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LEADING ARTICLE

# Targeted Small Molecules for Systemic Lupus Erythematosus: Drugs in the Pipeline

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**Abstract**
Despite the uncertainty of the pathogenesis of systemic lupus erythematosus, novel small molecules targeting specific intracellular mechanisms of immune cells are being developed to reverse the pathophysiological processes. These targeted molecules have the advantages of convenient administration, lower production costs, and the lack of immunogenicity. The Janus kinases, Bruton's tyrosine kinases, and spleen tyrosine kinases are important enzymes for activating downstream signals from various receptors on immune cells that include cytokines, growth factor, hormones, Fc, CD40, and B-cell receptors. Suppression of these kinases impairs cellular activation, differentiation, and survival, leading to diminished cytokine actions and autoantibody secretion. Intracellular protein degradation by immunoproteasomes, levered by the cereblon E3 ubiquitin ligase complex, is an essential process for the regulation of cellular functions and survival. Modulation of the immunoproteasomes and cereblon leads to depletion of long-lived plasma cells, reduced plasmablast differentiation, and production of autoantibodies and interferon-α. The sphingosine 1-phosphate/sphingosine 1-phosphate receptor-1 pathway is responsible for lymphocyte trafficking, regulatory T-cell/Th17 cell homeostasis, and vascular permeability. Sphingosine 1-phosphate receptor-1 modulators limit the trafficking of autoreactive lymphocytes across the blood–brain barrier, increase regulatory T-cell function, and decrease production of autoantibodies and type I interferons. This article summarizes the development of these targeted small molecules in the treatment of systemic lupus erythematosus, and the future prospect for precision medicine.

## 1 Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by an unpredictable clinical course with periods of exacerbation and remission. The pathogenesis of SLE remains elusive, and multiple genetic, epigenetic, environmental, and hormonal factors contribute to loss of self-tolerance and aberration of the adaptive and innate immune systems [1, 2]. Clearance of apoptotic materials, nuclear antigens, nucleosomes, and immune complexes by macrophages and complements is defective in SLE [3]. In addition, dysregulated neutrophil apoptosis and inefficient degradation of the neutrophil extracellular traps that contain DNA, histones, cytoplasmic granules, and other mediators in SLE increase the burden of nuclear autoantigens to the immune system [3–6]. Interaction of excessive apoptotic materials and immune complexes with the toll-like receptors (TLRs) 7/9 leads to the activation of the plasmacytoid dendritic cells (pDCs) and release of type I interferons (IFNs) and interleukin (IL)-6, which in turn enhance monocyte maturation, impair apoptosis of T cells, and activate B-cell proliferation and autoantibody production [7–9]. Increased maturation of myeloid dendritic cells in SLE promotes IL-17 production by T cells [10] and the defective functions of the regulatory T cells (Tregs) and B cells also contributes to hyperactivity of the immune cells [11, 12].

Cytokines are secreted by cells of the immune systems for mutual communication and orchestration of the immune response [13], and may exhibit proinflammatory or anti-inflammatory properties, or both, depending on the microenvironment [14]. Production of cytokines is dysregulated in SLE, which may either be the primary pathogenetic process or secondary to the imbalance of immune pathways, such as the Th1/Th2 and Th17/Treg [15]. Patients with SLE have abnormal expression or levels of serum cytokines, such as the IFNs (IFNα, IFNγ), ILs (IL-2, IL-6, IL-10, IL-12, IL-15, IL-17, IL-21, IL-23), and B-cell activation factor (BAFF) [14]. The peripheral blood BAFF and IFN gene signatures

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**Key Points**

Small molecules that target the Janus kinases, Bruton's tyrosine kinases, spleen tyrosine kinases, immunoproteasomes, cereblon, and sphingosine 1-phosphate receptor-1 are developed for the treatment of malignant and autoimmune disorders, including systemic lupus erythematosus.

These targeted small molecules have the advantages of convenient administration, lower production costs, and the lack of immunogenicity.

Some of these compounds, such as deucravacitinib, orelabrutinib, and iberdomide, have shown promise in phase II trials. Other small molecules, zetomipzomib and cenerimod, are undergoing phase II/III trials in systemic lupus erythematosus and lupus nephritis.

Genetic and molecular profiling may help stratify patients to choose the most appropriate targeted therapies in future.

With more treatment modalities available for systemic lupus erythematosus, the treat-to-target approach is increasingly feasible in clinical practice.

of patients with SLE correlate with disease activity, particularly musculoskeletal and dermatological disease [16–18]. The dysregulation of the cytokine network contributes to inhibition of Treg activity but promotion of MHC expression, Th17 differentiation, T/B-cell activation and survival, and autoantibody production [15].

The increased knowledge of the intracellular mechanisms has led to the development of novel agents for the treatment of autoimmune diseases, including SLE. Inhibition of the receptor-associated Janus kinases (JAKs) provides a novel approach in suppressing the downstream signals of multiple cytokines and growth factors [1]. Suppression of the intracellular Bruton's tyrosine kinase (BTK) and spleen tyrosine kinase (SYK), which are cytosolic non-receptor proteins essential for B-cell receptor signaling, leads to impaired B-cell activation, differentiation, and survival, as well as expression of the costimulatory molecules, and production of antibodies and cytokines [19, 20]. This BTK/SYK inhibition also affects the functions of other immune cell types such as the macrophages, neutrophils, mast cells, and basophils. Modulation of the immunoproteasomes and cereblon E3 ligase, which play an important role in intracellular protein degradation, results in depletion of long-lived plasma cells, reduction of B-cell differentiation to plasmablasts, and the production of autoantibodies and IFNα [21, 22]. The sphingosine 1-phosphate (S1P)/S1P receptor-1 (S1PR1) pathway influences lymphocyte trafficking, Treg/Th17 cell homeostasis, and vascular permeability [23]. The S1PR1 modulators diminish trafficking of autoreactive lymphocytes across the blood–brain barrier, increase Treg function, and decrease the production of autoantibodies and type I IFNs [24].

Small molecules that target JAKs, BTKs, SYKs, immunoproteasomes, cereblon, and S1PR1 are being developed for the treatment of malignant and autoimmune disorders. In contrast to the biologic disease-modifying anti-rheumatic drugs, which are large molecules that require parenteral administration, small molecules are orally available and enter the cellular cytoplasm to exert their effects directly. Targeted small molecules have the advantages of convenient administration, lower production costs, and the absence of immunogenicity. This article summarizes the current evidence of these small molecules in the treatment of SLE, and the prospect for precision medicine. Table 1 lists the different mechanisms of action of targeted small molecules that are being evaluated in SLE.

## 2 Janus Kinase (JAK) Inhibitors

The JAK-signal transducer and activator of transcription (STAT) is one of the most important intracellular signaling pathways that mediates proliferation, maturation, differentiation, activation, migration, and survival of almost all cell types [25]. The JAKs transduce signals from multiple cytokines of the IL and IFN families, hormones, and hemopoietic growth factors [26]. The type I cytokine receptors comprise common γ chain (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21), gp130 family (IL-6), p40 subunit (IL-12, IL-23), and common β chain receptors (erythropoietin, thrombopoietin, and granulocyte-macrophage colony-stimulating factor), whereas the type II cytokine receptors are mainly associated with IL-10 and the type I/II IFNs [27]. Binding of cytokines and other soluble factors to their receptors results in activation of receptor-associated JAKs through cross-phosphorylation of each other [1]. The activation of the JAKs requires two JAK isoforms, either as homodimers or heterodimers, which in turn recruit and activate the STAT family of proteins that undergo phosphorylation of the tyrosine or serine residue. Upon activation, the STATs undergo a conformation change to form active homodimers, heterodimers, or tetramers that migrate to the nucleus and activate gene transcription [28]. There are four JAK enzymes, namely JAK1, JAK2, JAK3, and the non-receptor tyrosine protein kinase TYK2 and seven mammalian STATs, namely STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6 [29, 30].

The JAK inhibitors are small molecules that selectively block the adenosine triphosphate-binding site in the JH1 (catalytic kinase) domain of the JAK kinases [31]. With different selectivity to the JAKs and their corresponding

STATs, the JAK inhibitors inhibit the actions of different combinations of cytokines and growth factors that are relevant to the pathophysiology of a number of immune and non-immune disorders such as SLE, inflammatory joint, skin, and bowel diseases, myeloproliferative disorders, and the cytokine storm related to severe COVID-19 infection [32].

### 2.1 JAK Inhibitors in Murine and Experimental Lupus

In murine models of SLE, JAK-2 inhibition reduced anti-dsDNA, serum cytokines, proteinuria, and IgG/C3 deposition in the glomeruli, leading to improvements of renal function, histology, and survival [33, 34]. Moreover, JAK2 inhibition suppressed the renal expression of monocyte chemotactic protein-1, IFNγ, and class II MHC and reduced infiltration by T cells and macrophages [33, 34]. In a study of NZB/WF1 mice, targeting JAK3 was effective in slowing down the course of experimental lupus nephritis (LN) [35]. Tofacitinib, a JAK1/3 inhibitor, has been shown to mitigate renal and skin disease in murine lupus by a reduction in IFN gene expression, anti-dsDNA levels, and $CD4^+$ T-cell activation through upregulation of TGFβ type I receptor expression [36–39]. JAK1/2 inhibition by baricitinib has been shown to attenuate autoimmune features and renal inflammation in murine lupus by suppressing aberrant B-cell activation and podocyte abnormalities [40].

### 2.2 JAK Inhibitors in Human SLE

T lymphocytes from patients with active SLE were shown by in vitro studies to have an over-expression of the IFN regulatory factor-related genes, IFI35 and IFITM1, two JAK genes (JAK1/JAK2), and two STAT signaling genes (STAT1/STAT2) [41]. Pathway network analyses suggested that the IFN regulatory factor-related genes were regulated through the JAK-STAT pathway. Levels of STAT1 protein were significantly increased in SLE $CD4^+$ T cells compared with patients with rheumatoid arthritis (RA) and healthy controls, and were associated with lower activated Treg counts and more SLE flares on the follow-up, suggesting enhanced STAT1 signaling may be involved in the dysregulation of Treg homeostasis [42].

**Table 1** Targeted small molecules in SLE: drugs in the pipeline

| Targets | Drugs | Disease | Stage of development | Remarks |
|---|---|---|---|---|
| JAK | Tofacitinib | SLE | Phase Ib/IIa | – |
| | | CLE | Phase I/II | – |
| | Solcitinib | SLE | Phase II | Terminated for inefficacy and AEs |
| | Filgotinib | CLE | Phase II | – |
| | Baricitinib | SLE | Phase III | Inconclusive results |
| | Deucravacitinib | SLE | Phase II | Phase III just registered |
| | Beprocitinib | SLE | Phase II | Just completed |
| BTK | Ibrutinib | – | – | – |
| | Fenebrutinib | SLE | Phase II | Negative results |
| | Evobrutinib | SLE | Phase II | Negative results |
| | Orelabrutinib | SLE | Phase II | Promising results |
| SYK | Fostamatinib | SLE | Phase II | Withdrawn |
| | Lanraplenib | CLE, MLN | Phase II | – |
| Proteasomes | Bortezomib | SLE | Open series | – |
| | Carfilzomib | – | – | – |
| | Ixazomib | LN | Phase II | Terminated |
| | Zetomipzomib | SLE | Phase Ib | Phase II in preparation |
| Cereblon | Lenalidomide | CLE | Open series | – |
| | Iberdomide | SLE | Phase II | Promising results |
| | Mezigdomide | – | – | – |
| S1PR1 | Fingolimod | – | – | – |
| | Ozanimod | – | – | – |
| | Amiselimod | SLE | Ib | – |
| | Cenerimod | SLE | Phase II/III | Phase III just started |

*AEs* adverse events, *BTK* Bruton's tyrosine kinase, *CLE* cutaneous lupus erythematosus, *JAK* Janus kinase, *LN* lupus nephritis, *MLN* membranous lupus nephritis, *S1PR1* sphingosine 1-phosphate receptor-1, *SLE* systemic lupus erythematosus, *SYK* spleen tyrosine kinase

Moreover, activation of the STAT protein upon stimulation by cytokines and IFNs appear to be related to genetic factors. The STAT4 risk allele rs7574865[T] in patients with SLE was associated with an increased phosphorylation response of the STAT4 protein to IL-12 and IFN-α stimulation [43]. Conversely, selective inhibition of TYK2 and JAK2 effectively blocked in-vitro IL-12 and IFN-γ-induced activation of the peripheral blood mononuclear cells (PBMCs) from patients with the STAT4-risk allele. In addition, autoantibody and IgG production from SLE B cells was abrogated by the addition of ruxolitinib (a JAK1/2 inhibitor) and stattic (a STAT3 inhibitor) to the culture system, indicating the JAK/STAT3 pathway is involved in the control of autoantibody production in SLE [44].

Genome-wide association studies have identified a number of genes that confer susceptibility to SLE, including the STAT genes [45–48]. The STAT4 risk allele was associated with the presence of the anti-dsDNA antibody [49] and more severe manifestations such as renal disease [50] in patients with SLE. While the exact functional significance of the STAT4 polymorphism remains to be elucidated, the STAT4 risk allele was postulated to confer an increased sensitivity of immune cells to IFNα signaling in SLE [43, 51], leading to enhanced cellular activation, B-cell differentiation, and autoantibody production [52].

#### 2.2.1 Tofacitinib

Tofacitinib, a pan-JAK inhibitor with more potent action on JAK1/3, has been licensed for the treatment of RA and ulcerative colitis [53, 54]. In a phase Ib/IIa, double-blind, randomized controlled trial (RCT), 30 patients with SLE were randomized in a 2:1 ratio to receive tofacitinib (5 mg twice daily) or placebo (PBO) and the primary outcome was safety at day 84 [55]. Tofacitinib was well tolerated in patients studied without unexpected serious adverse events (SAEs), disease worsening, or thromboembolism (Table 2). Lipid profile, arterial stiffness, type I IFN gene signature, and circulating neutrophil extracellular traps improved with tofacitinib treatment. The improvement of laboratory parameters was more robust in patients with the STAT4 risk allele, which was associated with a more severe clinical phenotype of SLE. Two other phase I/II studies on cutaneous lupus were registered (NCT03159936; NCT03288324).

#### 2.2.2 Solcitinib and Filgotinib

Solcitinib is a selective JAK1 inhibitor. A phase II RCT of solcitinib in non-renal SLE (NCT01777256) was prematurely terminated after recruiting 50 patients for a lack of efficacy (no improvement in IFN transcriptional biomarker expression) on an interim analysis, along with two cases (4%) of drug reaction with eosinophilia and systemic symptoms and four (8%) other cases of reversible liver derangement [56, 57] (Table 2). Filgotinib is another selective JAK1 inhibitor that has been approved for ulcerative colitis [58] and RA (in Europe) [59]. Phase II trials are being arranged for its efficacy in cutaneous lupus (NCT03134222) and membranous lupus nephropathy (NCT03285711) but there are no registered trials in non-renal SLE.

#### 2.2.3 Baricitinib

Baricitinib is a JAK1/2 inhibitor approved for RA [60], alopecia areata [61], atopic dermatitis [62], and severe COVID-19 infection [63, 64]. In a phase II PBO-controlled RCT, 314 adult patients with autoantibody-positive SLE who had active joint and/or skin disease, and a clinical SLEDAI score $\geq 4$ were randomly assigned to receive two doses of baricitinib (2 mg/day and 4 mg/day) or PBO in addition to standard-of-care (SOC) therapy that included glucocorticoids (GCs), antimalarials, non-steroidal anti-inflammatory drugs, or a single immunosuppressive agent (methotrexate, azathioprine, or mycophenolate mofetil) [65]. The primary efficacy endpoint was resolution of skin disease or arthritis at week 24, which was achieved in 67%, 58%, and 53%, respectively, of patients receiving baricitinib 4 mg, 2 mg, and PBO (baricitinib 4 mg vs PBO; $p = 0.04$). Secondary outcomes, namely the achievement of the SLE Responder Index-4 (SRI-4) response (64% vs 48%; $p = 0.02$) and the lupus low disease activity state (LLDAS) [38% vs 26%; $p = 0.04$], were also more frequent in baricitinib 4-mg than PBO-treated patients.

While the extent and severity of skin lesions (assessed by the Cutaneous Lupus Erythematosus Disease Area and Severity Index [CLASI]) did not improve any better with baricitinib, tender joint counts showed a greater reduction in the baricitinib 4-mg group than the PBO group of patients ($-6.9$ vs $-5.6$ joints; $p = 0.04$). Improvement in the number of swollen joints, however, was not greater with baricitinib. Moreover, baricitinib 4-mg treatment did not lead to greater changes in levels of anti-dsDNA and complement C3 compared to PBO, and no correlation could be observed between the drop in anti-dsDNA/IgG with the SRI-4 response [66]. Nevertheless, elevated levels of IL-12 p40, IL-6, messenger RNA expression of STAT1-target, STAT2-target, and STAT4-target and multiple IFN responsive genes were reduced with baricitinib treatment [67].

The occurrence of adverse events (AEs) was similar among the three groups of patients. Serious AEs were numerically more common in the baricitinib than PBO groups. The rate of serious infection was higher in the

**Table 2** Targeted small molecules in SLE: data from major clinical trials

| Author(s), year | Drug | Sample size (*n*) | Study design | Inclusion criteria | Clinical efficacy | AEs |
|---|---|---|---|---|---|---|
| Hasni et al. 2021 [55] | Tofacitinib | 30 | RCT (p1) | SLE, mild/moderate activity | Not powered for efficacy; ↓ SLEDAI-2K, BILAG scores (without flares) at day 84 with tofactinib; ↓ IFN gene signature and circulating NETs (more marked in those with STAT4 risk allele) | AEs not significantly ↑ with tofacitinib; no SAEs, opportunistic infections, HZ, or thromboembolic events |
| Kahl et al. 2015 [56] | Solcitinib | 50 | RCT (p2) | SLEDAI ≥ 8, no renal or NP features | Only 18 patients analyzed at week 12; 5/18 with treatment and 0/5 with PBO achieved SRI-4 response | Liver derangement in 6 patients 9–42 days after treatment; 2 of these patients fulfilled criteria of DRESS; study terminated |
| Morand et al. 2023 [68]; Petri et al. 2023 [69] | Baricitinib | 760 and 775 | Two RCTs (p3) | ≥ 1 BILAG A/≥ 2 BILAG B, SLEDAI ≥ 6, cSLEDAI ≥ 4 | Primary endpoint, SRI-4, at week 52 met in BRAVE I (57% vs 46%) but not in BRAVE II (47% vs 46%); secondary endpoints, e.g., SRI-4 at week 24, time to first severe flare, GC sparing, and achievement of LLDAS were not met in either study | No significant ↑ in SAEs and TEAEs in baricitinib vs PBO group; no new safety signals |
| Morand et al. 2023 [70] | Deucravacitinib | 363 | RCT (p2) | ≥ 1 BILAG A/≥ 2 BILAG B, cSLEDAI-2K ≥ 6 with skin/joint disease | Primary endpoint, SRI-4, at week 32 met by the deucravacitinib 3-mg and 6-mg groups vs PBO (58% vs 34%; 50% vs 34%); secondary endpoints, SRI-4, LLDAS, and BICLA response at week 48 also met in deucravacitinib 3-mg group; more patients achieved ≥ 50% ↓ CLASI score and combined swollen/tender joint counts in deucravacitinib 3-mg group | AEs similar across treatment and PBO groups, except ↑ rates of infections, rash, and acne with treatment. No ↑ SAEs, opportunistic, TB infections, MACEs, or thrombosis with treatment |
| Isenberg et al. 2021 [95] | Fenebrutinib | 260 | RCT (p2) | SLEDAI ≥ 8; PGA ≥ 1 | Primary endpoint, SRI-4, at week 48 not met with fenebrutinib vs PBO; BICLA response rate also not met | More SAEs and withdrawals due to AEs in the fenebrutinib 200mg group vs PBO; but no ↑ in serious infections |
| Wallace et al. 2023 [92] | Evobrutinib | 469 | RCT (p2) | SLEDAI-2K ≥ 6, including cSLEDAI-2K ≥ 4 | Primary endpoint, SRI-4, at week 52 not met with evobrutinib vs PBO; secondary endpoints also not met | No significant ↑ in TEAEs and serious TEAEs, including serious infections, but more withdrawals due to elevated liver enzymes with evobrutinib |
| Li et al. 2022 [96] | Orelabrutinib | 60 | RCT (p2) | SLEDAI-2K ≥ 5 | SRI-4 responses at week 12 significantly higher in orelabrutinib vs PBO groups | AEs and TEAEs numerically higher in orelabrutinib vs PBO group, mostly mild/moderate in severity |

**Table 2** (continued)

| Author(s), year | Drug | Sample size (*n*) | Study design | Inclusion criteria | Clinical efficacy | AEs |
|---|---|---|---|---|---|---|
| Ishii et al. 2018 [130] | Bortezomib | 14 | RCT | Refractory SLE | Numerically higher SRI-4 response rate in treatment vs PBO group | 50% patients withdrew because of AEs; infections, headache, polyneuropathy, skin allergy, nausea, and ↓ Igs reported in other case series |
| Merrill et al. 2022 [147] | Iberdomide | 288 | RCT (p2) | SLEDAI-2K ≥ 6, including cSLEDAI-2K ≥ 4 | Primary endpoint, SRI-4 response rate, at week 24 was significantly higher in iberdomide 0.45 mg group vs PBO group (54% vs 35%); higher SRI-4 rates in those with SLEDAI ≥ 10 and high IKZF3 expression and IFN signature at baseline | AEs and SAEs not ↑ with iberdomide vs PBO; numerically more respiratory tract, urinary tract infections, and neutropenia with iberdomide |
| Tanaka et al. 2020 [160] | Amiselimod | 17 | Open-label (p1b) | SLEDAI-2K ≥ 4 | SLEDAI drop ≥ 4 points in 7/17 subjects at week 24 | Most common AE was upper respiratory tract symptoms (mild) and lymphopenia (led to withdrawal in 5 patients; not associated with infections); no cardiotoxicity observed |
| Hermann et al. 2019 [161] | Cenerimod | 49 | RCT (p1/2) | SLEDAI-2K ≥ 2, with active MSK or mucocutaneous manifestations | Greater improvement in the modified SLEDAI-2K score and anti-dsDNA titer at week 12 in cenerimod vs PBO group | No ↑ TEAEs in cenerimod vs PBO group; dose-dependent drop in lymphocyte count and heart rate with cenerimod, but not clinically relevant |

*AEs* adverse events, *BICLA* BILAG-based Composite Lupus Assessment, *BILAG* British Isles Lupus Assessment Group, *CLASI* Cutaneous Lupus Erythematosus Disease Area and Severity Index, *cSLEDAI* clinical SLEDAI, *DRESS* drug rash with eosinophilia and systemic symptoms, *GC* glucocorticoid, *HZ* herpes zoster, *IFN* interferon, *Ig* immunoglobulin, *LLDAS* lupus low disease activity state, *MACE* major adverse cardiovascular event, *MSK* musculoskeletal, *NETs* neutrophil extracellular traps, *NP* neuropsychiatric, *p1* phase I, *p2* phase II, *p3* phase III, *PBO* placebo, *PGA* Physicians' Global Assessment, *RCT* randomized controlled trial, *SAE* serious AE, *SLE* systemic lupus erythematosus, *SLEDAI* SLE Disease Activity Index, *SRI-4* SLE Response Index-4, *TEAE* treatment-emergent adverse event, *TB* tuberculosis, ↓ decreased, ↑ increased

baricitinib 4-mg group (6%) than the baricitinib 2-mg group (2%) or PBO group (1%). Only one patient who tested positive for the antiphospholipid antibodies developed a deep vein thrombosis after baricitinib treatment (4 mg/day).

The favorable result of this phase II RCT led to two subsequent phase III RCTs of baricitinib in non-renal SLE (SLE-BRAVE I; NCT03616912 and SLE-BRAVE II; NCT03616964) [68, 69] (Table 2). Participants were patients with autoantibody-positive SLE with ≥ 1 BILAG A or ≥ 2 BILAG B scores, total SLEDAI ≥ 6, and clinical SLEDAI ≥ 4 and were receiving background therapy with stable doses of GCs, a single antimalarial, or other immunosuppressive drug. Similar to the phase II study [65], these patients were randomized to baricitinib 4 mg/day, 2 mg/day, or PBO. The primary efficacy endpoint was SRI-4 response at week 52, which was met in SLE-BRAVE-I (57% vs 46%; $p = 0.02$) but not SLE-BRAVE-II (47.4% vs 45.6%) despite an identical study design. Secondary endpoints that included SRI-4 response at week 24, time to first severe flare, GC sparing, and achievement of LLDAS were not met in either study. Although the musculoskeletal and mucocutaneous domains on SLEDAI and BILAG improved significantly with baricitinib 4 mg versus PBO in the SLE-BRAVE-I study, this was not observed in the SLE-BRAVE-II study. The safety of baricitinib was consistent with the known profile of the drug, with an increased risk of serious infections but not venous thromboembolism. The inconsistent results of these two RCTs render the efficacy of baricitinib in SLE inconclusive. A long-term extension study of baricitinib in SLE is in progress (SLE-BRAVE-X).

#### 2.2.4 Deucravacitinib

Deucravacitinib is a selective Tyk-2 inhibitor that blocks the downstream signaling of IL-12, IL-23, IL-10, and the type I IFNs. In a phase II RCT (PAISLEY), 363 patients with autoantibody-positive SLE with active disease (≥ 1 BILAG A or ≥ 2 BILAG B scores, clinical SLEDAI-2K ≥ 6 with skin or joint involvement) were randomly assigned to receive three dosage regimens of deucravacitinib (3 mg twice daily, 6 mg twice daily, 12 mg once daily) or PBO in addition to background medications [70]. Subjects with severe or life-threatening organ manifestations of SLE were excluded. A protocol-based GC taper was required from week 8 to 20, whereas a further GC taper from week 32 to 40 was optional.

The primary endpoint of this RCT was the SRI-4 response at week 32, which was met by the deucravacitinib 3-mg and 6-mg twice-daily groups compared to PBO (58.2% vs 34.4%; $p < 0.001$ and 49.5% vs 34.4%; $p = 0.02$, respectively) [Table 2]. Secondary endpoints, such as the SRI-4 response, achievement of LLDAS, and the BICLA response at week 48 were also significantly higher in the deucravacitinib 3-mg twice-daily group versus PBO. Moreover, significantly more patients in the deucravacitinib 3-mg twice-daily group achieved a ≥ 50% reduction in the CLASI score and combined swollen/tender joint counts. Deucravacitinib treatment resulted in a greater improvement in anti-dsDNA titer and complement levels. Moreover, all dosages of deucravacitinib, but not PBO, were associated with a reduction in the IFN signature through 44 weeks of treatment.

Deucravacitinib was well tolerated, with no increase in AEs, SAEs, or infective complications including herpes zoster infection observed. The most common AEs (≥ 10%) reported in deucravacitinib-treated patients were upper respiratory tract infection, nasopharyngitis, headache, and urinary tract infection. Cancer incidence was similar between deucravacitinib and PBO and there were no deaths, thrombotic events, opportunistic infections, or tuberculosis. A phase III RCT (POETYK SLE-1) has just been registered (NCT05617677).

#### 2.2.5 Beprocitinib

Beprocitinib is a selective JAK1/Tyk2 inhibitor with a promising mechanism in the treatment of SLE through inhibition of the downstream signal of IL-10, IL-12, IL-23, and the type I IFNs. A phase II RCT in non-renal SLE (NCT03845517) has just completed recruitment.

## 3 Bruton's Tyrosine Kinase Inhibitors (BTKis)

The BTK is a cytoplasmatic tyrosine kinase belonging to the family of tyrosine kinase expressed in hepatocellular carcinoma [71] and expressed in most hematopoietic cells, including the B cells and terminally differentiated plasma cells, monocytes/macrophages, dendritic cells, natural killer cells, mast cells, and platelets [20]. The BTK mediates the signaling of several immune receptors, including the B-cell receptor and Fc receptor [72]. In B cells, BTK plays an essential role in the downstream signal pathways through the B-cell receptor [73, 74] and enhances the sensitivity of the B cells to the Toll-like receptor signaling event such as germinal center formation, CD80 expression, IL-1, IL-6, IFNγ, and anti-nuclear autoantibody production [75]. In addition, BTK is involved in differentiation, phagocytosis, production of cytokines, and other inflammatory mediators of other innate myeloid immune cells [76]. In mast cells, BTK plays an important role in mediating Fcε receptor signaling for the chemotactic response [77]. Finally, BTK also activates platelets via the glycoprotein VI receptor [78] and osteoclast differentiation [79].

The engagement of the B-cell receptor initiates intracellular signaling that involves phosphorylation of SYK, leading to partial activation of BTK, which in turn autophosphorylates to full activation and orchestrates consequent

phosphorylation of its immediate downstream effector, phospholipase Cγ2, ultimately leading to calcium influx and activation of multiple downstream signaling pathways and transcription factors, including nuclear factor of activated T cells, extracellular signal-regulated kinase, and nuclear factor-κB [20]. Bruton's tyrosine kinase and SYK are also involved in the signaling of the BAFF and CD40 receptors that activate the non-canonical nuclear factor-κB pathway [72]. These signals are crucial for the regulation of cellular differentiation, proliferation, survival, and activation that leads to costimulatory molecule expression and the production of antibodies and cytokines.

The BTK inhibitors (BTKis) are small molecules that inhibit the activity of BTK and have been developed for the treatment of various B-cell malignancies for their antiproliferation effects [80]. Ibrutinib is the first-in-class BTKi approved for B-cell proliferative disorders. However, AEs such as cardiotoxicity (atrial and ventricular arrythmia, cardiomyopathy, hypertension) and bleeding (platelet dysfunction) may result in treatment interruption or discontinuation [81]. Newer generation BTKis are now available to overcome treatment resistance to first-generation agents and minimize off-target kinase activity for better safety profiles [82].

### 3.1 BTKis and Murine Lupus

In two classical models of spontaneous murine lupus (NZB/W and MRL/lpr), BTK inhibition reduced the number of splenic B cells and anti-dsDNA titers, delayed the onset of proteinuria, and ameliorated kidney inflammation [83–86]. Cutaneous and neuropsychiatric lesions in the MRL/lpr mice were also attenuated by administration of a BTKi [87]. In the lupus-prone B6.Sle1 and B6.Sle1.Sle3 mice, BTK inhibition was effective in dampening humoral and cellular immunity, and glomerulonephritis [88]. Moreover, inhibiting BTK has been shown to reduce autoantibodies and suppress arthritis and nephritis in TLR7- and IFN-driven murine lupus models [89]. Finally, in the NZB/W F1 mouse model, evobrutinib, a newer BTKi, suppressed B-cell activation, reduced autoantibody production and plasma cell numbers, and normalized B- and T-cell subsets, leading to reduced kidney damage [90].

### 3.2 BTKis in Human SLE

Bruton's tyrosine kinase expression was shown to be higher in PBMCs from patients with SLE than healthy controls, and correlated with the disease activity score, anti-dsDNA, complement levels, and proteinuria [91]. However, in patients with LN, no relationship between BTK expression and histologic activity index was observed. Bruton's tyrosine kinase is an attractive target for SLE treatment because its modulation does not cause B-cell depletion. Moreover, BTK is expressed in multiple immune cell types and its inhibition may enhance therapeutic effect beyond B-cell modulation. A couple of clinical trials of BTKis have been performed in SLE.

Evobrutinib, a highly selective and central nervous system-penetrating oral BTKi, was tested in a phase II RCT of autoantibody-positive SLE [92]. In this study, 469 patients with SLE with a SLEDAI-2K score ≥6 (including a clinical SLEDAI-2K score ≥4) despite SOC treatment were randomly assigned to oral evobrutinib 25 mg once daily, 75 mg once daily, 50 mg twice daily, or PBO. Primary efficacy endpoints were SRI-4 at week 52 and SRI-6 at week 52 in the high disease activity subpopulation (Table 2). At week 52, none of the evobrutinib groups achieved a significantly higher SRI-4 rate than the PBO group. The SRI-6 response rates were also similar across all the four arms in the high disease activity subgroup. No clinically meaningful differences with evobrutinib versus PBO in the changes in organ-specific disease activity, lupus serology, immunoglobulin levels, annualized flare rate, quality of life, or GC usage were observed at week 52. All doses of evobrutinib were well tolerated, with no dose effect observed for treatment-emergent adverse events (TEAEs).

Fenebrutinib is a second-generation, non-covalent, highly selective, reversible oral BTKi that has shown efficacy in phase I/II RCTs of RA [93] and refractory B-cell malignancies [94]. A large phase II dose-ranging study was conducted in 260 patients with moderately and severely active autoantibody-positive SLE who were receiving SOC (SLEDAI-2K ≥8; Physician Global Assessment score ≥1) [95]. Patients with proliferative LN, nephrotic range proteinuria, neuropsychiatric disease, and the antiphospholipid syndrome were excluded. Participants were randomized to receive fenebrutinib 200 mg twice daily, 150 mg once daily, or PBO. A GC taper was recommended from weeks 0 to 12 and from weeks 24 to 36. The primary endpoint was SRI-4 response at week 48. Although fenebrutinib reduced the BTK-dependent plasmablast RNA signature, anti-dsDNA, and IgG/IgM levels but increased C4 levels relative to PBO, the proportion of patients who achieved the SRI-4 response was not significantly higher in the treatment groups than the PBO group at week 48 (52%/51% vs 44%) [Table 2]. Similarly, the BICLA response rate at week 48 was not significantly different between the fenebrutinib- and PBO-treated patients (42%/53% vs 41%). Adverse events, however, were not significantly more common with fenebrutinib compared with PBO but the frequency of SAEs was numerically higher.

Orelabrutinib is an oral, highly selective, irreversible inhibitor of BTK. A phase Ib/II RCT was conducted in China in 60 patients with seropositive SLE with active disease (SLEDAI score ≥5) [96]. Patients were randomized to receive three doses of orelabrutinib or PBO for 12 weeks in addition to the SOC. The primary outcome, SRI-4 response rate, was higher

in any dose of orelabrutinib than PBO (Table 2). Overall, AEs were mild to moderate and the majority of TEAEs were not severe. The reasons for the discrepancies of results in these three RCTs are not immediately apparent and further phase III RCTs of the BTKis in SLE are of interest.

## 4 Spleen Tyrosine Kinase Inhibitors (SYKis)

Spleen tyrosine kinase is a non-receptor tyrosine kinase that belongs to the Zeta-associated protein kinase of the 70-kDa (ZAP70) family [97]. Spleen tyrosine kinase is primarily expressed in hemopoietic cells, including B cells, immature T cells, macrophages, neutrophils, and mast cells that are involved in both adaptive and innate immune responses. In immune cells, SYK signals through multiple receptors such as B cells, pre-T cells, Fc, and TLRs [98]. It catalyzes the phosphorylation of a receptor-associated protein complex known as an immunoreceptor tyrosine based-activation motif that further activates the SYK itself. Spleen tyrosine kinase autophosphorylates and activates adapter proteins that are involved in several intracellular signal transduction pathways, including PI3K/Akt, Ras/ERK, PLCγ/NFAT, Vav-1/Rac, and IKK/NKκB [99]. Via these actions, SYK regulates the proliferation, survival, differentiation, activation, degranulation, and cytokine production of the immune cells.

### 4.1 SYKi and Murine Lupus

Spleen tyrosine kinase expression is abnormally increased in the skin lesions of lupus prone mice [100]. The SYK inhibitor (SYKi), fostamatinib, has been shown to ameliorate kidney and skin disease in female MRL/lpr or BAK/BAX lupus-prone mice [100]. Administration of fostamatinib before or after disease onset was effective in delaying the onset of proteinuria and renal failure, reducing kidney infiltrates, and improving the survival of the NZB/NZW mice without suppressing autoantibody titers [101]. Lanraplenib, a selective SYKi, was also shown to retard the progression of LN-like disease in NZB/W mice and reduce glomerular IgG deposition and serum proinflammatory cytokines [102]. Other newer generation SYKis have also been shown to retard the progression of LN in the lupus mouse models [103, 104].

### 4.2 SYKi in Human Immune-Mediated Diseases

Fostamatinib has been tested in various immune-mediated diseases such as RA, chronic immune thrombocytopenia, autoimmune hemolytic anemia, and IgA nephropathy [105]. It is the first SYKi approved for the treatment of chronic immune thrombocytopenia by blocking signal transduction through Fcγ receptors involved in the antibody-mediated destruction of platelets by immune cells [106]. Fostamatinib was studied in patients with RA who had an inadequate response to methotrexate or the tumor necrosis factor inhibitors [107, 108]. In both phase III RCTs, although the efficacy of fostamatinib was observed, AEs of concern such as hypertension, diarrhea, neutropenia, headache, and elevation of liver parenchymal enzymes occurred not infrequently in a dose-dependent manner. A higher dose of fostamatinib would lead to better efficacy but is limited by its toxicities. Another phase II trial of a selective SYKi, GS-9876, in RA did not report efficacy, although the drug was well tolerated [109]. As a result, the drug is not further developed for RA.

Hyperexpression of SYK in lupus T cells influences the expression of a number of cytokines, enzymes, and receptors that are involved in the pathogenesis in SLE [110, 111]. Increased frequency of a SYK bright CD27- memory-like B-cell population, which might be a source of increased plasma cells, was demonstrated in patients with SLE compared with healthy controls [112]. Lanraplenib was tested in 19 patients with moderate-to-severe cutaneous lupus in a phase II proof-of-concept RCT [113]. Although the drug was well tolerated, the primary efficacy endpoint of the change in CLASI score was not met. Another phase II study of filgotinib and lanraplenib in nine patients with lupus membranous nephropathy reported some efficacy of the former. However, because of the limited number of participants receiving lanraplenib and the high drop-out rate, no conclusion could be drawn [114]. There are no other registered studies of the SYKis in SLE or LN.

## 5 Proteasome Inhibitors

The ubiquitin-proteasome system (UPS) is the key mechanism for selective degradation of the majority of intracellular proteins that is critical for the maintenance of cellular homeostasis and regulation of cellular functions such as survival and proliferation [21]. Alterations in the UPS are linked to oncogenesis [115]. The 26S constitutive proteasome is expressed ubiquitously in body tissues, including the heart, kidney, and liver, whereas the variant proteasome, known as the immunoproteasome, which has a high homology in the catalytic activity subunits to the constitutive proteasome, is expressed in immune cells, such as lymphocytes and monocytes [116]. Inhibition of both types of proteasomes leads to increased cellular apoptosis and reduced proliferation, whereas selective inhibition of the immunoproteasomes results in cytokine suppression and anti-inflammatory activities in ex-vivo models [117]. Bortezomib, carfilzomib, and ixazomib are non-selective proteasome inhibitors that simultaneously

suppress both the constitutive and immunoproteasomes. They are developed for their anti-tumor effects to treat multiple myeloma and mantle cell lymphoma.

Long-lived plasma cells are capable of producing protective antibodies but also play an essential role in autoreactive immunologic memory that leads to the generation of autoantibodies in SLE [118]. In contrast to short-lived plasmablasts, long-lived plasma cells are resistant to conventional immunosuppressive and B-cell depletion therapies. Persistence of these cells is associated with refractory disease activity or flares in patients with SLE.

### 5.1 Proteasome Inhibitors in Murine Lupus

Bortezomib and delanzomib have been shown to deplete plasma cells, reduce anti-dsDNA titers, and alleviate renal disease in the NZB/W F1 and MRL/lpr mice [119–121]. Treatment of the lupus-prone mice with carfilzomib, bortezomib, or the immunoproteasome-specific inhibitors such as ONX0914 prevented disease progression and abrogated glomerulonephritis, along with a reduction in autoantibody levels and production of IFNα by TLR-activated pDCs in vitro and in vivo [122]. Administration of zetomipzomib (KZR-616), a selective immunoproteasome inhibitor, in lupus mice led to a durable improvement of renal disease, a reduction in anti-dsDNA antibodies, and renal IgG deposition without affecting normal T-cell-dependent responses [123].

### 5.2 Proteasome Inhibitors in Human SLE

Small open case series have shown the efficacy of bortezomib in refractory human SLE manifestations, including LN [124–128]. A significant depletion of both short- and long-lived plasma cells in peripheral blood and bone marrow, leading to a reduction in autoantibody and serum immunoglobulin levels, was observed after bortezomib administration [129]. In a series of 12 patients with refractory SLE, bortezomib treatment led to a sustained improvement in disease activity for 6 months [125]. Serum antibody levels significantly declined, with a greater effect on anti-dsDNA than vaccine-induced protective antibody titers. However, 11 (92%) patients experienced AEs and four (33%) experienced SAEs. The commonly reported AEs were infections (16%), nausea (16%), headache (16%), polyneuropathy (11%), fever (11%), and allergic skin reactions (11%). Although most AEs were mild/moderate in severity and resolved completely, bortezomib was discontinued in seven (58%) patients. Another series of 12 female patients with refractory LN also reported persistent hypogammaglobulinemia (16.6%) and sensory neuropathy (16.6%), which led to bortezomib withdrawal [127]. In a small RCT conducted in Japan, 14 patients with SLE with refractory disease were treated with either bortezomib or PBO [130] (Table 2). Efficacy was not demonstrated at week 24. Four (50%) patients treated with bortezomib withdrew from the protocol and three others (38%) did not complete the minimal protocol requirement because of SAEs. The action of bortezomib is short-lived and continuous B-cell inhibition may be needed to achieve sustained plasma cell depletion and renal efficacy [131]. In fact, sequential administration of bortezomib and belimumab has been used successfully in two patients with SLE with refractory renal disease and/or pulmonary hemorrhage [132].

The narrow therapeutic index of the current non-selective proteasome inhibitors limits their clinical use in SLE. Highly selective immunoproteasome inhibitors are developed to enhance tolerability. Zetomipzomib is the first-in-class irreversible, tripeptide epoxyketone-based, selective immunoproteasome inhibitor that specifically targets the inflammatory cells [133]. The drug was shown to reduce the production of proinflammatory cytokines from human PBMCs, block T-cell production of IFN-γ, tumor necrosis factor-α, and granulocyte-macrophage colony-stimulating factor, and the differentiation of B cells to plasmablasts [123]. Interim results from a phase Ib open-labeled study (NCT03393013) showed the efficacy of zetomipzomib in SLE and LN with an acceptable AE profile [134]. Further RCTs are expected.

## 6 Cereblon E3 Ligase Modulators

As previously mentioned, degradation of intracellular protein by the UPS is a major mechanism for cellular hemostasis and survival. The protein cereblon (CRBN) is a substrate receptor of the cullin-ring ligase-4 ($CRL4^{CRBN}$) E3 ubiquitin ligase complex that allows tagging of polyubiquitin chains to promote degradation of target proteins that are traditionally difficult to modulate by direct pharmacological means (e.g., transcription factors and oncoprotein) [135]. Cereblon E3 ligase modulators (CELMoDs) are synthetic agents that leverage the UPS to enhance the selective degradation of disease-promoting proteins. Drugs such as lenalidomide and pomalidomide were developed for treating myeloma before the actual mechanisms are known. In fact, they are CELMoDs that induce degradation of Ikaros and Aiolos, which are transcriptional factors with a zinc finger-based structure that regulate multiple genes involved in lymphocyte function and differentiation [22]. Highly potent CELMODs such as iberdomide (CC-220) and mezigdomide are now undergoing clinical trials in myeloma and autoimmune diseases [135, 136].

Ikaros and Aiolos are encoded by the IKZF1 and IKZF3 genes, respectively [137]. Polymorphisms in these two genes are associated with SLE susceptibility [138, 139]. Ikaros is widely expressed in hemopoietic precursor cells and plays a role in the development of B cells and pDCs, which are the

main source of type I IFN in patients with SLE. In contrast, Aiolos has a more restricted expression in pre-B/mature B cells and is required for the differentiation into long-lived plasma cells [137]. The CRBN, IKZF1, and IKZF3 genes were over-expressed in PBMCs of patients with SLE compared with healthy controls and in-vitro iberdomide administration resulted in a reduced production of anti-dsDNA and antiphospholipid antibodies from cultured PBMCs [140]. Moreover, peripheral blood $CD19^+$ B cells isolated from patients with SLE showed a significant reduction in TLR7 and IFNα-mediated production of immunoglobulins, reduced differentiation into plasmablasts and antibody production, as well as IKZF1 and IKZF3 gene expression (naive B cells and plasmablasts) upon iberdomide administration in vitro [141].

### 6.1 Cereblon Modulators in Murine Models

In female NZB/WF1 mice, treatment with thalidomide (10 mg/kg) showed a significant reduction in proteinuria, immune complex accumulation, and glomerular and tubular damage, which was coupled with a decrease in serum anti-dsDNA, IgG2a/2b, and nuclear translocation of NF-κB in kidney tissues [142]. In vitro treatment with thalidomide has also been shown to reduce proliferation and co-stimulatory molecule expression of splenic $CD4^+$ T cells isolated from C57BL/6 mice [143].

### 6.2 Cereblon Modulators in Human SLE

Thalidomide and lenalidomide are effective treatments for refractory cutaneous lupus [144]. However, most studies were small, retrospective, and lacked a control group. Peripheral polyneuropathy was reported in 15–80% of thalidomide-treated patients without a clear relationship with the duration of use, although reversibility was observed in 70% of cases upon drug withdrawal. Lenalidomide appeared to be less neurotoxic, but relapses occurred in 25–75% cases upon drug cessation. Teratogenicity, cardiovascular toxic effects, and thromboembolism, especially in older and high-risk patients [145], limit their use in SLE.

Iberdomide is a high-affinity CELMoD that targets the hemopoietic transcription factors Ikaros and Aiolos for proteasomal degradation [146]. In a 12-week, proof-of-concept, phase IIa, PBO-controlled dose-escalating RCT, 42 patients (33 patients completed the protocol) with active SLE were assigned to receive four doses of iberdomide or PBO [146]. The most common TEAEs were nausea, diarrhea, and upper respiratory tract infections that were not severe. There was a dose-dependent reduction in peripheral blood total B cells and pDCs, coupled with an improvement of the Physician Global Assessment and the CLASI scores.

A subsequent phase II RCT of 288 patients with seropositive SLE with moderate-to-severe disease activity (SLEDAI score $\geq 6$ and clinical SLEDAI $\geq 4$) was performed. Subjects with severe neuropsychiatric renal disease or the antiphospholipid syndrome were excluded. Patients were randomly assigned to three doses of iberdomide (0.15 mg, 0.30 mg, 0.45 mg/day) or PBO [147] (Table 2). The primary endpoint was the SRI-4 response at week 24, which was achieved at a significantly higher rate in the iberdomide 0.45-mg group than PBO (54% vs 35%; $p = 0.01$). The SRI-4 rates were higher in those with a SLEDAI score $\geq 10$, high IKZF3 (Aiolos) expression, and a high IFN signature at baseline [147, 148]. Iberdomide treatment resulted in a SRI-4 response in all patients (100%) with an extremely high IFN signature and reduced anti-dsDNA in those with elevated levels at baseline. In patients with a CLASI score $\geq 10$, numerically more patients had a CLASI-50 improvement in the iberdomide 0.45-mg group than the PBO group. Changes in joint counts and other secondary outcomes were not significantly different between the treatment and PBO groups. Moreover, neutropenia, upper respiratory tract, and urinary tract infection were more common in iberdomide-treated patients. Regarding laboratory parameters, iberdomide treatment reduced peripheral B cells (including those expressing the BLyS receptor gene and in switched memory B cells) and pDCs, but increased Tregs and IL-2 at week 24 in a dose-dependent manner [148]. This suggests that iberdomide is capable of reversing the immunological abnormalities in SLE. Further clinical trials of iberdomide in SLE are warranted.

## 7 Sphingosine 1-Phosphate Receptor (S1PR) Modulators

Sphingosine 1-phosphate (S1P) is a bioactive lipid molecule that binds to G protein-coupled S1P receptors (S1PRs) and affects cell proliferation, survival, and migration. Among the S1PR isoforms, S1PR1, expressed on leukocytes and endothelial cells, is an important mediator of lymphocyte trafficking, Treg/Th17 cell homeostasis, and vascular permeability [149]. Four S1PR1 modulators have been approved for the treatment of multiple sclerosis and ulcerative colitis [23]. Fingolimod binds to multiple S1PRs, halts lymphocyte egress from secondary lymphoid tissues, and reduces inflammation in the central nervous system. Newer generation compounds such as ozanimod, siponimod, and ponesimod have greater specificity for S1PR1, which may contribute to fewer AEs.

The S1PR1 modulators could ameliorate disease activity of SLE by reducing the trafficking of autoreactive lymphocytes and differentiation of the Th17 cells, enhancing the number and function of the Tregs, and decreasing

autoantibody production [150]. In addition, these modulators increase the endothelial cell barrier function and blood–brain barrier function, and reduce expression of the adhesion molecules for leukocyte transmigration and type I IFN production by pDCs in response to viral or oligonucleotide stimulation [24]. These mechanisms are potentially beneficial for renal, neuropsychiatric disease and atherosclerotic injury in SLE.

### 7.1 S1PR1 Modulators in Murine Lupus

Modulators of the S1PR1, such as ozanimod, fingolimod, amiselimod, cenerimod, and KRP-203, have been shown to attenuate renal disease and improve survival in multiple murine lupus models [151–156]. Fingolimod reduced the number of T cells and B cells in the thymus, indicating increased lymphocyte apoptosis is a major mechanism of the drug [154, 157]. Fingolimod has also been shown to improve certain neuropsychiatric features of the MRL/lpr mice, such as depression-like behavior, memory deficits, and leukocyte infiltration of the choroid plexus [158, 159]. The protective effects of fingolimod on the central nervous system are likely contributed to by the direct action on the microvascular endothelial cells and strengthening of the blood–brain barrier. Cenerimod or amiselimod was shown to reduce peripheral blood $CD19^+$ B cells, $CD4^+$ and $CD8^+$ T cells, plasma cells, anti-dsDNA antibodies splenomegaly, lymphadenopathy, plasma and tissue levels of IFNα, as well as tumor necrosis factor, IL-6, BAFF, and IL-10 in the lupus mice [151, 155]. Other S1PR1 modulators have also been shown to induce peripheral lymphopenia and reduce lymphocyte infiltration and IgG/C3 deposition to the kidneys of these mice [152, 153, 155, 156].

### 7.2 S1PR1 Modulators in Human SLE

An open-label phase Ib safety trial of amiselimod was conducted in 17 patients with SLE with mild/moderate activity [160]. Lymphopenia was observed in all patients after treatment but none developed serious infections, cardiotoxicity, or SAEs. A reduction in anti-dsDNA antibodies occurred in the majority of patients who had elevated levels before treatment (Table 2).

A proof-of-concept PBO-controlled RCT of oral cenerimod was conducted in 49 patients with seropositive SLE with active mucocutaneous or musculoskeletal disease [161]. Cenerimod treatment led to a significant dose-dependent reduction in the total lymphocyte count. At week 12, further improvement in the modified SLEDAI-2K score and anti-dsDNA titer was observed in the treatment than the PBO group (Table 2). No increase in TEAEs was reported with cenerimod but a small but non-clinically relevant drop in the heart rate was observed in the first 6 h of drug administration. A phase II RCT has just completed (NCT03742037) and a phase III RCT (OPUS-1) has started recruitment (NCT05648500).

## 8 Tailor-Made Therapy for SLE: Are We There Yet?

Systemic lupus erythematosus is a clinically and serologically heterogeneous disease. There are considerable inter-ethnic differences in the tolerability of medications and the treatment responses to unified protocols in research settings [162–164]. In two pivotal RCTs of anifrolumab (a monoclonal antibody against type I IFN receptor) in non-renal SLE [165, 166], greater treatment responses relative to PBO were achieved in patients with high IFN signatures at baseline [167]. A phase Ib/IIa RCT of tofacitinib in SLE also revealed a stronger reduction in IFN signatures in patients with the STAT4 risk allele [55]. Finally, patients with higher IFN and IKZF3 expression were found to have a better clinical response to iberdomide [147, 148]. Collectively, these observations suggest the possibility of genetic profiling to determine the choice of targeted therapies in patients with SLE to achieve the best therapeutic effects. Urine proteomics and molecular profiling of renal tissues by transcriptomic analyses may help reflect intrarenal activity that correlates with treatment refractoriness to guide therapeutic approaches [168–170]. However, until these genomic and proteomic biomarkers are adequately validated in different ethnic groups, the choice of treatment modalities in SLE still depends on clinical judgment based on ethnicity, anticipated treatment adherence and tolerability, organ function, and the presence of medical comorbidities. It is hoped that patient stratification by comprehensive molecular techniques is possible in the future to help patients choose the most appropriate and cost-effective individualized therapies.

## 9 Conclusions

The development of novel therapeutics in SLE is fraught with difficulty and disappointment. Many novel agents have halted progression for the negative results from pivotal RCTs. With the improvement in patient stratification, adjustment of background immunosuppression, and assessment of study endpoints, we are now having more approved drugs in SLE [171]. A number of targeted small molecules are undergoing clinical trials in patients with SLE. Tyk2 inhibition appears to be most promising [70] and phase II/III results are eagerly awaited. However, the recent concern of thromboembolism and cancer risk in post-marketing studies of RA, particularly in older patients with a cardiovascular risk [172], has led to caution of the

use of JAK inhibitors in patients with SLE, who are also prone to thrombosis and malignancies. Two BTKis did not show benefits in SLE [92, 95] but a third showed promising results [96]. Although the SYKis showed efficacy in RA [107, 108], toxicities limited their further development in RA and SLE. The narrow therapeutic index of the conventional non-selective proteasome inhibitors such as bortezomib has limited their clinical use. However, the selective immunoproteasome inhibitor, zetomipzomib, has an improved safety profile [134] and is undergoing further trials in SLE. The cereblon modulator, iberdomide, presented encouraging results in SLE from a recent phase II RCT [147]. Finally, a selective modulator of the S1PR1 receptor, such as cenerimod, has started phase II/III studies in SLE. A new era of SLE therapies is expected in the next couple of years when the results of these trials are ready, and the treat-to-target approach in SLE is increasing feasible.

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