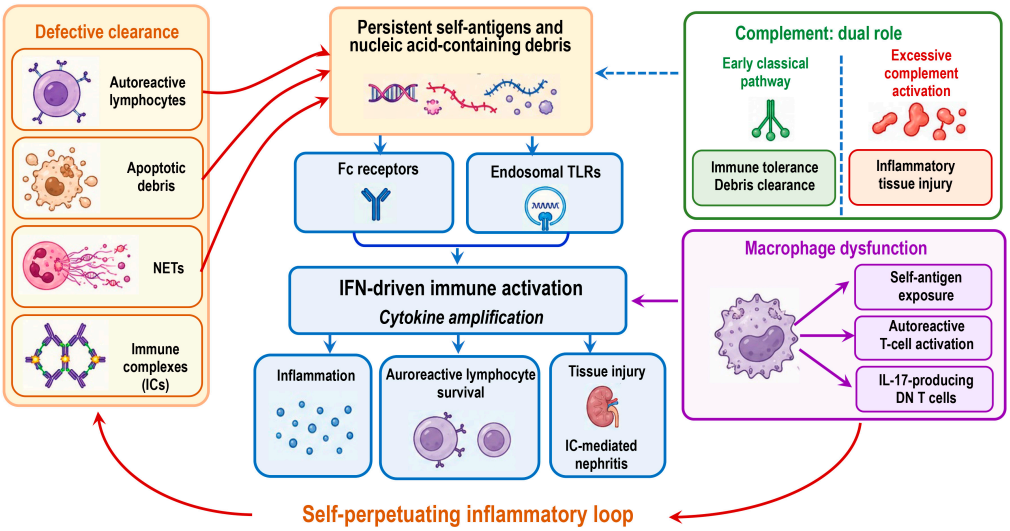


Figure 3. Impaired clearance of immune cells and debris in SLE. Defective clearance of autoreactive lymphocytes, apoptotic debris, NETs, and ICs sustains self-antigen exposure and nucleic acid sensing in SLE. These events activate Fc receptors and endosomal TLRs, amplifying IFN-driven signaling, while complement imbalance and macrophage dysfunction further promote self-perpetuating inflammatory loop, causing autoreactive lymphocyte survival and tissue injury. The dashed arrow in the upper part of the figure indicates that, due to the dual role of complement, its effect on the generation of self-antigens and nucleic acid-containing debris is uncertain but may be partial. Abbreviations: DN, double negative ($CD4^-/CD8^-$); Fc, fragment crystallizable; ICs, immune complexes; NETs, neutrophil extracellular traps. For abbreviations not defined here, refer to the preceding figures or the Abbreviations section at the end of the manuscript.

2.4. Genetic Susceptibility and Therapeutic Implications

SLE has a substantial heritable component, with both common polygenic susceptibility loci and rare high-impact variants converging on pathways involved in nucleic-acid sensing, IFN-I signaling, complement and immune-complex handling, and lymphocyte activation. Genome-wide association and sequencing studies have identified numerous susceptibility loci, including HLA and Fcγ receptor genes, *IRF5*, *STAT4*, *PTPN22*, *TNFAIP3*, *BLK*, *BANK1*, *TNFSF4*, and *ITGAM*, many of which encode proteins involved in toll-like receptor (TLR) and IFN-I signaling, immune regulation, or immune-complex clearance [7,12,20–22].

Rare monogenic or oligogenic forms provide more direct mechanistic links between genotype and lupus phenotypes. Deficiency of early classical-pathway complement components, loss-of-function variants in *DNASE1L3* or *TREX1*, and gain-of-function variants in *TLR7* or its trafficking regulator *UNC93B1* can impair nucleic-acid clearance or enhance endosomal nucleic-acid sensing [12,18,20,22]. In particular, recently described *UNC93B1* variants that augment TLR7/8 signaling illustrate how human genetics can validate pathogenic pathways that are already being targeted pharmacologically [22]. Collectively, these findings provide a genetic rationale for therapeutic strategies targeting TLR7/8, the IFN-I pathway, tyrosine kinase 2 (TYK2), and B-cell activation, although the ability of individual genetic variants to predict treatment response has not yet been established in clinical trials. Genetic manipulation remains primarily a tool for mechanistic investigation and preclinical target validation in SLE. Genetically modified lupus-prone mouse models and CRISPR-Cas9 knock-in or knockout approaches have been used to reproduce lupus-like phenotypes or alter disease severity, including *UNC93B1* gain-of-function models and *Aicda* disruption in BXSB mice [22,23]. CRISPR-based interrogation of coding and regulatory variants may further help define causal pathways and identify precision therapeutic targets; however, direct correction of disease-associated variants remains preclinical. Clinical application of gene editing in SLE is currently more advanced for the engineering of cellular therapies than for correction of inherited susceptibility variants. CRISPR-edited allogeneic CD19-directed cellular products, including hypoimmune chimeric antigen receptor-T (CAR-T) cell platforms designed to reduce allorejection, have entered early-phase clinical evaluation in SLE [24].

However, efficacy data for gene-edited products remain limited, and genome editing itself is not an established treatment for SLE. Thus, at present, genetic and genome-editing approaches should be regarded mainly as platforms for mechanistic discovery, target validation, disease modeling, and cellular-product engineering rather than as direct gene-correction therapies

3. Targeted Therapeutic Strategies in SLE

Targeted SLE therapies aim to reduce chronic toxicity by selectively inhibiting pathogenic immune pathways while preserving protective immunity. Because systemic SLE, LN, cutaneous lupus erythematosus (CLE), and treatment-refractory disease differ in organ involvement, background therapy, therapeutic goals, and outcome definitions, evidence from these populations is considered separately rather than assumed to be interchangeable.

In the discussion below, regulatory approval and randomized Phase 3 evidence are given greatest weight, followed by randomized Phase 2 studies, early-phase trials, uncontrolled cohorts or case series, and preclinical studies. Registered but unpublished trials are described as ongoing and are not interpreted as evidence of efficacy. Selected negative trials are retained when they inform target validation or explain limitations of a therapeutic strategy. SRI-4 and British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) evaluate systemic disease using different composite rules, cutaneous lupus erythematosus disease area and severity index (CLASI)-based measures assess cutaneous activity, and renal response endpoints incorporate proteinuria, kidney function, rescue therapy, and glucocorticoid exposure; these outcomes are therefore not directly interchangeable across trials. Representative clinical evidence is summarized in Table 1.

Table 1. Representative clinical evidence for established and advanced targeted therapies in SLE and LN.

Therapy/Target	Phenotype Population and Background Therapy	Development Phase/Sample Size	Primary Endpoint and Results	Key Safety or Evidence Limitations	References
A. Systemic SLE (non-renal or mixed organ involvement)					
Anifrolumab/anti-IFNAR1 mAb (IV)	Moderate-to-severe non-renal SLE on standard therapy; severe active LN and neuropsychiatric lupus excluded	TULIP-2, Phase 3 RCT; *N* = 362; 52 CRISPR-Cas9; approved. TULIP-1, Phase 3 RCT: SRI-4 primary endpoint not met	BICLA, week 52 in TULIP-2: 47.8% vs. 31.5% (difference 16.3 points; 95% CI 6.3 to 26.3)	SAEs 8.3% vs. 17.0%; herpes zoster 7.2% vs. 1.1%; one death (pneumonia) on anifrolumab	[25,26]
Anifrolumab/anti-IFNAR1 mAb (SC)	Moderate-to-severe SLE on standard therapy	TULIP-SC, Phase 3 RCT; *N* = 367 (184 vs. 183); 52 weeks	BICLA, week 52: 56.2% vs. 37.1% (difference 19.1; 95% CI 9.0 to 29.2)	SAEs 11.9% vs. 10.4%; herpes zoster 3.8% vs. 1.1%; interim analysis (*N* = 220) gave 59.4% vs. 43.9%	[27]
Belimumab/anti-BAFF mAb	Active, autoantibody-positive SLE on standard therapy	BLISS-52 (*N* = 865) and BLISS-76 (*N* = 819), Phase 3 RCTs; approved	SRI-4, week 52, 10 mg/kg vs. placebo: 57.6% vs. 43.6% (BLISS-52); 43.2% vs. 33.5% (BLISS-76)	Fewer severe flares; CIs and SAE rates are given in the cited trials	[28,29]
Telitacicept/TACI-Fc (BAFF and APRIL)	Active SLE (China) on standard therapy	Phase 3 RCT; *N* = 335 (167 vs. 168); 52 weeks; approved in China	Modified SRI-4, week 52: 67.1% vs. 32.7% (adjusted difference 34.5; 95% CI 24.3 to 44.7)	SAEs 7.2% vs. 14.3%; more upper respiratory infections, lower immunoglobulins, and injection-site reactions; Chinese population only	[30]
Obinutuzumab/anti-CD20 mAb	Active non-renal SLE; excluded proliferative or membranous LN; standard therapy	ALLEGORY, Phase 3 RCT; *N* = 303; 52 weeks	SRI-4, week 52: 76.7% vs. 53.5% (adjusted difference 23.1; 95% CI 12.5 to 33.6)	SAEs 15.9% vs. 11.9%; infection and immunoglobulin monitoring needed	[31]
Dapirolizumab pegol/anti-CD40L (PEGylated Fab′)	Moderate-to-severe active systemic SLE on stable standard therapy	PHOENYCS GO, Phase 3 RCT; *N* = 321 randomized (315 in the full analysis set); 48 weeks; confirmatory Phase 3 ongoing	BICLA, week 48: 50% vs. 35% (difference 14.6; 95% CI 3.3 to 25.8)	SAEs 10% vs. 15%; one myocardial infarction and one death (sepsis) on dapirolizumab; week 24 BICLA (key secondary) not met (47% vs. 38%); long-term safety and durability remain to be defined.	[32]
Ianalumab/anti-BAFF~~R~~ receptor mAb	Moderate-to-severe SLE	Phase 2 RCT; Phase 3 SIRIUS-SLE 1/2 ongoing	SRI-4: improved, with GC tapering and flare control	Phase 2 only; B-cell depletion requires infection and immunoglobulin monitoring	[33]
Nipocalimab/anti-FcRn mAb	Moderate-to-severe SLE on background medication	JASMINE-SLE, Phase 2 RCT; *N* = 228 (three arms); abstract only; Phase 3 GARDENIA ongoing	SRI-4, 15 mg/kg vs. placebo: week 24, 53.5% vs. 46.7% ($p = 0.081$); week 52, 53.6% vs. 39.7% ($p = 0.020$)	Modest week 24 difference (primary endpoint tested at a prespecified two-sided α of 0.10); week 52 p values are nominal; no peer-reviewed report; the 5 mg/kg dose did not meet the week 24 endpoint	[34,35]
Upadacitinib/JAK1 inhibitor	Moderately to severely active SLE	SLEek, Phase 2 RCT; *N* = 341 (five arms); 48 weeks, extension to	SRI-4 with GC ≤ 10 mg/day, week 24: 54.8% with 30 mg vs. 37.3%	Extension had no placebo group; no new safety signals through week 104	[36,37]

	on standard therapy	Week 104; Phase 3 SELECT-SLE ongoing	with placebo ($p = 0.028$; prespecified $\alpha = 0.1$); high-dose combination with elsubrutinib 48.5% ($p = 0.081$)		
Deucravacitinib/TYK2 inhibitor	Active systemic SLE; background therapy	PAISLEY, Phase 2 RCT; $N = 363$; Phase 3 POETYK SLE-1/2 ongoing	Week 32 SRI-4: 58.2% with 3 mg BID vs. 34.4% with placebo (OR 2.8; 95% CI 1.5 to 5.1); 49.5% with 6 mg BID and 44.9% with 12 mg QD; gains in pain, fatigue, and quality of life	Phase 2 only; Phase 3 confirmation required; infections and cutaneous adverse events (about 34% at higher doses) were more frequent	[38–40]
Orelabrutinib/BTK inhibitor	Active SLE	Phase 2b RCT; topline sponsor-reported; Phase 3 underway	SRI-4, week 48, 75 mg: 57.1% vs. 34.4%	Partly sponsor-reported; Phase 3 ongoing	[41,42]
Sirolimus/mTORC1 inhibitor	Active SLE	Multicenter Phase 3 RCT; conference report	SRI-4, week 24: 53% vs. 23%	Peer review pending; safety data not reported	[43]
B. Lupus nephritis					
Belimumab/anti-BAFF mAb (IV)	Active LN; standard therapy (MMF, or CYC followed by azathioprine) plus GCs; belimumab vs. placebo	BLISS-LN, Phase 3 RCT; $N = 448$; 104 weeks; approved	PERR, week 104: 43% vs. 32% (OR 1.6; 95% CI 1.0 to 2.3); CRR 30% vs. 20% (OR 1.7; 95% CI 1.1 to 2.7)	Add-on evidence in LN; renal endpoints should not be compared directly with SRI/BICLA. Renal event or death: HR 0.51 (95% CI 0.34 to 0.77); SAEs 25.9% vs. 29.9%; benefit shown only as add-on to standard therapy	[44]
Voclosporin/calcineurin inhibitor	Active LN; MMF + low-dose GCs	AURORA 1, Phase 3 RCT; $N = 357$ (179 vs. 178); AURORA 2 extension to 3 year; approved	CRR, week 52: 41% vs. 23% (OR 2.65; 95% CI 1.64 to 4.27)	SAEs 21% vs. 21%; nephrotoxicity, hypertension, and metabolic effects require monitoring; not studied in non-renal SLE	[45–47]
Obinutuzumab/anti-CD20 mAb	Active proliferative LN; MMF + GCs	REGENCY, Phase 3 RCT; $N = 271$; 76 weeks; NOBILITY, Phase 2; $N = 125$; approved (US)	CRR, week 76: 46.4% vs. 33.1% (adjusted difference 13.4; 95% CI 2.0 to 24.8)	SAEs 32.4% vs. 18.2% in REGENCY, mainly infections	[48–50]
Anifrolumab/anti-IFNAR1 mAb	LN on standard therapy	TULIP-LN, Phase 2 RCT; $N = 147$, modified intention to treat $N = 145$; Phase 3 IRIS ongoing (NCT05138133)	Primary endpoint not met; numerical renal benefit with the intensified regimen	Negative primary result (24 h UPCR ratio vs. placebo 1.03; 95% CI 0.62 to 1.71); CRR at week 52: 31.1% placebo, 16.3% basic regimen, 35.5% intensified regimen (normal p values); benefit of the intensified regimen awaits IRIS	[51]
Rituximab/anti-CD20 mAb (off-label)	SLE (EXPLORER) and LN (LUNAR) on standard therapy	EXPLORER (Phase 2/3, $N = 257$) and LUNAR (Phase 3, $N = 144$) RCTs; (negative)	Primary endpoints not met	Used off-label in selected refractory disease despite negative Phase 3 results	[52,53]
C. Cutaneous or skin-predominant disease					
Enpatoran/TLR7/8 antagonist (oral)	Skin manifestations of CLE or SLE (WILLOW	Phase 2 RCT; Cohort A $N = 102$ (100 efficacy) Phase 3 ELOWEN-1/2 (CLE) ongoing	Cohort A primary endpoint (dose–response in CLASI-A at week 16) met ($p = 0.0002$)	Evidence is mainly cutaneous	[54]

	Cohort A); standard therapy				
Enpatoran/TLR7/8 antagonist (oral)	Moderate-to-severe SLE (WILLOW Cohort B); standard therapy	Phase 2 RCT; Cohort B *N* = 354	Cohort B: week 24 BICLA 57.7%, 48.6%, and 49.1% with 25, 50, and 100 mg BID vs. 39.4% with placebo; primary dose–response endpoint not met ($p = 0.14$)	Systemic benefit not shown; supports phenotype-specific activity.	[55]
Litifilimab/anti-BDCA2 mAb	SLE with joint and cutaneous disease (LILAC); cutaneous lupus (AMETHYST)	LILAC, Phase 2 RCT (Part A SLE *N* = 132; Part B CLE *N* = 128); Phase 3 TOPAZ-1/2 (SLE) and Phase 2b/3 AMETHYST (CLE) ongoing	LILAC: improved joint and cutaneous disease and IFN-associated biomarkers; AMETHYST: cutaneous improvement reported	Phase 2 only; AMETHYST results are registry-level pending peer review	[56]

Evidence is defined in Section 3. Agents with only Phase 1 or 2 evidence and no Phase 3 program, including cellular therapies, are discussed in the text with their evidence. Abbreviations: APRIL, a proliferation-inducing ligand; AZA, azathioprine; BAFF(R), B-cell activating factor ~~(receptor)~~; BDCA2, blood dendritic cell antigen 2; BID, twice daily; BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; BTK, Bruton's tyrosine kinase; CI, confidence interval; CLASI-A, cutaneous lupus erythematosus disease area and severity index-activity; CLE, cutaneous lupus erythematosus; CRR, complete renal response; CYC, cyclophosphamide; Fc, fragment crystallizable; FcRn, neonatal Fc receptor; GC, glucocorticoid; HR, hazard ratio; IFNAR1, type I interferon receptor subunit 1; IV, intravenous injection; JAK, Janus kinase; mAb, monoclonal antibody; mTOR, mechanistic target of rapamycin; LN, lupus nephritis; MMF, mycophenolate mofetil; OR, odds ratio; PERR, primary efficacy renal response; QD, once daily; RCT, randomized controlled trial; SAE, serious adverse event; SC, subcutaneous injection; SRI-4, SLE responder index-4; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor; TYK2, tyrosine kinase 2; UPCR, urine protein-to-creatinine ratio.

3.1. Strategies Targeting Innate Immune Sensing Pathways

Self-derived nucleic acids from apoptotic debris, immune complexes, and NETs activate endosomal TLR7/9 in plasmacytoid dendritic cells (pDCs) and B cells, and TLR8 mainly in myeloid cells. Downstream myeloid differentiation factor 88 (MyD88)–interleukin-1 receptor-associated kinase (IRAK) signaling promotes IFN-I inflammatory cytokine production, B-cell activation, autoantibody formation, and tissue injury. Therefore, TLRs, MyD88-IRAK signaling, and pDCs are attractive therapeutic targets [57,58] (Figure 4).

3.1.1. Direct TLR Inhibition

Direct TLR blockade is among the most advanced innate-sensing strategies, but efficacy is phenotype-dependent. Enpatoran, an oral TLR7/8 antagonist, suppressed the IFN gene signature and was generally well tolerated [59]. In the Phase 2 WILLOW trial, patients with skin manifestations of CLE or SLE (Cohort A) showed dose-dependent benefit, whereas the systemic BICLA endpoint was not met in moderate-to-severe SLE (Cohort B) [54,55]. The evidence for enpatoran is therefore mainly cutaneous and the Phase 3 ELOWEN-1/2 trials are ongoing only in active cutaneous lupus populations. Afimetoran and E6742 have shown target engagement and preliminary clinical activity in earlier-stage studies [60,61], but confirmatory evidence is not yet available.

DS-7011a, a TLR7-specific antagonistic monoclonal antibody (mAb), has shown acceptable safety and preliminary activity in early SLE studies, although efficacy data are limited to a conference abstract [62,63]. Hydroxychloroquine also interferes with endosomal nucleic acid sensing but acts as a broad antimalarial immunomodulator rather than a selective TLR inhibitor [57].

3.1.2. MyD88–IRAK Pathway Inhibition

MyD88–IRAK inhibition remains less clinically advanced [64]. Edecesertib, an oral IRAK4 inhibitor, showed preclinical activity [65], but its Phase 2 CLE trial was terminated without reported efficacy results (ClinicalTrials.gov: NCT05629208). Other IRAK1/4 inhibitors or degraders remain clinically unvalidated in SLE [57]. Thus, despite strong biological rationale, this pathway requires substantially more clinical validation.

3.1.3. pDC-Directed Inhibition

Targeting pDCs provides an upstream approach to suppress IFN-I production. Litifilimab, an anti-blood dendritic cell antigen 2 (BDCA2) mAb, has shown the strongest evidence: The Phase 2 LILAC trial improved joint and cutaneous disease and reduced IFN-associated biomarkers [56]. The Phase 2/3 AMETHYST trial also reported improvement in cutaneous disease, although peer-reviewed results remain pending (ClinicalTrials.gov: NCT05531565). Phase 3 CLE and the TOPAZ-1/2 SLE trials are ongoing (ClinicalTrials.gov: NCT04895241 and NCT04961567). In contrast, daxdilimab, an anti-ILT7/LILRA4 mAb that depletes pDCs, showed pharmacodynamic activity but failed the primary endpoint in the Phase 2 RECAST SLE trial, leading to termination of further systemic SLE and LN development (ClinicalTrials.gov: NCT04925934 and NCT05540665).

Overall, the evidence for innate-sensing and pDC-directed therapy is mainly cutaneous and mostly from Phase 2 trials. Enpatoran and litifilimab have the strongest clinical support, but the systemic benefit of enpatoran was not shown, and afimetoran, E6742, and DS-7011a remain early-stage candidates. Most MyD88-IRAK4 inhibitors and other pDC-depleting strategies have not demonstrated consistent clinical efficacy. Effective and promising therapies targeting innate immune-sensing pathways are illustrated in Figure 4 and the distinction between skin-predominant and systemic trial populations for enpatoran is shown in Table 1.

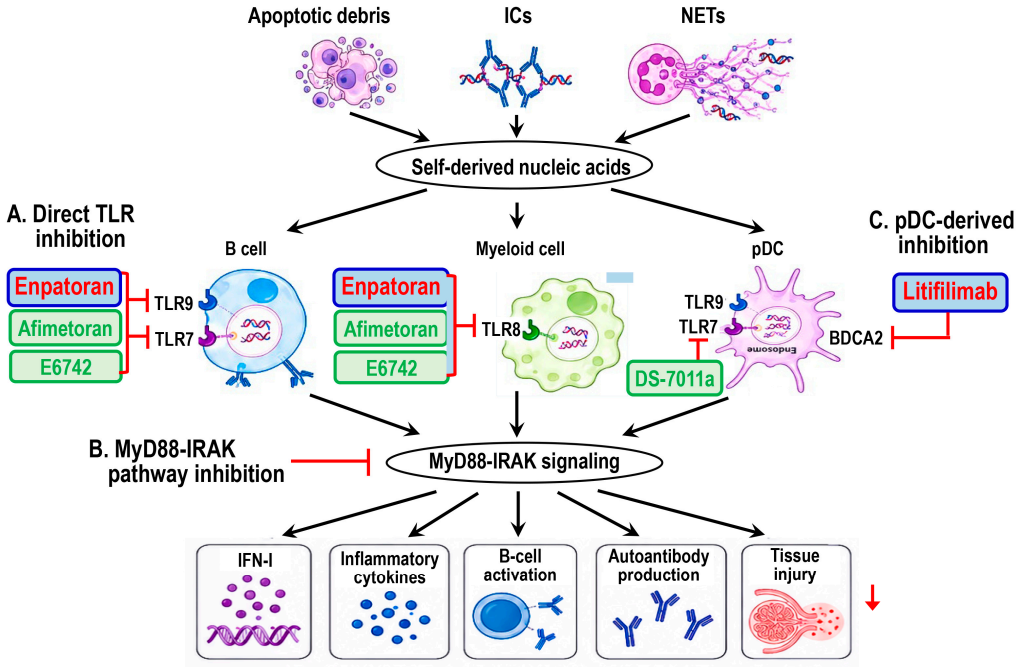


Figure 4. Therapeutic strategies targeting innate immune-sensing pathways in lupus. Self-derived nucleic acids activate TLR7/9 in B cells and pDCs and TLR8 in myeloid cells, converging on MyD88–IRAK signaling to promote IFN-I production, inflammation, B-cell activation, autoantibody generation, and tissue injury. Enpatoran and litifilimab, shown in red within light-blue boxes, have the strongest clinical evidence, particularly in cutaneous lupus, whereas afimetoran, E6742, and DS-7011a, shown in green within light-green boxes, remain promising. Black arrows indicate positive

effects, whereas the red downward arrow indicates inhibitory effects. Red blunt-ended lines represent drug-mediated inhibition. Abbreviations: BDCA2, blood dendritic cell antigen 2; IRAK, interleukin-1 receptor-associated kinase; MyD88, myeloid differentiation primary response 88; pDCs, plasmacytoid dendritic cells. For abbreviations not defined here, refer to the preceding figures or the Abbreviations section at the end of the manuscript.

3.2. Strategies Targeting Cytokines and Cytokine-Receptor Pathways

Cytokines regulate innate immune activation, lymphocyte differentiation, plasma-cell survival, and tissue injury in SLE. Therapeutic development has focused mainly on IFN-I and interleukin (IL) pathways, and the B-cell survival factors such as B-cell activating factor (BAFF, also known as BLyS) and a proliferation-inducing ligand (APRIL).

3.2.1. IFN-Targeted Therapies

IFN-directed approaches include direct cytokine neutralization and receptor blockade. Anifrolumab, an IFN-I receptor subunit 1 (IFNAR1) mAb that blocks signaling by all IFN-I subtypes, is the most established IFN-directed therapy. The Phase 2 MUSE and Phase 3 TULIP-1/2 trials, and long-term extension studies [66] demonstrated improvements in global and cutaneous disease activity and glucocorticoid (GC) reduction, with TULIP-2 (N = 362) meeting its BICLA primary endpoint (47.8% vs. 31.5% at week 52; adjusted difference 16.3 percentage points, 95% CI 6.3 to 26.3; serious adverse events 8.3% vs. 17.0%; herpes zoster 7.2% vs. 1.1%) and supporting approval of intravenous anifrolumab for moderate-to-severe SLE [25], whereas TULIP-1 did not meet its SLE responder index (SRI)-4 primary endpoint [5,26]. Subcutaneous anifrolumab also improved week 52 BICLA responses in BLISS-LN AURORA 1 (56.2% vs. 37.1% for placebo; difference 19.1 percentage points, 95% CI 9.0 to 29.2; N = 367; serious adverse events 11.9% vs. 10.4%) [27]. Although the Phase 2 TULIP-LN trial did not meet its primary endpoint, an intensified regimen showed numerical renal benefit, and the Phase 3 IRIS trial is evaluating this approach in proliferative LN (ClinicalTrials.gov: NCT05138133) [51].

Earlier IFN-α-specific approaches were less successful. IFN-α kinoid reduced the IFN gene signature but lacked confirmatory late-stage efficacy, while sifalimumab and rontalizumab were discontinued after insufficient or inconsistent clinical benefit, potentially reflecting disease heterogeneity and incomplete IFN-I blockade [67–69]. The therapeutic roles of IFN-γ and IFN-λ remain uncertain [70].

3.2.2. IL-Targeted Therapies

Low-dose recombinant IL-2 is a promising strategy that aims to restore T-cell regulation by preferentially expanding $CD4^{+}CD25^{high}FOXP3^{+}$ Treg cells. In a multicenter randomized Phase 2b trial (152 patients randomized; per-protocol analysis of 136 completers), it produced dose-dependent Treg expansion and higher week 12 SRI-4 responses than placebo, with clinical and serological benefits sustained through week 24 [71,72]. Further studies are needed to define optimal dosing, durability, and broader clinical applicability.

In contrast, engineered IL-2 agonists such as efavaleukin alfa and rezpegaldesleukin increased Treg numbers but failed to produce sufficient clinical benefit, leading to discontinuation of some programs for futility (ClinicalTrials.gov: NCT04433585) [73]. Other IL-directed approaches have also been disappointing: secukinumab (IL-17A) failed in Phase 3 LN, ustekinumab (IL-12/23) failed to confirm Phase 2 activity in Phase 3, and guselkumab (IL-23p19) did not improve proteinuria in LN [74–76]. IL-6/IL-6R inhibitors, including tocilizumab, sirukumab, and PF-04236921, have likewise shown no consistent clinical efficacy [77]. Thus, among IL-directed strategies, low-dose IL-2 currently retains the clearest therapeutic potential.

3.2.3. BAFF- and APRIL-Targeted Therapies

BAFF and APRIL support autoreactive B-cell survival, plasmablast differentiation, and plasma-cell persistence [69]. Belimumab, a BAFF-neutralizing antibody, is an established therapy for active SLE and LN. The Phase 3 BLISS-52 and BLISS-76 trials demonstrated higher SRI-4 responses and fewer severe flares [28,29], while BLISS-LN (N = 448) showed higher primary efficacy renal response (43% vs. 32%; odds ratio 1.6, 95% CI 1.0 to 2.3) and complete renal response (30% vs. 20%; odds ratio 1.7, 95% CI 1.1 to 2.7) and fewer renal-related events or deaths when belimumab was added to standard therapy, with serious adverse events in 25.9% and 29.9% of the belimumab and placebo groups, respectively [5,44]. Sequential belimumab with one cycle of rituximab did not improve disease control over belimumab alone in the Phase 3 BLISS-BELIEVE trial [78], and low dose belimumab reduced the risk of flares in a placebo-controlled trial [79].

Broader targeting of the BAFF/APRIL axis has also shown promise. Telitacicept, a transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI)-Fc fusion protein approved in China for active SLE, significantly improved modified SRI-4 responses in a 52-week Phase 3 trial in China (N = 335; 67.1% vs. 32.7%; adjusted difference 34.5 percentage points, 95% CI 24.3 to 44.7); serious adverse events occurred in 7.2% and 14.3% of the telitacicept and placebo groups, respectively, but upper respiratory tract infections, lower immunoglobulin levels, and injection-site reactions were more frequent with telitacicept and require monitoring [30,80,81]. Ianalumab combines BAFF receptor (BAFFR) blockade with antibody-dependent B-cell depletion and improved SRI-4 responses, GC tapering, and flare control in Phase 2; Phase 3 SIRIUS-SLE 1/2 and LN trials are ongoing (ClinicalTrials.gov: NCT05639114, NCT05624749, and NCT05126277) [33,82]. Earlier BAFF/APRIL-directed agents were less successful. Tabalumab and blisibimod were discontinued because of insufficient or inconsistent efficacy, while atacicept development has been limited by variable clinical benefit, hypogammaglobulinemia, and infection concerns [69,83,84].

Overall, cytokine-targeted therapy in SLE has achieved its greatest clinical success through blockade of IFN-I and B-cell survival pathways. Anifrolumab and belimumab are established effective therapies, but anifrolumab did not meet its primary endpoint in the Phase 2 LN trial. Telitacicept has shown substantial benefit in a Phase 3 trial in a Chinese population and is approved for active SLE in China. Low-dose recombinant IL-2 and ianalumab have also produced encouraging results, although optimal dosing, durability, and long-term efficacy require further validation. In contrast, most IFN-α-specific agents, other IL-directed therapies, engineered IL-2 agonists, and earlier BAFF/APRIL inhibitors have been limited by negative, inconsistent, or incomplete clinical evidence. Established and promising therapies targeting cytokine and cytokine receptor pathways are illustrated in Figure 5.

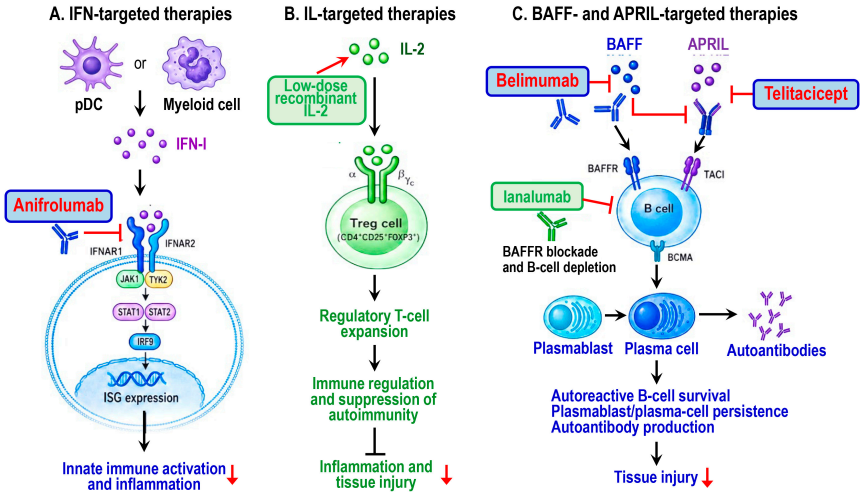


Figure 5. Therapeutic strategies targeting cytokines and cytokine-receptor pathways in lupus. (**A**) Anifrolumab blocks IFNAR1 and suppresses IFN-I signaling, with established efficacy in moderate-to-severe SLE. (**B**) Low-dose recombinant IL-2 preferentially expands regulatory T cells and remains a promising immunoregulatory therapy. (**C**) Belimumab neutralizes BAFF, telitacicept blocks both BAFF and APRIL through TACI-Fc, and ianalumab inhibits BAFFR while promoting B-cell depletion; these approaches reduce autoreactive B-cell survival, plasma-cell persistence, autoantibody production, and tissue injury. Anifrolumab, belimumab, and telitacicept, shown in red within light-blue boxes, indicate clinically effective therapies, whereas low-dose recombinant IL-2 and ianalumab, shown in green within light-green boxes, indicate promising therapies. Black arrows indicate positive effects, whereas the red downward arrow indicates inhibitory effects. Red blunt-ended lines represent drug-mediated inhibition. Abbreviations: APRIL, a proliferation-inducing ligand; BAFF(R), B-cell activating factor (receptor); Fc, fragment crystallizable; IFNAR1, type I interferon receptor subunit 1; IL-2, interleukin-2; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor. For abbreviations not defined here, refer to the preceding figures or the Abbreviations section at the end of the manuscript.

3.3. Targeting Immune-Cell Surface Molecules

Immune-cell surface molecules provide accessible targets for suppressing pathogenic B- and T-cell responses. Current strategies include B-cell and plasma-cell depletion, modulation of T-cell activation and co-stimulation, and receptor-mediated clearance of pathogenic antibodies.

3.3.1. B-Cell and Plasma-Cell Targets

B-cell-directed therapies target CD19, CD20, CD38, and B-cell maturation antigen (BCMA), extending from conventional B-cell depletion to elimination of antibody-secreting cells [85]. Among CD20-targeted therapies, obinutuzumab has the strongest clinical evidence. In the Phase 3 REGENCY trial, obinutuzumab plus standard therapy increased complete renal response at week 76 compared with placebo (46.4% vs. 33.1%; adjusted difference 13.4 percentage points, 95% CI 2.0 to 24.8; $N = 271$), supporting its U.S. approval for active LN [50,86]. Obinutuzumab had previously increased complete renal responses in the Phase 2 NOBILITY trial [48], and a post hoc analysis suggested preservation of kidney function [49]. Serious adverse events, mainly infections, were more frequent with obinutuzumab than with placebo (32.4% vs. 18.2%) [50]. Rituximab remains useful off-label in selected refractory SLE or LN, although it failed the primary endpoints of the Phase 2/3 EXPLORER and Phase 3 LUNAR trials (negative) [52,53,77,87].

Other anti-CD20 antibodies, ocrelizumab and ofatumumab, have not established clinical roles, and the anti-CD22 antibody epratuzumab failed Phase 3 efficacy endpoints

[88–90]. These limitations have shifted development toward deeper CD19-, CD38-, and BCMA-directed depletion.

The therapies discussed in this subsection differ in target, cell type, and mechanism and should not be grouped together. They comprise autologous CD19-directed CAR-T cells; allogeneic CD19-targeted T cells; allogeneic CD19-CAR-natural killer (NK) cells; dual CD19/BCMA CAR-T cells; BCMA × CD3 bispecific T-cell engagers (teclistamab); and anti-CD38 antibodies (daratumumab, CM313, and felzartamab). Their evidence is early-stage: it comes from Phase 1 or 2 studies, case series, and case reports or from conference abstracts and registered trials without results, and none of these therapies has completed a Phase 3 trial in SLE.

In small uncontrolled studies of severe refractory SLE, CD19-directed cellular therapies have been associated with marked clinical responses. CD19-CAR-T therapy has been reported to produce B-cell depletion, serological improvement, and drug-free remission over limited follow-up [24,91,92]. Autologous CD19-CAR-T case series have reported drug-free remission in selected patients, and early studies of allogeneic CD19-targeted T cells and CD19-CAR-NK cells have also reported SRI responses, lupus low disease activity state (LLDAS), or Definition of Remission in SLE (DORIS) remission [92,93]. However, these studies are uncontrolled or early phase and do not yet establish comparative efficacy, durability, or sustained immune tolerance. Longer follow-up is required to define relapse, infection, cytopenias, hypogammaglobulinemia, and the kinetics and quality of immune reconstitution.

Targeting plasmablasts and plasma cells may overcome persistence of autoantibody production after conventional B-cell depletion [94]. The anti-CD38 antibody daratumumab produced marked responses in refractory SLE; in a subsequent single-arm open-label, single-center Phase 2 study of 10 patients, serum anti-dsDNA antibodies (primary endpoint) fell by week 12, and all patients achieved SRI-4 (secondary endpoint) at week 12, declining to 70% at week 36; however, hypogammaglobulinemia requiring immunoglobulin replacement occurred in five patients [95]. CM313, another anti-CD38 mAb, also showed encouraging dose-dependent SRI-4 responses in a randomized Phase Ib/IIa study, and a subcutaneous Phase 2 study of CM313 is ongoing (ClinicalTrials.gov: NCT06791772), while felzartamab remains under clinical evaluation in a Phase 1b trial of active LN (ClinicalTrials.gov: NCT06064929) [96].

BCMA, a receptor for BAFF and APRIL that is preferentially expressed on plasmablasts and plasma cells, is increased in SLE and correlates with disease severity, supporting its evaluation as a biomarker and therapeutic target [97]. BCMA-directed approaches have also produced early responses: in a Phase 1 study, dual CD19/BCMA-targeted CAR-T therapy achieved both LLDAS and DORIS remission in 12 of 15 refractory patients by week 12, and the BCMA × CD3 bispecific antibody teclistamab induced rapid clinical and serological remission in individual refractory cases (case reports) [98–100]. These observations come from a small uncontrolled series and individual case reports; whether BCMA-directed approaches can durably eliminate autoreactive plasma cells, and at what cost in infection and hypogammaglobulinemia, cannot be concluded until controlled trials with longer follow-up are available [98].

Deep B-cell or plasma-cell depletion has been proposed to reset the autoreactive immune repertoire, so that autoimmunity does not recur after the depleting agent is withdrawn. This concept rests on mechanistic rationale and on small uncontrolled studies with short follow-up. It has not been tested in randomized trials, and durable remission, immune reconstitution, long-term safety, and restoration of immune tolerance have not been established. Until such data are available, these therapies should be regarded as investigational, and immune resetting should be read as a hypothesis rather than a demonstrated outcome.

3.3.2. T-Cell Targets and Co-Stimulatory Pathways

Selective modulation of pathogenic T-cell activation may suppress T–B-cell collaboration while preserving protective immunity [101]. Itolizumab, an anti-CD6 antibody that inhibits CD6–activated leukocyte cell adhesion molecule (ALCAM) signaling, showed acceptable safety and exploratory reductions in proteinuria in the Phase 1b EQUALISE LN study, warranting randomized confirmation [102]; the data are available only as a conference abstract.

Among co-stimulatory pathways, CD40–CD40L blockade has generated the strongest clinical evidence. Dapirolizumab pegol, a PEGylated anti-CD40L antibody fragment, increased the week 48 BICLA response to 50% versus 35% with placebo in the Phase 3 PHOENYCS GO trial (321 randomized patients; difference 14.6 percentage points, 95% CI 3.3 to 25.8), with serious adverse events in 10% vs. 15% of patients and one thromboembolic event (myocardial infarction) in the dapirolizumab group, although the key secondary BICLA endpoint at week 24 was not met [32]; a confirmatory Phase 3 trial is ongoing (ClinicalTrials.gov: NCT06617325). Iscalimab, an anti-CD40 antibody, also improved proteinuria in a Phase 2 LN study [103,104], while dazodalibep, a non-antibody CD40L antagonist, remains under Phase 2 evaluation (ClinicalTrials.gov: NCT05201469). Earlier approaches targeting autoreactive T cells or other co-stimulatory pathways, including rigerimod, abatacept, and rozibafusp alfa, failed to demonstrate consistent efficacy in later-stage SLE or LN trials. These results favor selective CD40–CD40L modulation over broader suppression of T-cell activation.

3.3.3. Fc Receptor-Targeted Autoantibody Clearance and Complement Blockade

Beyond direct targeting of immune-cell surface molecules, receptor-mediated clearance of pathogenic antibodies and blockade of their downstream effector pathways provide complementary therapeutic strategies. The neonatal Fc receptor (FcRn) prolongs immunoglobulin G (IgG) survival by protecting it from lysosomal degradation and thus FcRn blockade provides a complementary strategy for reducing pathogenic IgG without directly depleting B cells or plasma cells. Nipocalimab, an anti-FcRn monoclonal antibody, was reported to meet its week 24 SRI-4 primary endpoint at 15 mg/kg in the Phase 2 JASMINE-SLE trial ($N = 228$ across three arms; 53.5% vs. 46.7%; $p = 0.081$, tested at a prespecified two-sided α of 0.10) and had higher SRI-4 responses than placebo at week 52 (53.6% vs. 39.7%; nominal $p = 0.020$), accompanied by reductions in total IgG, anti-dsDNA antibodies, and circulating immune complexes [34]. These data are available only as a conference abstract. A Phase 3 GARDENIA trial is ongoing (ClinicalTrials.gov: NCT07438496) [35].

Intravenous immunoglobulin (IVIG) provides broader Fc receptor modulation and autoantibody neutralization and remains useful in selected refractory cases, particularly when conventional immunosuppression is constrained by pregnancy or infection [105]. Complement inhibition has a more phenotype-specific role. Eculizumab has shown benefit mainly in SLE/LN complicated by thrombotic microangiopathy, whereas evidence for routine complement blockade in SLE or LN remains limited [77,106].

Overall, the best-established immune-cell surface-targeted therapy is anti-CD20 B-cell depletion with obinutuzumab, whereas selective T-cell co-stimulation blockade and FcRn-mediated IgG reduction are supported by a Phase 3 trial of dapirolizumab pegol and Phase 2 data for nipocalimab, respectively. Obinutuzumab has the strongest evidence among surface-targeted agents for active LN, while rituximab remains useful off-label in selected refractory disease. Early-stage evidence suggests activity of CD19-directed cellular therapies (autologous and allogeneic CD19-CAR-T cells and CD19-CAR-NK cells), CD38-targeted antibodies (daratumumab, CM313, and felzartamab), and BCMA-directed agents (dual CD19/BCMA-CAR-T cells and teclistamab). T–B-cell co-stimulation blockade,

comprising CD6–ALCAM inhibition (itolizumab) and CD40/CD40L blockade (dapirolizumab pegol, iscalimab, and dazodalibep), acts on T–B-cell collaboration rather than directly on plasma cells, and the FcRn-targeting agent nipocalimab has shown activity in a Phase 2 trial reported as an abstract. IVIG remains useful in selected refractory settings, whereas eculizumab is primarily reserved for complement-mediated complications. Further controlled studies are needed to confirm the durability and long-term safety of these emerging approaches. Effective and promising therapies targeting immune cell surface molecules are illustrated in Figure 6.

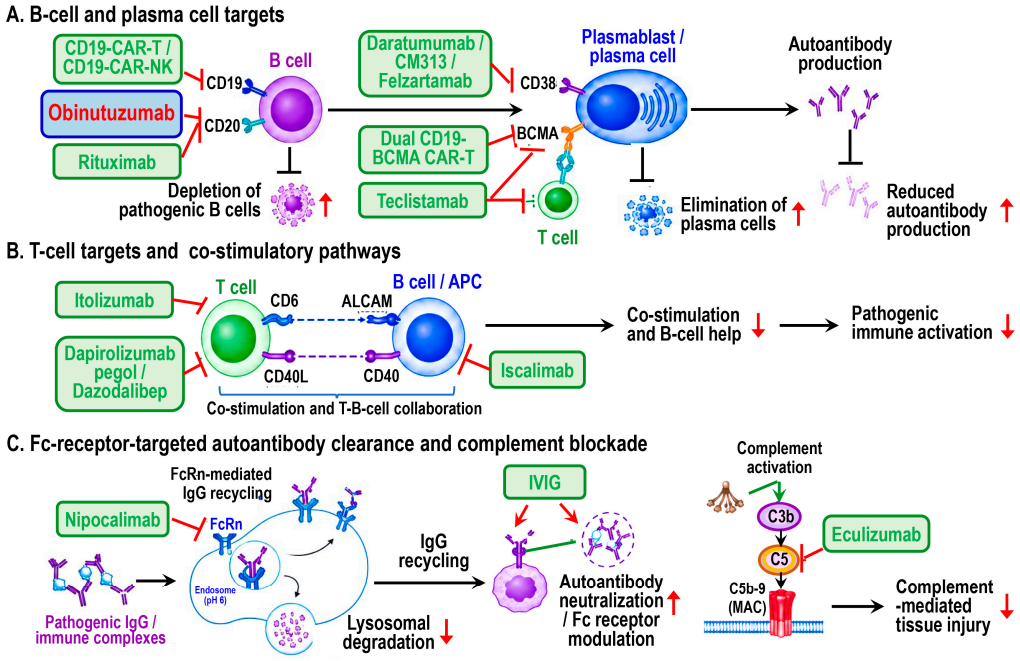


Figure 6. Targeting immune-cell surface molecules and antibody-effector pathways in SLE and LN. (**A**) B-cell and plasma-cell therapies target CD19, CD20, CD38, and BCMA to deplete pathogenic B cells and antibody-secreting cells. Obinutuzumab has Phase 3 evidence in active LN, whereas CD19-directed cellular therapies and CD38- and BCMA-targeted approaches remain earlier-stage strategies for refractory SLE. (**B**) T-cell-directed therapies modulate the CD6–ALCAM or CD40–CD40L co-stimulation, thereby reducing T-cell activation and T–B-cell collaboration. (**C**) FcRn blockade accelerates IgG degradation, IVIG has broader Fc receptor and immunomodulatory effects, and C5 inhibition is primarily relevant to selected complement-mediated complications. Obinutuzumab, shown in red within a light-blue box, indicates established Phase 3 efficacy for LN; agents shown in green within light-green boxes indicate investigational or emerging therapies with differing levels of evidence. Black arrows indicate positive effects, whereas black blunt-ended lines indicate negative effects. Red upward arrows and downward arrows indicate stimulatory and inhibitory effects, respectively. Red blunt-ended lines represent drug-mediated inhibition. Abbreviations: ALCAM, activated leukocyte cell adhesion molecule; BCMA, B-cell maturation antigen; CAR-T or NK, chimeric antigen receptor-T or NK cells; FcRn, neonatal Fc receptor; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; LN, lupus nephritis. For abbreviations not defined here, refer to the preceding figures or the Abbreviations section at the end of the manuscript.

3.4. Strategies Targeting Intracellular Immune Signaling Networks

Intracellular signaling pathways integrate cytokine, antigen receptor, and metabolic signals that regulate immune-cell activation, survival, differentiation, and inflammation. Major therapeutic targets include Janus kinase (JAK)-signal transducer and activator of transcription (STAT)/TYK2, nuclear factor kappa B (NF-κB)/Bruton's tyrosine kinase

(BTK), phosphoinositide 3-kinase (PI3K)/spleen tyrosine kinase (SYK)/$Ca2^{+}$-calmodulin-dependent protein kinase IV (CaMK-IV), calcineurin–nuclear factor of activated T cells (NFAT), and AMP-activated protein kinase (AMPK)-mechanistic target of rapamycin (mTOR) pathways, with clinical success largely dependent on pathway selectivity and safety.

3.4.1. JAK–STAT and TYK2 Pathways

JAKs transmit IFN- and cytokine-dependent signals through STAT transcription factors, while TYK2 mediates signaling by IFN-Is, IL-12, and IL-23 and influences Th1, Th17, and Tfh differentiation. Among JAK inhibitors, upadacitinib, a selective JAK1 inhibitor, has shown the strongest clinical potential. In the Phase 2 SLEek trial (N = 341), upadacitinib 30 mg improved SRI-4 responses with GC reduction (54.8% vs. 37.3% with placebo at week 24; $p = 0.028$, with a prespecified α of 0.1) and decreased flares, with benefits maintained through week 104 in an extension study that had no placebo group [36,37]. Phase 3 SELECT-SLE is ongoing (ClinicalTrials.gov: NCT05843643). Deucravacitinib, an allosteric TYK2 inhibitor, also improved SRI-4, pain, fatigue, and quality of life in the Phase 2 PAISLEY trial and is undergoing Phase 3 evaluation in POETYK SLE-1/2 [38–40].

Earlier JAK/TYK2 approaches were less successful. Tofacitinib showed biomarker activity but lacked confirmatory development, while baricitinib produced discordant Phase 3 results and was discontinued for SLE [107–109]. Filgotinib generated only limited exploratory evidence, and GLPG3667/cadefrecitinib failed its primary Phase 2 SRI-4 dose–response endpoint [110,111]. Elsubrutinib monotherapy and lower-dose combinations with upadacitinib were also discontinued for insufficient efficacy, with no clear added benefit from BTK inhibition [36,37].

3.4.2. NF-κB and BTK Pathways

NF-κB integrates B-cell receptor (BCR), TLR, tumor necrosis factor (TNF), IL-1, and BAFF signals and regulates inflammatory gene expression [112]. Broad NF-κB inhibition has not advanced clinically because of potential impairment of host defense. TNF blockade is also unsuitable for routine SLE because it may induce autoantibodies or lupus-like syndromes [113].

BTK integrates BCR, Fc receptor, and TLR signaling and is therefore an attractive target for B-cell-driven disease [114,115]. Orelabrutinib has shown the most encouraging results, with dose-dependent SRI-4 and biomarker improvements in early studies. In a Phase 2b trial (the topline results were sponsor-reported), week 48 SRI-4 responses were higher with 75 mg daily than with placebo (57.1% vs. 34.4%), together with improvements in SRI-6, BICLA, and GC tapering; Phase 3 development is underway (ClinicalTrials.gov: NCT05688696) [41,42]. Other BTK approaches have been less successful: evobrutinib did not show clinical efficacy in a Phase 2 trial [116], ibrutinib is limited by off-target and oncology-associated toxicities, fenebrutinib improved serological markers without clinical efficacy, and zanubrutinib has not yet reported public efficacy results [117–119].

3.4.3. PI3K, SYK, and CaMK-IV Pathways

PI3Kδ/γ, SYK, and CaMK-IV regulate B- and T-cell activation and immune tolerance, but clinical translation has been limited. PI3K inhibitors such as idelalisib, umbralisib, and duvelisib are restricted by infection, colitis, pneumonitis, hepatotoxicity, and limited autoimmune efficacy [120,121]. Leniolisib is effective for activated PI3Kδ syndrome and may have a precision-medicine role in SLE/LN associated with this disorder, but not in conventional SLE [122,123]. SYK inhibitors, including lanraplenib and fostamatinib, have not demonstrated convincing clinical efficacy and remain investigational [69].

3.4.4. Calcineurin–NFAT Pathways

Calcineurin inhibition is an established intracellular strategy in LN. Voclosporin, a calcineurin inhibitor, has the strongest evidence: when combined with mycophenolate mofetil (MMF) and low-dose GCs, it increased complete renal responses in the Phase 3 AURORA 1 trial ($N = 357$; 41% vs. 23%; odds ratio 2.65, 95% CI 1.64 to 4.27; serious adverse events 21% in both groups), with sustained proteinuria reduction and complete renal response, stable eGFR, and no new safety signal over up to 3 years in AURORA 2, a therapy for active LN [5,45–47]. Tacrolimus and cyclosporine are effective alone or in combination regimens but require monitoring for nephrotoxicity, hypertension, and metabolic adverse effects [124,125].

3.4.5. AMPK-mTOR and Proteostasis Pathways

Dysregulated AMPK–mTOR signaling contributes to T-cell dysfunction and impaired Treg activity in SLE [126,127]. Sirolimus (rapamycin), an mTORC1 inhibitor, may restore T-cell metabolic balance and Treg function. In a multicenter Phase 3 trial, conference-reported results showed a higher week 24 SRI-4 response with sirolimus than placebo (53% vs. 23%), although peer-reviewed confirmation is pending [43]. Other metabolic modulators, including metformin, N-acetylcysteine, statins, glycolysis inhibitors, and apremilast, remain adjunctive or investigational [128–130].

Targeted protein degradation is another promising strategy. Iberdomide, a cereblon E3-ligase modulator that promotes degradation of Ikaros and Aiolos, improved week 24 SRI-4 responses versus placebo in Phase 2 (54% vs. 35%), with additional activity in selected CLE subsets [131–133]. Further confirmatory studies are warranted.

Proteasome inhibition can also deplete antibody-producing plasma cells. Bortezomib has produced rescue responses in severe refractory SLE and LN but is limited by neuropathy, cytopenias, infection, and poor tolerability [77,134]. The selective immunoproteasome inhibitor zetomipzomib initially showed pharmacodynamic and proteinuria improvements, but its Phase 2b PALIZADE LN trial was terminated after several deaths and a regulatory clinical hold (reported only as a conference abstract) [135–137].

Overall, voclosporin (calcineurin–NFAT inhibition) is the only intracellular signaling-targeted agent with peer-reviewed Phase 3 evidence of benefit in LN. Upadacitinib, deucravacitinib, and orelabrutinib have shown encouraging activity in Phase 2 trials and are now in Phase 3, whereas the sirolimus result is conference-reported. Iberdomide also represents a promising protein-degradation strategy. Broader or less selective inhibition of JAK, BTK, PI3K, SYK, NF-kB, and proteostasis pathways has been limited by inconsistent efficacy, toxicity, or insufficient validation. Cross-trial comparisons should account for different populations, endpoints, and follow-up durations. Clinically effective and promising therapies targeting intracellular signaling networks are illustrated in Figure 7.

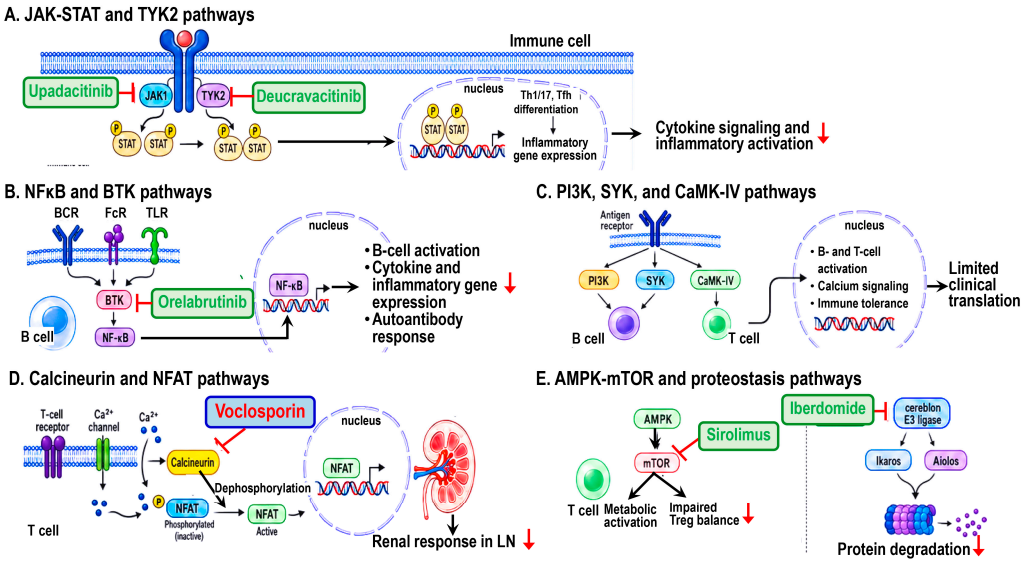


Figure 7. Targeting intracellular immune signaling networks in SLE and LN. Therapeutic strategies target JAK–STAT/TYK2 (**A**), NF-κB/BTK (**B**), PI3K/SYK/CaMK-IV (**C**), calcineurin–NFAT (**D**), and AMPK–mTOR/proteostasis pathways (**E**) to suppress cytokine signaling, immune-cell activation, and inflammatory responses. Voclosporin, a calcineurin inhibitor, has established efficacy in active LN, whereas upadacitinib, deucravacitinib, orelabrutinib, sirolimus, and iberdomide show clinical activity through selective pathway inhibition or protein degradation. Voclosporin, shown in red within a light-blue box, indicates a clinically effective therapy; other drugs, shown in green within light-green boxes, indicate promising therapies. Black arrows indicate positive effects, whereas red downward arrows indicate inhibitory effects. Red blunt-ended lines represent drug-mediated inhibition. We have added explanation of these symbols to the figure legend for greater clarity. Abbreviations: AMPK, AMP-activated protein kinase; BTK, Bruton's tyrosine kinase; CaMK-IV, Ca^{2+}/calmodulin-dependent protein kinase IV; JAK, Janus kinase; mTOR, mechanistic target of rapamycin; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor kappa B; PI3K, phosphoinositide 3-kinase; STAT, signal transducer and activator of transcription; SYK, spleen tyrosine kinase; TYK2, tyrosine kinase 2. For abbreviations not defined here, refer to the preceding figures or the Abbreviations section at the end of the manuscript.

3.5. Safety, Limitations, and Access

Efficacy must be weighed against the risks of immunosuppression, which accumulate when agents are added to standard therapy or to each other. Table 2 summarizes the major risks, suggested monitoring, and evidence caveats for each therapeutic strategy. Across B-cell- and plasma-cell-directed therapies, the principal concerns are serious infection, hypogammaglobulinemia, and impaired vaccine responses. In the Phase 3 REGENCY trial, serious adverse events, mainly infections, were more frequent with obinutuzumab than with placebo (32.4% vs. 18.2%); hypogammaglobulinemia requiring immunoglobulin replacement occurred in five of ten patients treated with daratumumab; and telitacicept was associated with lower immunoglobulin levels and more upper respiratory tract infections than placebo. Herpes zoster was more frequent with anifrolumab than with placebo (7.2% vs. 1.1% in TULIP-2). Calcineurin inhibitors require monitoring for nephrotoxicity, hypertension, and metabolic effects, and the immunoproteasome inhibitor zetomipzomib was stopped after deaths in a Phase 2b LN trial.

Cellular therapies and T-cell engagers carry risks that are not shared by conventional biologics, including cytokine release syndrome, neurotoxicity, B-cell aplasia with hypogammaglobulinemia, cytopenias, infection, and delayed immune reconstitution [24,91–93,98–100,138]. In the Phase 1 dual CD19/BCMA CAR-T series of 15 patients, cytokine

release syndrome was grade 1 in 86.7% of patients without immune effector cell-associated neurotoxicity syndrome, whereas grade ≥3 neutropenia occurred in all patients but was reversible [98]. Their safety in SLE is known only from small series with limited follow-up. Lymphodepletion, administration in specialized centers, and long-term follow-up are required, and the durability of benefit and the long-term consequences of sustained B-cell depletion remain unknown.

The limitations of the evidence also differ by strategy. For innate-sensing and pDC-directed therapy, benefit is largely confined to cutaneous disease. For cytokine-directed therapy, anifrolumab, belimumab, and telitacicept are supported by Phase 3 trials, but TULIP-LN did not meet its primary endpoint in LN. For JAK/TYK2 and BTK inhibitors, Phase 3 results are pending and several earlier agents were discontinued. For cellular, CD38-directed, and BCMA-directed therapies, evidence is limited to uncontrolled studies. Because response rates depend on the endpoint, results should be compared within rather than across trials.

Cost and access further limit the use of targeted therapies. Published economic evaluations of the established biologics suggest that cost-effectiveness depends strongly on drug price and on the willingness-to-pay threshold; in a US model of LN, belimumab and voclosporin had a 69% and 49% probability, respectively, of being cost-effective at a threshold of US$150,000 per quality-adjusted life-year [139]. Approval and reimbursement also differ between countries: telitacicept is approved for active SLE in China [30], obinutuzumab is approved for active LN in the United States [86], and the situation elsewhere varies. Cellular therapies require manufacturing capacity, lymphodepletion, and specialized centers, which makes them difficult to deliver outside tertiary centers, and their cost is likely to be prohibitive in many low- and middle-income countries, where the burden of lupus is high and access even to established biologics is limited. Cost-effectiveness data for the newer agents and for combination regimens are lacking, and trials rarely include enough patients from low- and middle-income countries to establish how well their results generalize.

Table 2. Major safety risks and monitoring considerations for targeted SLE therapies.

Therapeutic Strategy	Major Risks	Suggested Monitoring/Precautions	Evidence Caveat	References
IFN-I receptor blockade (anifrolumab)	Herpes zoster (7.2% vs. 1.1% in TULIP-2), upper respiratory and other infections, infusion and hypersensitivity reactions	Infection surveillance; review vaccination status, including herpes zoster, before treatment	Efficacy shown in SLE (TULIP-2); TULIP-LN did not meet its primary endpoint, and the intensified LN regimen is being tested in IRIS	[25,51]
BAFF, APRIL, and BAFFR targeting (belimumab, telitacicept, ianalumab; atacicept)	Infections; lower immunoglobulin levels with telitacicept; atacicept limited by hypogammaglobulinemia and infection concerns	Serum immunoglobulins; infection surveillance; vaccine responses	Telitacicept data come from a Chinese population; ianalumab evidence is Phase 2; atacicept development has been limited	[30,33,80–84]
Anti-CD20 therapy (obinutuzumab, rituximab)	Serious infection (SAEs 32.4% vs. 18.2% in REGENCY), hypogammaglobulinemia, impaired vaccine responses, infusion reactions	Immunoglobulins; B-cell counts; hepatitis B screening and vaccination before treatment	Phase 3 evidence for obinutuzumab; rituximab is off-label and failed EXPLORER and LUNAR	[31,48–50,86,87]
Anti-CD38 therapy (daratumumab, CM313, felzartamab)	Hypogammaglobulinemia requiring immunoglobulin replacement in 5 of 10 patients; infection	Immunoglobulins; infection surveillance; criteria for immunoglobulin replacement	Single-arm Phase 2 (N = 10) for daratumumab; CM313 Phase Ib/IIa; felzartamab Phase 1b without results	[95,96]

CD19-directed and dual-target cellular therapies (CAR-T, allogeneic T cell, CAR-NK)	Cytokine release syndrome; neurotoxicity; B-cell aplasia (recovery generally within months in published SLE series); infection; cytopenias; hypogammaglobulinemia; delayed immune reconstitution	Administration in specialized centers with CRS and neurotoxicity monitoring; immunoglobulins; infection prophylaxis; vaccination; long-term follow-up	Small uncontrolled studies and case series; durability and long-term safety unknown	[24,91–93,98,138]
BCMA × CD3 T-cell engagers (teclistamab)	Cytokine release syndrome; infection; hypogammaglobulinemia	Specialized-center administration; CRS and infection monitoring; immunoglobulins	Individual case reports only	[99,100]
JAK1 and TYK2 inhibition (upadacitinib, deucravacitinib; baricitinib discontinued)	Class concerns: serious infection, herpes zoster, venous thromboembolism, cardiovascular events, malignancy; laboratory abnormalities	Blood counts, lipids, and liver enzymes; infection screening and zoster vaccination; thrombosis risk assessment	Baricitinib gave discordant Phase 3 results; upadacitinib and deucravacitinib are Phase 2 with Phase 3 ongoing; the upadacitinib extension had no placebo group	[36–40,107–109]
BTK inhibition (orelabrutinib; ibrutinib)	Ibrutinib limited by off-target and oncology-associated toxicities; orelabrutinib safety in SLE not fully reported	Blood counts; infection surveillance; monitoring for bleeding and arrhythmia with ibrutinib	Orelabrutinib Phase 2b is partly sponsor-reported; fenebrutinib improved serology without clinical efficacy; elsubrutinib added no clear benefit	[41,116–119]
Calcineurin–NFAT inhibition (voclosporin, tacrolimus, cyclosporine)	Nephrotoxicity; hypertension; metabolic adverse effects	Blood pressure; renal function; glucose and lipids; drug levels for tacrolimus and cyclosporine	Phase 3 evidence for voclosporin in LN with MMF and low-dose GC, with no new long-term safety signal in AURORA 2; not established in non-renal SLE	[45,46,124,125]
mTOR inhibition and protein degradation (sirolimus, iberdomide)	Sirolimus: not reported in the conference abstract; iberdomide: more upper respiratory and urinary tract infections, neutropenia, and rash than placebo in Phase 2	Blood counts, lipids, and infection surveillance pending Phase 3 data	Sirolimus Phase 3 result is conference-reported only; iberdomide evidence is Phase 2	[43,131–133]
Proteasome inhibition (bortezomib, zetomipzomib)	Bortezomib: neuropathy, cytopenias, infection, poor tolerability; zetomipzomib: deaths and a regulatory clinical hold in PALIZADE	Neurologic examination and blood counts with bortezomib; zetomipzomib program halted	Bortezomib is a rescue therapy in refractory cases; PALIZADE was terminated and reported only as an abstract	[134–137]
Innate-sensing and pDC-directed therapy (enpatoran, afimetoran, E6742, DS-7011a; edecesertib; litifilimab; daxdilimab)	Generally well tolerated in early studies; long-term safety data lacking	Infection and laboratory monitoring according to trial protocols	Benefit mainly cutaneous; enpatoran missed the systemic BICLA endpoint; DS-7011a data are abstract-level; edecesertib terminated without results; daxdilimab failed Phase 2	[54–56,59–63]
T–B co-stimulation blockade: CD40/CD40L (dapirolizumab pegol, iscalimab, dazodalibep) and CD6–ALCAM (itolizumab)	One myocardial infarction and one death (sepsis) in PHOENYCS GO; thromboembolic risk with CD40L blockade is not excluded;	Thromboembolic events; infection surveillance	Phase 3 evidence only for dapirolizumab pegol (confirmatory trial ongoing); iscalimab and dazodalibep Phase 2; itolizumab abstract-level	[32,102–104]

	data for other agents limited			
FcRn blockade (nipocalimab)	Reduced total IgG; infection risk to be defined in peer-reviewed data	IgG levels; infection surveillance	Phase 2 data available only as an abstract; Phase 3 GARDENIA ongoing	[34]
Intravenous immunoglobulin (IVIG)	Thrombosis; renal injury; infusion reactions	Renal function; thrombotic risk assessment	Evidence from a systematic review in LN; used in selected refractory cases, for example when immunosuppression is limited by pregnancy or infection	[105]
Complement inhibition (eculizumab)	Meningococcal infection	Meningococcal vaccination or antibiotic prophylaxis	Benefit mainly in SLE or LN with thrombotic microangiopathy; routine use not supported	[77,106]
Sequential and combination regimens (Table 3)	Cumulative severe infection, cytopenia, hypogammaglobulinemia, impaired vaccine responses, delayed immune reconstitution	Immunoglobulins; blood counts; infection surveillance; timing of vaccination; avoidance of unnecessary overlap of immunosuppression	Controlled evidence is insufficient; BLISS-BELIEVE showed no benefit of adding rituximab to belimumab	[78,140–144]

Risks and monitoring items that are not drawn from the cited trials reflect general prescribing information and should be checked against current labels. Abbreviations: ALCAM, activated leukocyte cell adhesion molecule; BCMA, B-cell maturation antigen; CAR-T or NK, chimeric antigen receptor-T or NK cells; CRS, cytokine release syndrome; IgG, immunoglobulin G; NFAT, nuclear factor of activated T cells; pDC, plasmacytoid dendritic cell; other abbreviations as in Table 1.

3.6. Combination Therapy in SLE and LN

Combination strategies fall into three categories that differ in the strength of the evidence (Table 3): (A) a targeted agent added to standard immunosuppression, which has Phase 3 support in LN and in non-renal SLE; (B) sequential use of agents at separate times, which rests on Phase 2 trials, small cohorts, and retrospective studies; and (C) targeted–targeted combinations, which remain investigational and for which the completed trials have been negative or inconclusive. The trials in category A show the benefit of adding one agent to conventional therapy; they do not establish the efficacy of combining multiple targeted agents.

3.6.1. Established: Targeted Agent Added to Standard Therapy

The strongest evidence for combination therapy comes from active LN, where a targeted agent is added to MMF-based or cyclophosphamide (CYC)-based therapy with rapidly tapered GCs. In the Phase 3 BLISS-LN study, belimumab added to standard therapy increased primary renal efficacy and complete renal response rates and reduced renal-related events or death [44]. Belimumab may be combined with MMF or with low-dose CYC followed by azathioprine, according to patient characteristics and treatment tolerance. Voclosporin combined with MMF and low-dose GCs increased complete renal responses in the Phase 3 AURORA 1 trial, with benefits maintained during the AURORA 2 extension [46,47]. Obinutuzumab added to MMF and GCs similarly improved complete renal responses in the Phase 2 NOBILITY and Phase 3 REGENCY trials [48,50]. These data support adding a single targeted agent to standard therapy in active class III/IV LN, selected according to renal histology, proteinuria, extrarenal manifestations, fertility considerations, infection risk, and treatment toxicity [9,82,145,146]. An indirect network meta-analysis of six randomized trials in LN ranked obinutuzumab and belimumab highest for complete renal response among B-cell-targeting biologics added to standard care, although indirect comparisons cannot replace head-to-head data [147]. Obinutuzumab also

showed efficacy outside LN: in the Phase 3 ALLEGORY trial of active non-renal SLE (303 patients analyzed), obinutuzumab plus standard therapy increased the week 52 SRI-4 response compared with placebo plus standard therapy (76.7% vs. 53.5%; adjusted difference 23.1 percentage points, 95% CI 12.5 to 33.6) and improved all key secondary outcomes [31]; serious adverse events occurred in 15.9% and 11.9% of patients, respectively, and infection and immunoglobulin concentrations require monitoring.

3.6.2. Sequential Strategies

Sequential rituximab–belimumab therapy aims to deplete $CD20^+$ B cells and subsequently prevent BAFF-driven repopulation of autoreactive clones. In the Phase 2b BEAT-LUPUS trial (ISRCTN47873003; $N = 52$), belimumab initiated after rituximab reduced IgG anti-dsDNA antibody concentrations at week 52 (primary endpoint) and the risk of severe flares (hazard ratio 0.27, 95% CI 0.07 to 0.98; 3 vs. 10 events), although the difference was lost when moderate flares were included [140]. In the open-label Phase 2 CALIBRATE study ($N = 43$), belimumab following rituximab and CYC enhanced negative selection of autoreactive B cells but did not significantly improve complete or partial renal responses (52% vs. 41%, $p = 0.452$) [141]. Long-term follow-up of eight patients from the Phase 2 Synbiose study showed that six maintained clinical remission over a median of 6.8 years after rituximab–belimumab treatment, although the uncontrolled sample was too small to establish comparative efficacy [142]. In refractory LN, retrospective studies have also reported favorable renal responses when rituximab was followed by belimumab or the dual BAFF/APRIL inhibitor telitacicept [143,144]; in a multicenter cohort, objective renal remission occurred in 80.0% and 85.7% of patients receiving belimumab and telitacicept, respectively, without a statistically established difference between treatments [144]. These findings are hypothesis-generating because of the small, nonrandomized designs and the risks of infection and hypogammaglobulinemia.

Sequential depletion of B cells and long-lived plasma cells, for example anti-CD20 therapy followed by daratumumab, telitacicept, or BCMA-directed therapy, is biologically attractive in autoantibody-driven refractory disease. However, controlled evidence is insufficient, and cumulative risks include severe infection, cytopenia, hypogammaglobulinemia, impaired vaccine responses, and delayed immune reconstitution [143,144].

3.6.3. Investigational Targeted–Targeted Combinations

Specific targeted–targeted combinations remain under prospective evaluation, and the completed trials have been negative or inconclusive. The Phase 4 SYNERGY trial is evaluating belimumab, voclosporin, MMF, and GCs in proliferative LN and whether MMF can be withdrawn early after initial disease control (ClinicalTrials.gov: NCT07225387). The Phase 4 PRESERVE study, a single-arm study with a planned enrollment of 150 patients, is assessing voclosporin combined with belimumab, obinutuzumab, or anifrolumab on a background of MMF and GCs (ClinicalTrials.gov: NCT07611214). Neither study has yet reported efficacy or safety results. AB-101 is an allogeneic cord-blood-derived NK-cell product intended to enhance anti-CD20-mediated antibody-dependent cellular cytotoxicity; Phase 1 studies are evaluating AB-101 in combination with rituximab or obinutuzumab in class III/IV LN or other refractory SLE and in other B-cell-mediated autoimmune diseases, and lupus-specific efficacy results are unavailable (ClinicalTrials.gov: NCT06265220 and NCT06581562).

Lessons from negative and inconclusive combination trials: The Phase 3 BLISS-BELIEVE trial added a rituximab cycle shortly after belimumab initiation and did not improve disease control or remission over belimumab alone [78]. In CALIBRATE, a favorable immunologic effect on autoreactive B cells did not translate into better renal responses [141]. In the Phase 2 SLEek trial, upadacitinib 30 mg alone and the higher-dose combination with the BTK inhibitor elsubrutinib reduced disease activity and flares, whereas

elsubrutinib monotherapy and the lower-dose combination were discontinued for insufficient efficacy [36]. Responses were maintained through week 104 in the long-term extension without new safety signals [37], but because the extension lacked a placebo group and outcomes were similar for upadacitinib alone and the combination, a contribution from BTK inhibition has not been established, and upadacitinib monotherapy, rather than the combination, advanced to Phase 3. These trials show that a sound immunologic rationale does not guarantee clinical benefit and that the outcome may depend on sequence, interval, baseline phenotype, and B-cell biomarkers. Targeted–targeted combinations should therefore not be presumed superior to single-agent therapy until controlled trials show added benefit.Adjunctive and individualized strategies: Immune-complex clearance and complement-directed interventions may complement immunosuppression in selected patients but are not routine combination treatments. Valziflocept/SM101, a soluble FcγRIIB protein designed to neutralize immune complexes, showed early pharmacological activity but has not progressed to established SLE therapy [148]. Plasma exchange or complement inhibition should generally be reserved for selected complications, such as thrombotic microangiopathy, catastrophic antiphospholipid syndrome, severe complement-mediated vascular injury, or rare complement deficiencies [149–151]. Computational models integrating treatment frequency, drug–gene interactions, and predicted toxicity may assist future combination selection, but such models remain hypothesis-generating and require prospective clinical validation [152].

Overall, combination therapy in SLE and LN is supported by Phase 3 evidence only when a single agent, belimumab, voclosporin, or obinutuzumab, is added to standard therapy (category A). Sequential rituximab–belimumab therapy may benefit selected refractory patients, but efficacy appears to depend on treatment sequence and patient characteristics (category B). Targeted–targeted combinations, including dual B-cell/plasma-cell targeting and combined pathway inhibition, are investigational and require controlled evaluation of efficacy and cumulative safety (category C). Established, sequential, and investigational combination strategies, with their targets, trial outcomes, and supporting references, are summarized in Table 3.

Table 3. Established, sequential, and investigational combination strategies in SLE and LN.

Combination Agents	Target of Each Agent	Clinical Trials and Outcomes	References
A. Established: targeted agent added to standard therapy (shows the benefit of adding one agent; does not establish the efficacy of combining multiple targeted agents)			
Belimumab + standard LN therapy	BAFF neutralization plus MMF-mediated lymphocyte inhibition or CYC-based immunosuppression and GC-mediated anti-inflammatory activity	BLISS-LN (NCT01639339, P3): primary efficacy renal response was 43% versus 32%, and complete renal response was 30% versus 20%, compared with placebo plus standard therapy at week 104.	[44]
Voclosporin + MMF + low-dose GCs	Calcineurin–NFAT inhibition and podocyte stabilization combined with inhibition of lymphocyte purine synthesis and broad anti-inflammatory activity	Active LN. AURORA 1 (NCT03021499, P3): complete renal response at week 52 was 41% versus 23% with placebo. Active LN. AURORA 2 (NCT03597464, P3 extension): proteinuria reduction and complete renal response were sustained, eGFR remained stable, and no new safety signal emerged over up to 3 years.	[46,47]
Obinutuzumab + MMF + GCs	Potent type II anti-CD20-mediated B-cell depletion added to antiproliferative and anti-inflammatory therapy	Active LN. REGENCY (NCT04221477, P3): complete renal response at week 76 was 46.4% versus 33.1% with placebo.	[49,50]
Obinutuzumab + standard therapy in nonrenal SLE	$CD20^+$ B-cell depletion added to conventional background immunomodulation	Active non-renal SLE**.** ALLEGORY (NCT04963296, P3): week 52 SRI-4 response was 76.7% versus 53.5% with placebo; all key secondary outcomes also favored obinutuzumab; SAEs 15.9% vs. 11.9%.	[31]

B. Sequential strategies (agents given at separate times)			
Rituximab → belimumab	Rituximab depletes CD20⁺ B cells, then belimumab neutralizes BAFF and limits survival of repopulating autoreactive B cells	Refractory SLE. BEAT-LUPUS (ISRCTN47873003, P2b; *N* = 52): reduced IgG anti-dsDNA antibodies (primary endpoint) and severe flares (HR 0.27; 95% CI 0.07 to 0.98) compared with rituximab followed by placebo; the difference was lost when moderate flares were included.	[140]
Rituximab + CYC → belimumab	CD20⁺ B-cell depletion and alkylating lymphocyte suppression followed by BAFF blockade.	Refractory LN. CALIBRATE (NCT02260934, P2); *N* = 43, open-label): safe and enhanced negative selection of autoreactive B cells, but did not improve clinical renal efficacy (complete or partial response 52% vs. 41%; *p* = 0.452).	[141]
Rituximab → belimumab (long-term follow-up)	CD20⁺ B-cell depletion and lymphocyte suppression followed by BAFF blockade.	Severe refractory SLE. Synbiose follow-up: 6 of 8 patients maintained clinical remission over a median of 6.8 years; uncontrolled and too small for comparative conclusions	[142]
Rituximab → belimumab or telitacicept	CD20⁺ B-cell depletion followed by BAFF blockade or dual BAFF/APRIL blockade	Refractory LN. No prospective randomized registration; retrospective refractory-LN cohorts: objective renal remission was 80.0% with belimumab and 85.7% with telitacicept in a multicenter study; comparative superiority was not established.	[143,144]
C. Investigational targeted–targeted combinations			
Belimumab + one cycle of rituximab	BAFF blockade combined with CD20⁺ B-cell depletion	SLE. BLISS-BELIEVE (NCT03312907, P3): did not improve stringent disease-control or remission endpoints over belimumab alone in SLE.	[78]
Upadacitinib + elsubrutinib	JAK1 inhibition suppresses cytokine signaling; BTK inhibition targets BCR-, Fc receptor-, and TLR-mediated activation	SLE. SLEek (NCT03978520, P2): the higher-dose combination showed clinical activity, but lower-dose combination and elsubrutinib monotherapy were discontinued for insufficient efficacy. NCT04451772 (P2 extension): responses persisted to week 104, but superiority over upadacitinib monotherapy was not demonstrated.	[36,37]
Belimumab + voclosporin + MMF + GCs	BAFF blockade, calcineurin inhibition, lymphocyte antiproliferation, and broad anti-inflammatory activity	Proliferative LN. SYNERGY (NCT07225387, P4): recruiting; evaluates safety, renal response, and early MMF withdrawal. No efficacy results are available.	ClinicalTrials.gov.
Voclosporin + belimumab, obinutuzumab, or anifrolumab + mycophenolic acid + GCs	Calcineurin inhibition combined with BAFF blockade, CD20 depletion, or IFNAR1 blockade on a conventional LN-treatment background.	Active LN. PRESERVE (NCT07611214, P4): recruiting; single-arm, planned *N* = 150; efficacy and safety results are pending.	ClinicalTrials.gov.
AB-101 + rituximab or obinutuzumab	Allogeneic NK cells enhance anti-CD20-mediated antibody-dependent cytotoxic depletion of CD20⁺ B cells	Class III/IV LN or other refractory SLE (NCT06265220; AB-101 alone or with rituximab or obinutuzumab) and B-cell–mediated autoimmune diseases including SLE (NCT06581562; rituximab + AB-101) (P1): ongoing; lupus-specific outcomes have not been reported.	ClinicalTrials.gov.

Ongoing studies were identified from ClinicalTrials.gov; registered studies without reported results are not interpreted as evidence of efficacy. Abbreviations: BCR, B-cell receptor; NK cells, natural killer cells. For others, refer to the abbreviations listed in the back section.

4. Conclusions

Advances in SLE immunopathogenesis have enabled a transition from broad immunosuppression toward selective, mechanism-based treatment. Interconnected abnormalities in nucleic acid sensing, cytokine signaling, B- and T-cell activation, autoantibody

production, intracellular signaling, and impaired clearance sustain disease activity and provide multiple therapeutic targets.

The strongest clinical evidence supports inhibition of IFN-I and B-cell survival pathways, B-cell depletion, and calcineurin–NFAT signaling, represented by anifrolumab, belimumab, obinutuzumab, and voclosporin. Several emerging approaches, including selective TLR, JAK/TYK2 and BTK inhibition, FcRn blockade, plasma-cell targeting, and CD19-directed cellular therapy, are also promising but rest largely on Phase 2, uncontrolled, or abstract-level evidence. However, variable responses and safety concerns with many targeted agents emphasize the need for appropriate pathway selection and patient stratification. In LN, adding one targeted agent to standard immunosuppression improves renal outcomes, whereas targeted–targeted combinations have so far produced negative or inconclusive results and remain investigational. Infection risk, hypogammaglobulinemia, cost, and unequal global access further limit the use of many of these therapies.

5. Future Directions

Future SLE therapy should increasingly focus on precision treatment based on the dominant immunopathogenic mechanisms in individual patients. Biomarkers reflecting IFN activity, B- and plasma-cell abnormalities, autoantibody profiles, intracellular signaling, and organ involvement may help guide therapeutic selection and improve response.

Another priority is to determine the optimal timing, sequence, and combination of targeted therapies without compounding infection or immune-depletion risks. B- or plasma-cell depletion, including CD19-, CD38-, or BCMA-directed approaches, has been proposed to reset the autoreactive immune repertoire, but current evidence comes from small, uncontrolled studies with short follow-up, and durable remission, immune reconstitution, and long-term safety have not been established. Rational combinations targeting complementary pathways remain a hypothesis to be tested in controlled trials, because most targeted–targeted combinations studied so far have not shown added clinical benefit. Future trials should therefore integrate mechanistic biomarkers, phenotype-specific and organ-specific outcomes, and long-term safety to establish individualized strategies capable of achieving durable remission; whether immune tolerance can be restored remains an open question. Trials should also report cost-effectiveness and include diverse populations, so that benefits can be realized across health systems.

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Abbreviations

The following abbreviations are used in this manuscript: AMPK, AMP-activated protein kinase; ALCAM, activated leukocyte cell adhesion molecule; APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BAFFR, BAFF receptor; BCMA, B-cell maturation antigen; BCR, B-cell receptor; BDCA2, blood dendritic cell antigen 2; BICLA, British Isles Lupus Assessment Group–based Composite Lupus Assessment; BTK, Bruton's tyrosine kinase; CaMK-IV, $Ca2^{+}$-calmodulin-dependent protein kinase IV; CAR-T cell, chimeric antigen receptor T cell; CI, confidence interval; CLASI-A, cutaneous lupus erythematosus disease area and severity index–activity; CLE, cutaneous lupus erythematosus; CRR, Complete renal response; CRS, cytokine release syndrome; CYC, cyclophosphamide; DORIS, Definition of Remission in SLE; eGFR, estimated glomerular filtration rate; Fc, fragment crystallizable; FcRn, neonatal Fc receptor; GC, glucocorticoid; HR, hazard ratio; IFN, interferon; IFN-I, type I interferon; IFNAR1, type I interferon receptor subunit 1; IgG, immunoglobulin G; IL, interleukin; IRAK, interleukin-1 receptor-associated kinase; IVIG, intravenous immunoglobulin; JAK, Janus kinase; LLDAS, lupus low disease activity state; LN, lupus nephritis; mAb, monoclonal antibody; MMF, mycophenolate mofetil; mTOR, mechanistic target of rapamycin; MyD88, myeloid differentiation primary response 88; NETs, neutrophil extracellular traps; NFAT, nuclear factor of activated T cell; NF-κB, nuclear factor kappa B; NK cell, natural killer cell; OR, odds ratio; pDC, plasmacytoid dendritic cell; PERR, primary efficacy renal response; PI3K, phosphoinositide 3-kinase; RCT, randomized controlled trial; SAE, serious adverse event; SLE, systemic lupus erythematosus; SRI, SLE responder index; STAT, signal transducer and activator of transcription; SYK, spleen tyrosine kinase; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor; Tfh, follicular helper T cell; Tfr, follicular regulatory T cell; Th, helper T cell; TLR, toll-like receptor; TNF, tumor necrosis factor; Tph, peripheral helper T cell; Treg, regulatory T cell; TYK2, tyrosine kinase 2; UPCR, urine protein-to-creatinine ratio.

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