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Review Article

New and emerging therapies for systemic lupus erythematosus

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ABSTRACT

Systemic Lupus Erythematosus (SLE) and lupus nephritis treatment is still based on non-specific immune suppression despite the first biological therapy for the disease having been approved more than a decade ago. Intense basic and translational research has uncovered a multitude of pathways that are actively being evaluated as treatment targets in SLE and lupus nephritis, with two new medications receiving FDA approval in the last 3 years. Herein we provide an overview of targeted therapies for SLE including medications targeting the B lymphocyte compartment, intracellular signaling, co-stimulation, and finally the interferons and other cytokines.

1. Introduction

Systemic lupus erythematosus (SLE) currently is mainly treated with non-specific immunosuppression, which is sometimes associated with severe toxicity. Recent scientific advancements in the development of biologics and small molecules have led to the design of novel agents that target pathways involved in SLE pathogenesis. Three such agents have already received FDA approval, while numerous ongoing clinical trials are investigating the efficacy of other promising therapeutic options that have the potential to revolutionize SLE treatment.

The evaluation of the efficacy of these agents in clinical trials involves the use of a range of outcome measures [1]. Commonly used measures to assess disease activity include the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), the British Isles Lupus Assessment Group (BILAG) index, the Physician's Global Assessment (PGA), and average prednisone-equivalent daily corticosteroid dose. The SLEDAI and BILAG are the basis for composite outcome measures used in clinical trials. These include the SLE response index (SRI), the British Isles Lupus Assessment Group–based Composite Lupus Assessment (BICLA), and the Lupus Low Disease Activity State (LLDAS) [1]. The SRI response is defined as a minimum 4-point improvement in SLEDAI without new BILAG A, more than one new BILAG B domain, or a worsening of PGA by 0.3 or more [2]. The SRI score can be customized depending on the required SLEDAI score decrease, such as SRI-5 or SRI-6, which correspond to 5 or 6 points decrease in SLEDAI score, respectively. On the other hand, the BICLA response is defined as an improvement in the active domain of BILAG, without worsening in any other BILAG domain and an increase in SLEDAI-2 K or increase $\geq$0.3 in the PGA [3]. Since SRI response requires complete improvement in some manifestations but not necessarily in all organs, while BICLA response requires only partial improvement but across all organs, the choice of the primary endpoints can impact the study results [1]. The exact definition of the composite measure LLDAS, varies among studies, but it generally involves achieving a SLEDAI-2 K $\leq$ 4, no activity in certain organ systems, absence of new features of active disease, PGA $\leq$1 and a prednisone dose $\leq$7.5 mg/day [4].

In addition to these overall outcome composite measures, there are also organ-specific outcomes: These include the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) which is used to assess skin disease [5] and joint counts for lupus arthritis [6]. Since lupus nephritis (LN) is a common and morbid complication of SLE, kidney-specific outcome measures are also used in clinical trials [7,8]. The complete renal response (CRR) and the primary efficacy renal response (PERR) at 12 or 24 months are the outcome measures commonly utilized as outcome measures for LN, as they are considered the best predictors of long-term outcomes. The specific definition of these outcomes varies across trials but generally includes factors such as the proteinuria level, improvement from baseline of the glomerular filtration rate (GFR), and no use of rescue treatment [9,10].

The development of treatment modalities with better efficacy-toxicity profiles, as well as the incorporation of these new medications in the treatment algorithm remain unmet needs for SLE and especially LN [9]. A recent multinational study demonstrated that SLE disease control remains suboptimal in a significant number of patients, leading to negative consequences such as organ damage, glucocorticoid exposure, poor quality of life, and mortality [11].

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In this review, we will explore some of the promising treatment options that are currently being evaluated in SLE (Table 1 and Fig. 1).

2. B Cell Inhibition

A hallmark of SLE is the excessive production of autoantibodies, particularly against nuclear self-antigens, which deposit in tissues and trigger complement activation, and target-organ damage. B-cells and especially plasma cells, have a primary role in the production of these autoantibodies, thereby rendering them an important target for the development of new therapeutic interventions for SLE [12,13].

2.1. B Lymphocyte Stimulator (BLyS)/A Proliferation-Inducing Ligand (APRIL)

BLyS is a protein that promotes the survival and differentiation of B cells and is important in the pathogenesis of SLE. Belimumab, a recombinant humanized monoclonal antibody targeting soluble BLyS, received FDA approval for treatment in SLE in 2011, marking a milestone after decades of scarcity in therapeutic developments for the disease. More recently it was also approved for use in LN [14]. Belimumab is effective when added to the standard of care, in patients with low complement (C3 or C4) levels and/or positive anti-double-stranded (ds) DNA. It has demonstrated sustained reduction in disease activity for up to 10 years, reducing flares and exhibiting a steroid-sparing effect [15]. Concerns about psychiatric side effects were reported but overall it has a favorable safety profile [16]. Belimumab was studied specifically in patients of Black African ancestry and although it was numerically superior to placebo in terms of SRI-4, its effect did not reach statistical significance [17].

In a phase III trial (BLISS-LN), Belimumab added to standard care for active LN showed significant improvement in PERR and CRR, leading to FDA approval for LN [7]. An open-label extension of BLISS-LN demonstrated maintained efficacy and an acceptable safety profile [18]. However, a post-hoc analysis revealed that while Belimumab was effective in improving renal function in patients with proliferative LN, it is not as effective in patients with membranous disease or with a baseline protein/creatinine ratio of $\geq$3 g/g [19].

Belimumab was also studied in combination with Rituximab (see below 2.2), an antibody that depletes B cells by targeting the surface molecule CD20, primarily in LN. The rationale for combining these two anti-B cell therapies is based on the observation that after B cell depletion with Rituximab and subsequent repopulation, serum BLyS levels -the target of Belimumab- were significantly higher during relapse than during disease remission or pre-Rituximab flares. The hypothesis was that BLyS may play a central role in driving disease flares after B cell repopulation post-Rituximab treatment [20]. Although combination treatment led to significant reductions in anti-dsDNA antibody levels, improvements in certain metrics of disease activity were observed in some studies [21,22] but not in others [23].

A phase III trial (NCT03747159; SynBioSe-2), of adding to the standard of care, Belimumab followed by Rituximab in patients with LN is currently ongoing.

In general, Belimumab has an established role in adult SLE disease and a promising one in LN, with ongoing evaluation in several clinical trials to explore its full potential. A systematic review evaluating the real-world effectiveness of Belimumab has demonstrated that the use of Belimumab is associated with decreases in flare frequency as well as a persistent long-term reduction in SLEDAI score and prednisone-equivalent use [24]. A real-world observational study from China including patients with LN ($n = 61$) demonstrated that the use of Belimumab may also slow down GFR decline [25].

Current and future research includes phase IV trials evaluating Belimumab's effects on T cells (NCT04447053), low-disease activity SLE (NCT04515719), and predictive models for refractory manifestations (NCT04893161), a phase III trial to assess Belimumab in combination

Table 1
Approved and promising targeted therapies in Systemic Lupus Erythematosus and Lupus Nephritis.

Molecular target	Treatment	Status
B cells		
BLyS/APRIL/ BAFF-R	Belimumab (anti-BLyS antibody)	Approved for SLE and LN Ongoing trials: Phase IV (low disease activity SLE) Phase IV (SLE) evaluating the effects on T cells Phase IV (SLE) to determine a predictive model of response in SLE with refractory manifestations Phase IV (early SLE) Phase III (SLE) combination with IL-2 Phase III (LN) combination with Rituximab
	Telitacicept (anti-BLyS/ APRIL antibody)	FDA fast track designation Conditional marketing approval in China Phase IIb and Phase III trials (SLE) completed in China with positive results Ongoing trials: Phase II (LN) Phase III (SLE) Phase III (SLE) combination trial with IL-2
	Ianalumab (anti- BAFF-R antibody)	Phase II trial (SLE) showed positive results Ongoing trials: Phase III (SLE): SIRIUS-SLE-1, and − 2 Phase III (LN): SIRIUS-LN
CD 20	Rituximab (chimeric anti-CD20 antibody)	Two Phase III trials, EXPLORER (SLE) and LUNAR(LN), did not meet primary endpoint Included in clinical guidelines for refractory disease
	Obinutuzumab (type II anti-CD20 antibody)	Phase II trial (LN) showed numerical superiority over placebo (NOBILITY) Ongoing trials: Phase III (SLE): ALLEGORY Phase III (LN): REGENCY, OBILUP
CD19/BCMA	CAR-T cells (anti-C19, anti-BCMA and anti-CD19/BCMA)	In a proof-of-concept open label studies, CAR-T treated patients achieved sustained drug free remission (refractory SLE and LN) Ongoing Trials: Numerous Phase I/II (refractory SLE and LN)
Immuno-Proteasome	Zetomipzomib (KZR-616)	Positive results in uncontrolled early study in SLE and LN (MISSION) Ongoing trials: Phase IIb (LN): PALIZADE
Intracellular signaling		
BTK	Orelabrutinib (BTK inhibitor)	Phase I/II in SLE showed preliminary efficacy Ongoing trials: Phase II (SLE)
Calcineurin	Tacrolimus (calcineurin inhibitor)	Phase III and IV trials in LN with positive results Ongoing trials: Phase IV (LN): Induction (open label vs. Mycophenolate), Maintenance (efficacy in steroid tapering)
	Voclosporin (calcineurin inhibitor)	Approved for LN Ongoing trials: Phase II (SLE): DIVERT Phase III (LN in adolescents)
mTOR	Rapamycin (mTORC1 direct inhibitor)	Phase II/III with positive results in SLE

(*continued on next page*)

Table 1 (*continued*)

Molecular target	Treatment	Status
		Ongoing trials: Phase II (SLE) Phase II/III (proteinuric LN)
	N-acetylcysteine (anti-oxidant, mTOR inhibitor)	Phase I/II with positive results in SLE Ongoing trials: Phase II (SLE): SNAC
JAK/STAT	Deucravacitinib (TYK2 inhibitor)	Phase II trial in SLE with positive results Ongoing trials: Phase II (cutaneous lupus) Phase III (SLE): POETYK SLE-1 and 2
	Upadacitinib (JAK-1 (less so JAK-3) inhibitor)	Phase II trial in SLE with positive results (Upadacitinob monotherapy or in combination with the BTK inhibitor Elsubrutinib) Ongoing trials: Phase III (SLE): SELECT-SLE
Co-stimulation		
CD154(40 L)/ CD40	Dapirolizumab Pegol (pegylated anti-CD40L antibody)	Phase II trial with numerical Improvement in disease activity measures over placebo but the primary efficacy endpoint was not met Ongoing trials: Phase III (SLE)
CD6/ALCAM	Itolizumab (anti-CD6 antibody)	Phase Ib study with positive results (EQUALISE) in SLE
Cytokines		
Interleukin-2	low dose IL-2	One Phase II study showed efficacy despite not achieving primary endpoint Ongoing trials: Phase II (SLE) Phase III (SLE) combination with Telitacicept Phase III (SLE) combination with Belimumab Phase III (LN) comparison to human umbilical cord mesenchymal stem cells
Type I IFN	Anifrolumab (anti-IFN receptor subunit 1 antibody)	Approved for SLE Phase II trial in LN, the primary endpoint was not met but showed benefit in secondary outcomes Ongoing trials: Phase III (LN): IRIS Phase III (SLE) evaluation in Asian population Phase III (SLE) evaluating a subcutaneous formulation: TULIP-SC Phase I (SLE-vasculopathy)
pDC	Litifilimab (anti-BDCA2 antibody)	Phase I and Phase II trial showed promising results for skin and/or joint involvement Ongoing trials: Phase III (SLE): TOPAZ-1, −2, EMERALD Phase II/III trial (refractory cutaneous SLE): AMETHYST
Other		
Small molecule	Cenerimod (S1P1 modulator)	Phase I/II trial showed encouraging but not definite results Ongoing trials: Phase III (SLE): OPUS-1 and OPUS-2
Mesenchymal stem cells	Mesenchymal stem cells	Phase I/II open label studies in SLE showed efficacy that lasted several months Phase II double-blind study in LN was negative Ongoing trials: Phase I/II (SLE and LN) Phase III (SLE): combination with IL-2

with IL-2 in SLE, (NCT05262686) and cohort studies aiming to determine its preventive potential for LN development (NCT05585671) and identify histopathological biomarkers predicting response to LN therapies, at the time of diagnosis (NCT05358652).

Besides Belimumab, Tabalumab, a human monoclonal anti-BLyS antibody that neutralizes both soluble and membrane-bound BLyS, has been evaluated in SLE. Two large 52-week phase III clinical trials, ILLUMINATE-1 [26] and ILLUMINATE-2 [27] evaluated the efficacy of Tabalumab in patients with moderately active SLE. In both trials, Tabalumab led to positive serological changes including anti-dsDNA antibodies, complement and immunoglobulin levels, as well as total B cell count. However, its efficacy was marginal as the primary endpoint of SRI-5 response was only met in one of the trials (38.4% in the Tabalumab group vs. 27.7% in the placebo group, $p = 0.002$) and no significant difference was observed in the other trial. In these trials, tabalumab was found to be a safe treatment modality, although there were some concerns about depression and suicidality [26,27]. These disappointing results led to discontinuation of its development.

A different approach to block BLyS is Blisibimod, a peptibody consisting of a tetrameric BLyS-binding domain fused to a human IgG1 Fc region, that neutralizes both membrane-bound and soluble forms of BLyS. Encouraging results were demonstrated in a phase IIb trial (PEARL-SC) [28], but subsequent trials did not support the initial enthusiasm. In the phase III CHABLIS-SC1 trial [29] including 442 patients with active SLE (≥10 SELENA-SLEDAI), Blisibimod demonstrated significant improvement in several parameters such as steroid-sparing effect, complement levels, SLE autoantibodies levels, B cell count, and proteinuria. However, the primary endpoint of SRI-6 was not met as the placebo group exhibited a very high response rate (42.3%) compared to previous studies (vs Blisibimod 46.9%). The high response rate in the placebo group may be attributed to the confounding effect of high background steroid use in these patients. The safety profile of Blisibimod was acceptable with diarrhea and urinary and upper respiratory tract infections being the most frequent adverse events observed [29]. The subsequent phase III trials were withdrawn (CHABLIS-SC2, NCT02074020) or terminated (CHABLIS7.5, NCT02514967). Currently, no ongoing trials are investigating Blisibimod in SLE.

Early on in the development of anti-BLyS therapies, it was realized that a molecule related to BLyS, APRIL (A PRoliferation-Inducing Ligand) may play an equally important role in the development, survival and differentiation of autoreactive B cells. Targeting, therefore, both BLyS and APRIL in SLE was pursued using Atacicept: Atacicept is a human recombinant fusion protein that consists of the extracellular portion of the transmembrane activator and cyclophilin ligand interactor (TACI) receptor (which binds to both BLyS and APRIL), and a slightly altered Fc part of human IgG1. The neutralization of both BLyS and APRIL by Atacicept leads to the inhibition of B cell survival and differentiation by neutralizing BLyS, APRIL the BLyS-APRIL heterodimers [30,31]. Its development though has been challenging.

A phase II trial APRIL-LN, evaluating Atacicept safety in LN was halted due to severe chest infections in 3 patients receiving the agent. However, there were indications that background treatment may have contributed to this outcome, as prior trials did not indicate a particular increase in serious infection rates [32]. Two subsequent phase II trials,

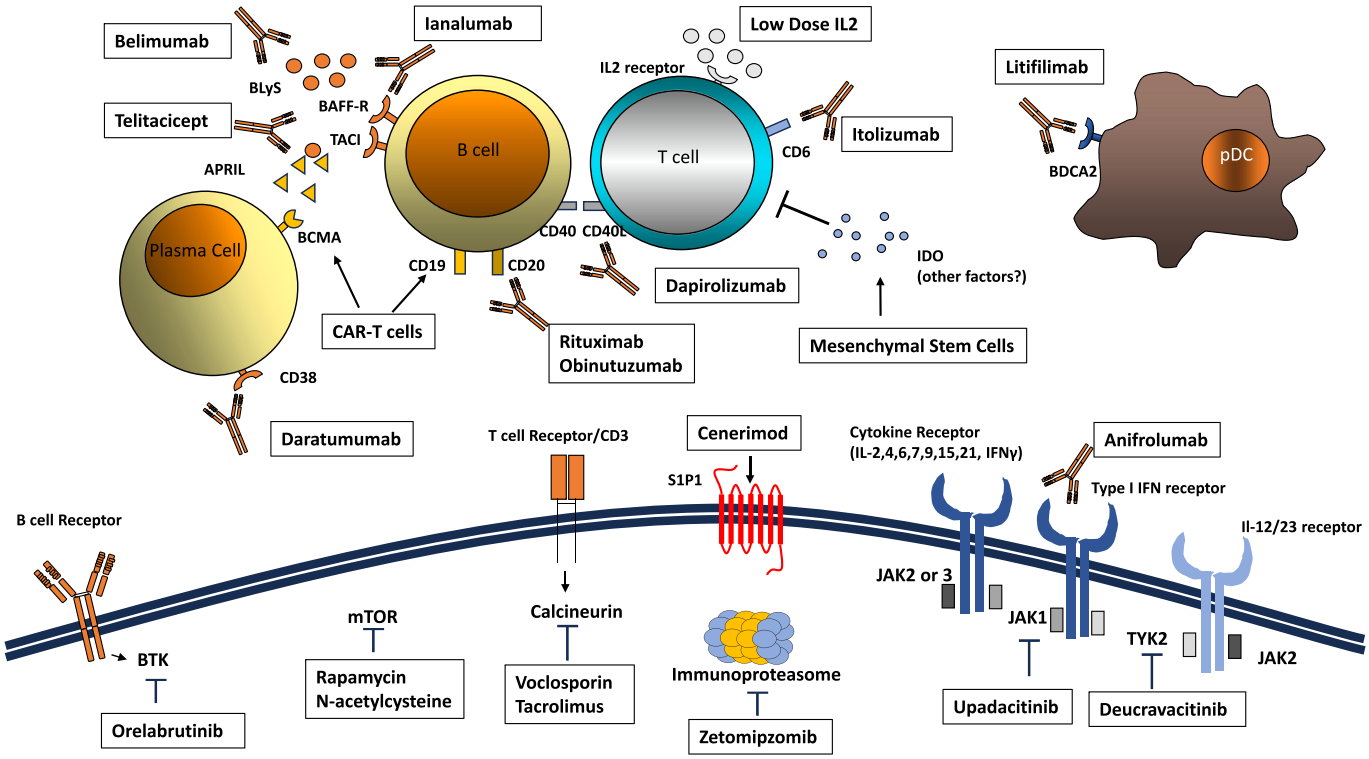

Fig. 1. Immunologic targets and promising therapies in SLE. Relevant signaling pathways (in black) and medications that target them (in boxes) are depicted. BLyS: B Lymphocyte Stimulator; APRIL: A Proliferation-Inducing Ligand; BAFF-R: B Cell Activating Factor Receptor; TACI: Transmembrane Activator and Cyclophilin ligand Interactor; CAR: Chimeric Antigen Receptor; BCMA: B Cell Maturation Antigen; IDO: Indoleamine 2,3-Dioxygenase; BDCA2: Blood pDC Antigen 2; pDC: plasmacytoid Dendritic Cells; BTK: Bruton Tyrosine Kinase; mTOR: mammalian Target Of Rapamycin; S1P1:Shongosine-1 Phosphate receptor subunit 1; JAK: Janus Kinase; TYK2: Tyrosine Kinase 2.

APRIL-SLE and ADDRESS II, demonstrated the efficacy of Atacicept in reducing disease activity in SLE [33,34]. In the APRIL-SLE trial, a Phase II/III study, two fatal infections in the 150 mg arm led to the termination of that arm [35]. Even though Atacicept use was associated with a significant decrease in total Ig levels vs placebo (median reduction, IgG: 38% vs 3%, IgA 58% vs 2%, IgM: 69% vs 1%), the deaths were not attributed to low immunoglobulin levels. From an efficacy standpoint, the Atacicept 150 mg arm was the only one to meet the primary and secondary endpoints: there was a reduction in BILAG A or B flare rates (OR:0.48, $p = 0.002$), time to first flare (HR: 0.56, $p = 0.009$), improvement in anti-dsDNA antibody levels (decrease:38% vs 14%), and C3 and C4 levels ($p < 0.001$, median change: 15.4% vs 4.1% and 49.5% vs −0.4%, respectively) [34]. A post-hoc analysis of this trial identified that elevated BLyS and APRIL levels were associated with the response to Atacicept, potentially serving as response predictors [35].

The phase IIb ADDRESS II trial evaluated Atacicept while implementing a risk mitigation strategy to monitor immunoglobulins and infections. While this study did not meet its primary end point of SRI-4 response at 24 weeks, Atacicept use resulted in a significant decrease in the risk of severe flares. Moreover, a separate evaluation of the high disease activity (SLEDAI-2 K $\geq$ 10) or serologically active (anti-dsDNA$\geq$15 IU/m and C3 < 0.9 g/L and/or C4 < 0.1 g/L) populations showed significant improvements in SRI-4 and SRI-6 response rates with both 75 mg and 150 mg doses of Atacicept [33]. A post hoc analysis showed that patients with high activity on Atacicept 150 mg were more likely to reach LLDAS, or remission (clinical SLEDAI-2 K of 0, prednisolone $\leq$5 mg per day and PGA $\leq$0.5) than placebo [36]. In a long-term extension study of the ADDRESS II trial, the safety profile of Atacicept was acceptable and the efficacy was sustained for up to 144 weeks in the remaining patients [37].

At present, there are no ongoing studies investigating Atacicept in non-renal SLE, despite the efficacy shown in a subset of patients. Even though the APRIL-SLE trial excluded patients with moderate-to-severe glomerulonephritis, it did include patients with 'low grade' nephritis and showed that Atacicept-treated patients demonstrated better renal function measures compared to those who received placebo, suggesting the potential therapeutic efficacy in LN [34,38]. Despite these encouraging results, the COMPASS LN trial, a phase III study (NCT05609812) to evaluate the effectiveness of weekly 150 mg Atacicept in LN, was suspended while the APRIL-LN trial was halted for safety issues.

Similar to Atacicept, Telitacicept is a recombinant TACI-Ig fusion protein that inhibits both BLyS and APRIL. The drug has been granted fast-track designation by the FDA in 2020 and conditional marketing approval in China in 2021 for the treatment of active seropositive SLE based on the results of a phase II trial. In this randomized phase IIb trial [39], conducted in China, which included 249 patients with seropositive moderate-to-severe SLE (SELENA-SLEDAI score $\geq$ 8), Telitacicept demonstrated significant improvement in SRI-4 rates at 48 weeks compared to placebo, at all the doses tested (Telatacicept 80 mg: 71.0%, $p < 0.0001$; 160 mg: 68.3%, $p = 0.0001$; 240 mg: 75.8%, $p < 0.0001$, placebo 33.9%). The most common adverse events reported were respiratory tract infections and injection site reactions, but there was no difference in the frequency of adverse events between groups ($p > 0.05$).

A phase III placebo-controlled trial (NCT04082416) conducted in China ($n = 335$) also demonstrated significant improvement in SRI-4 response with 160 mg SC Telitacicept as an addition to standard therapy (82.6% vs. 38.1%, $p < 0.001$), with the difference achieving significance as early as week 4 and lasting until week 52 ($p < 0.01$ for all the time points). The drug was well-tolerated, and serious adverse events were observed more commonly in the placebo group (14.3% vs 7.2%) [40]. In addition to these trials, a cohort of 20 patients with SLE in China, showed a significant increase in SRI-4 response rate (80% patients) and a significant reduction of proteinuria with Telitacicept use for 4–45 weeks. The drug also enabled a significant decrease in steroid

usage, and discontinuation of immunosuppressive agents in 28% of the patients, while adverse events were manageable [41]. Case reports also described the successful use of Telitacicept in achieving disease activity reduction and significant improvement of renal involvement, or treating refractory cutaneous manifestations, indicating its potential use in LN and challenging SLE cutaneous manifestations [42,43].

Telitacicept is currently undergoing investigation in several clinical trials to further assess its safety and efficacy in treating SLE. These trials are primarily conducted in China and include a phase I trial with five different dosing schedules (NCT05247203), a phase II trial in LN (NCT05680480), and a phase III trial comparing Telitacicept to IL-2, while also evaluating their combination (NCT05339217). In addition, phase IV studies are underway to investigate the efficacy of Telitacicept in early SLE (NCT05899907) or to explore predictive biomarkers of efficacy and the mechanism of differences in its efficacy using proteomic and metabolomic analysis (NCT05666336), while a prospective cohort (NCT05588830) is examining the combination of belimumab and Telitacicept in LN. A phase III (NCT05306574) is currently underway in the United States to evaluate Telitacicept in moderately to severely active SLE. Overall, while Telitacicept shows promise as a future therapy for SLE, further studies are needed to confirm its potential.

The search for effective treatments targeting BLyS/APRIL is ongoing. New agents, such as Povetacicept (ALPN-303), a TACI-Fc variant that binds with high affinity to both APRIL and BLyS, have been developed to overcome the limitations of current B-cell inhibitors. ALPN-303 has shown superior efficacy in preclinical studies compared to anti-BLyS antibodies and wild-type TACI-Fc [44,45]. In a phase I study in healthy volunteers, it demonstrated an acceptable safety and tolerability profile, as well as dose-dependent pharmacokinetics and expected pharmacodynamic effects on circulating immunoglobulin and B-cell populations, suggesting its potential in treating B-cell and/or autoantibody-related diseases such as SLE [46]. An ongoing phase I trial (NCT05732402), RUBY-3, is evaluating its potential use in autoimmune kidney disorders, including LN. Ianalumab (VAY736), a B-cell depleting monoclonal antibody that targets BAFF-R (B Cell Activating Factor Receptor), showed in a phase 2b study significant improvement in a composite measure of SRI-4 response and sustained corticosteroid reduction (15/34 patients in the actively treated group vs. 3/33 patients in the placebo-treated patients) [47]. Ianalumab will be further evaluated in multiple studies in SLE and LN: one phase II trial (NCT03656562), that also evaluates Iscalimab (an anti-CD40 antibody), and three phase III trials, SIRIUS-SLE-1 and -2 (NCT05639114, NCT05624749, respectively) and SIRIUS-LN (NCT05126277).

In general, therapies directed towards BLyS or APRIL have shown a favorable safety profile in patients with moderately active SLE. However, their efficacy appears to be somewhat limited, as trials evaluating these therapies resulted in statistically significant differences from the control group but showed a modest effect size. The latest compounds in this category, such as Telitacicept and Povetacicept, which inhibit both BLyS and APRIL, and Ianalumab which inhibits BLyS receptor, hold a promise for better efficacy without sacrificing safety.

2.2. CD20

Therapy targeting CD-20, in contrast with BLyS blockade which alters B cell survival and differentiation to plasma cells, eliminates B cells through apoptosis, antibody-dependent cell-mediated cytotoxicity, or antibody-dependent phagocytosis, without affecting plasma cells. Rituximab, a chimeric anti-CD20 monoclonal antibody, has been used off-label to treat refractory SLE for the past two decades [48]. Concerns for suboptimal effectiveness as well as infusion-related hypersensitivity reactions informed the development of next generation anti-CD20 molecules such as Ocrelizumab, Ofatumumab, and Obinutuzumab.

The two pivotal 52-week phase III trials evaluating Rituximab in SLE (EXPLORER [49]) and LN (LUNAR [50]) did not meet their primary endpoints, defined by BILAG and renal response rate, respectively, over 52 weeks. However, in the EXPLORER trial Rituximab did show a significant benefit in African American and Hispanic patients with non-renal SLE [49]. Moreover, in the LUNAR trial, there was significantly greater improvement in proteinuria with Rituximab after 78 weeks vs. standard of care alone (complete or partial renal response: 73.6% vs 56.9%, $p = 0.04$). Standard of care only-treated patients were also significantly more likely to require rescue therapy, and higher steroid doses, suggesting a potential steroid-sparing effect of Rituximab [50]. Both Phase III trials showed significant improvements in serological markers of SLE disease activity and the safety and tolerability of Rituximab was acceptable [49,50]. This was further demonstrated in the RITUXILUP cohort, which included 50 patients with LN, treated with a steroid-avoiding protocol consisting of Rituximab and methylprednisolone induction followed by mycophenolate mofetil (MMF). Under this protocol, 90% of patients experienced partial or complete renal response after 37 weeks [51].

According to the current guidelines, Rituximab may be considered as a last resort in organ-threatening, refractory disease [52]. Currently, two phase IV trials are underway to evaluate the safety and efficacy of Rituximab in induction of remission in moderate to severe SLE (NCT04127747) or proliferative LN (GLUREDLUP, NCT05207358) and one to evaluate BLyS as biomarker of response (NCT05659407). The GLUREDLUP trial will compare RITUXILUP and MMF with the EURO-LUPUS regimen, which consists of cyclophosphamide and corticosteroids followed by azathioprine (AZA).

Ocrelizumab is a fully humanized anti-CD20 agent, which compared to Rituximab, elicits more antibody-dependent cell-mediated and less complement-dependent cytotoxicity in vitro. Two phase III trials, BEGIN (NCT00539838) and BELONG (NCT00626197), evaluated the efficacy and safety of Ocrelizumab in patients with SLE enrolling patients with SLE without moderate to severe glomerulonephritis, and with proliferative LN respectively. Both trials were terminated early, due to a lack of beneficial effect (BEGIN trial) or safety concerns related to an increased risk of severe infections in the Ocrelizumab-treated groups (BELONG trial); further development of Ocrelizumab was then halted [53].

Ofatumumab, another fully humanized anti-CD20 Ab, has been also evaluated as a treatment option for SLE. Compared to Rituximab, Ofatumumab exhibits increased complement-dependent and antibody-dependent cell-mediated cytotoxicity. Ofatumumab was initially used in patients who are unable to tolerate Rituximab, with positive results [54–56]. A single-center retrospective case series of 16 Rituximab -intolerant patients with SLE who received Ofatumumab, showed that Ofatumumab was a well-tolerated (14/16 of patients), safe, and effective alternative. B-cell depletion was achieved in the majority of patients (12/14) and was associated with improvement of serological markers of disease activity (ANA, anti-dsDNA, complement levels). In addition, half of the patients with LN (6/12) achieved remission of their LN within 6 months. During a median follow-up of 28 weeks, only 5/16 patients experienced serious infections, and no cases of death or malignancy were reported. Despite these positive observations, there is still a lack of high-quality randomized control trials evaluating the efficacy and safety of Ofatumumab in SLE [57].

Obinutuzumab is a type II humanized anti-CD20 monoclonal antibody that binds to the CD20 antigen in a different manner than type I anti-CD20 antibodies such as Rituximab and Ocrelizumab. It is associated with greater antibody-dependent cellular cytotoxicity and direct B-cell killing, resulting in less reliance on complement-dependent cytotoxicity. While previous trials examining type I anti-CD20 in LN did not show a difference in efficacy compared to placebo, they did indicate that the renal response was associated with the rapidity, degree, and duration of peripheral B-cell depletion. Given Obinutuzumab's enhanced B-cell cytotoxicity compared to these agents, the NOBILITY phase II trial was conducted to evaluate Obinutuzumab in LN [58].

In the NOBILITY study, 125 patients with proliferative LN received Obinutuzumab or placebo, in combination with standard therapies (MMF and corticosteroids). The study found that patients who received

Obinutuzumab had significantly improved renal responses compared to the control group, with no new safety concerns. There were numerical differences between the groups in complete response both at week 52 (primary endpoint, percentage difference, 12%, $p = 0.115$) while at week 104 the difference did reach statistical significance (percentage difference, 19% $p = 0.026$). Other measures evaluated such as renal response, eGFR, proteinuria, and serologies also showed greater improvement in the actively treated vs. placebo groups. The depletion of B cells observed with Obinutuzumab was more rapid and potent compared to Rituximab in a prior study. The treatment effect of Obinutuzumab seemed to be more pronounced among patients with high levels of proteinuria at baseline and those with class IV LN (with or without coexisting membranous component) [58].

After these relatively encouraging results of NOBILITY, three phase III trials are recruiting SLE patients to further evaluate Obinutuzumab. Two trials will evaluate the efficacy and safety of Obinutuzumab in patients with SLE (ALLEGORY, NCT04963296) and SLE with Class III or IV ± V LN (REGENCY- NCT04221477). The third study will evaluate specifically its efficacy in achieving renal remission of proliferative LN without the addition of oral steroids (OBILUP- NCT04702256). The studies are expected to be completed in 2026, 2028, and 2031, respectively.

Among the molecules developed to target CD20, are: A. MIL62 a glycoengineered type II anti-CD20 Ab with almost fully afucosylated N-glycans in the Fc region that showed better activity compared to Rituximab in vitro and Obinutuzumab in vivo [59]; B. SBI-087, a small modular immunopharmaceutical protein (SMIP) that binds to CD20 [60]; C. Mosunetuzumab an anti-CD20/CD3 bispecific antibody that has been approved for use in the treatment of follicular lymphoma [61]. In a phase I trial involving patients with SLE and Rheumatoid Arthritis (RA), SBI-087 was well-tolerated and demonstrated long-lasting depletion of B cells. While the study was published in 2016, [60] there have been no further studies on the use of SBI-087 in the treatment of SLE since then. Nonetheless, MIL62 and Mosunetuzumab are currently being evaluated in a phase II/III (NCT05796206) and a phase Ib study (NCT05155345) respectively.

Based on current guidelines and clinical practice, CD20-targeting agents can be considered as a last-resort treatment for refractory disease or organ-threatening complications. Of the available anti-CD20 agents, Obinituzumab holds some promise to become a viable option for patients with LN but its effect above and beyond standard of care seem limited.

2.3. CD22

CD22, is a cell surface molecule that plays a key role in regulating B cell activation and migration. Epratuzumab is a humanized anti-CD22 antibody that targets this molecule. The EMBLEM phase II trial [62] showed positive outcomes with Epratuzumab, with no safety concerns. However, in the larger and more stringently conducted EMBODY phase III trials [63], although Epratuzumab had an acceptable safety profile, it failed to replicate its favorable effects. There was no significant difference in the primary endpoint of BICLA at week 48, nor in steroid use, flares, or disease activity assessed by other measures such as SLEDAI-2 K, BILAG, or modified SRI (post-hoc analysis). This failure was attributed to high rates of dropouts, high placebo response rates, suboptimal dosing, and inadequate optimization of standard care [63].

Despite the negative results of the EMBODY trials, an open-label extension study (EMBODY 4; NCT01408576) was conducted, and the results are yet to be published in a peer-reviewed journal. Post-hoc analysis of the EMBODY 1 and 2 trials revealed a promising response to Epratuzumab in a subgroup of SLE patients with associated Sjogren's syndrome and positive anti-SSA antibodies [64]. Currently, there are no trials planned to further investigate the use of Epratuzumab in SLE.

2.4. CD19

Obexelimab, is a humanized monoclonal antibody designed to bind the CD19 surface antigen and the FcγRIIb on B cells using its antibody variable domain and its Fc-engineered domain respectively. This co-ligation causes FcγRIIb inhibition and leads to inhibition of B cells without depleting them, in contrast to Rituximab [65].

A placebo-controlled phase II study (NCT02725515) was conducted to determine the efficacy of Obexelimab in maintaining SLE remission, using the BOLD study design [66]. Immunosuppressive medications (excluding antimalarials and low-dose prednisone) are withdrawn and patients with nonlife or organ-threatening SLE are given IM high-dose methylprednisolone, which leads to clinical improvement. The patients then are randomized to active therapy or placebo. The proportion of patients without loss of improvement (LOI) and time to LOI (flare) post-initial steroid burst are the major endpoints. The latest data from this particular study showed that LOI was numerically (but not statistically) more likely in the placebo population than the Obexelimab-treated patients and there was a significant improvement in time to flare ($p = 0.025$). Moreover a higher percentage of patients treated with Obexelimab achieved and maintained LLDAS (30.8% vs 13.5%, $p = 0.0453$) between months 6 and 8 compared to placebo [67]. Currently, no ongoing trials are evaluating Obexelimab in SLE.

2.5. CAR T Cells

A novel strategy to B cells depletion in SLE is the use of genetically engineered T cells expressing chimeric antigen receptors (CARs). These recombinant cell surface proteins, CARs, can bind to the target antigens and transmit cytoplasmic signaling. Anti-CD19 CAR T cells are currently used to treat refractory B cell malignancies. When the CAR is bound to CD19+ cells, its cytoplasmic domains CD28 and CD3ζ activate a cytotoxic response against the target cell, while also promoting T cell proliferation. Given the diverse array of autoantibodies observed in SLE, using anti-CD19 CAR T cells to broadly deplete B cells (and short-lived plasma cells) is a strategy to consider after promising results in several murine lupus studies [68].

Currently, data in humans are limited to case reports and case series. In a 20-year-old patient with severe and refractory SLE and active LN, in which B-cell targeting therapies failed, autologous anti-CD19 CAR T-cell infusion resulted in serological and clinical remission within five weeks. Disease activity, proteinuria, and anti-dsDNA Abs rapidly decreased, and complement levels increased [69]. In a follow-up study from the same group, five patients with refractory SLE were treated successfully with autologous-engineered anti-CD19 CAR-T cell therapy. Before infusion, patients underwent lymphodepletion. Post-infusion, CAR-T cells rapidly expanded, leading to B-cell depletion, with both serological and clinical improvements in SLE, including rapid loss of anti-dsDNA Abs and improvement of LN. All patients achieved remission according to DORIS criteria at three months post-infusion, which was maintained for a median follow-up of eight months without any add-on therapy. Notably, the circulating CAR T cells expanded until around 9 days followed by a rapid decline of their levels in the peripheral blood. Moreover, the B cells that reappeared were naïve without class-switched B cell receptors and did not induce disease flare during the observation period [70]. Overall, the anti-CD19 CAR T cells were well tolerated, with only mild cytokine-release syndrome reported and no infections.

Along the same lines, T cells have been also used to target both B and plasma cells using a bispecific CAR molecule against both CD19 (B cells) and the B cell maturation antigen (BCMA, plasma cells). In a proof-of-concept study from China, combination CAR T cells infusion in 13 lupus nephritis patients led to a profound B cell depletion and elimination of all immunoglobulins (including autoantibodies) from the circulation. The B cells did rebound on average after 90 days and there was evidence that IgM production was restored within 150 days. 3/13 patients who were followed up for more than one year, were in reported

symptomatic remission [71].

Despite the very promising reports so far, the results should be interpreted with caution given the size of the studies and the lack of a control group. This is particularly important given the lymphodepletion regimen that included fludarabine and cyclophosphamide, drugs that may significantly impact the disease [72]. Moreover, the depletion of both B cells and plasma cells with combination CAR T cells may lead to profound immune suppression for a significant period of time post-therapy. What these treatments promise though, is that they can induce long term drug-free remission, a hypothesis that still need to be proven. Numerous phase I and II studies using CD19- (NCT05765006, NCT05474885, NCT03030976, NCT05030779, NCT06106906, NCT06153095, NCT05085418, NCT06106893, NCT05988216, NCT06222853, NCT05938725), BCMA- (NCT06222853) or CD19/BCMA- (NCT05858684, NCT05474885) CAR T cell therapy, are currently underway in SLE and LN.

2.6. CD38

Daratumumab, is a CD38 antibody that has already received approval for use in treating multiple myeloma. CD38 glycoprotein is abundantly expressed in long-lived plasma cells, which play a significant role in the generation of antibodies, potentially including SLE-related autoantibodies. Evidence of Daratumumab's effectiveness in SLE is limited in case reports describing its use in refractory cases, with very good serological and clinical response [73,74]. Two phase II trials, one in patients with refractory SLE (DARALUP, NCT04810754) and the other in patients with active LN (NCT04868838) are underway.

2.7. Proteasome

It has been suggested that the suboptimal effectiveness of therapeutic agents targeting CD20 in SLE may be attributed to the absence of CD20 expression in long-lived plasma cells, which may be significant sources of pathogenic antibodies. Inhibition of proteasome represents a potential therapeutic strategy to reduce plasma cells and thereby decrease auto-antibody production in SLE. Inhibition of the proteasome results in the accumulation of misfolded proteins, which triggers a response leading to apoptosis. Given the ability of plasma cells to produce antibodies at high rates, they are particularly susceptible to proteasome inhibitors [75,76].

Bortezomib is a proteasome inhibitor that is already approved for use in plasma cell malignancies. Bortezomib has been shown to target CD20-negative plasma cells, while sparing their precursors [76,77]. Small trials and case reports have suggested that Bortezomib may be effective in treating refractory SLE [76,78] and LN [79–81]. A meta-analysis in 2021 of 29 patients with refractory SLE from three studies [76,79,81] demonstrated that Bortezomib significantly reduces disease activity as assessed by the SLEDAI scores (OR = 11.30, $p < 0.00001$) [82]. Furthermore, a nationwide study conducted in Sweden, involving twelve patients with refractory SLE (11 renal involvement; 1 CNS) showed that the combination of Bortezomib and corticosteroids significantly reduced disease activity through the 6 and 12-month follow-up, and decreased proteinuria [80].

However, results from a small multicenter randomized placebo-controlled trial ($n = 14$) showed no significant difference in anti-dsDNA and SRI-4 response rates between patients receiving Bortezomib and placebo [83]. In addition, Bortezomib therapy has been associated with several side effects, including neuropathy, thrombocytopenic purpura, hypogammaglobulinemia, and fever, so its use should be limited in refractory cases, while also considering the ambiguity of evidence supporting its efficacy [84]. At present no trials are investigating the use of Bortezomib or other proteasome inhibitors such as Carfilzomib and Denlazomib.

Zetomipzomib (KZR-616), selectively inhibits the immunoproteasome class found predominantly in immune effector cells, in contrast to Bortezomib's inhibition of both the constitutive and immunoproteasome, and thus may have fewer side effects. Following pre-clinical studies, Zetomipzomib was evaluated in patients with SLE and/or LN in an open label phase Ib/II clinical trial (MISSION, NCT03393013). Zetomipzomib improved disease activity, reduced proteinuria, and decreased the levels of anti-dsDNA Ab, while maintaining a well-tolerated safety profile without toxicities associated with proteasome inhibitors in this uncontrolled study [85]. Furthermore, interim results specifically in patients with active proliferative LN, were also positive [86]. 6/17 patients who completed 24 week-treatment achieved complete renal response with Zetomipzomib maintaining a safe and tolerable profile over the six-month treatment period. Zetomipzomib will be assessed in a phase IIb placebo-controlled study in patients with LN (PALIZADE).

Overall, proteasome inhibitors, despite their potential as a treatment option for SLE are associated with severe toxicity. A promising alternative lies in solely inhibiting the immunoproteasome, and ongoing research is underway to confirm its potential.

3. Intracellular Signaling

3.1. Bruton Tyrosine Kinase (BTK)

Bruton tyrosine kinase (BTK) is an intracellular kinase that plays a critical role in the signaling pathway of multiple cells, especially B cells. BTK is essential for the activation, survival, and development of B cells, and plays an important role in antigen presentation and antibody production through its involvement in the BCR signaling pathway. Genetic mutations of the *BTK* gene can result in agammaglobulinemia and loss of mature B cells. Furthermore, BTK is implicated in the pathogenesis of autoimmunity and certain types of cancers. Ibrutinib, a BTK inhibitor, is an approved therapy for B-cell malignancies [87].

Alterations in the BTK signaling pathway have been observed in patients with SLE, with BTK+ cells in the blood being associated with disease activity, anti-dsDNA antibodies, C3 levels, and proteinuria. Moreover, in murine SLE models, BTK inhibitors have been shown to reduce kidney damage [87]. Two BTK inhibitors, Fenebrutinib and Evobrutinib, have been assessed in phase II trials for treating SLE. Fenebrutinib demonstrated pathway inhibition and acceptable safety in a study with 260 patients, but at 48 weeks, there was no significant difference in SRI-4 response compared to placebo [88]. Similarly, Evobrutinib, was tested in a larger SLE population of 469 patients and showed tolerability but lacked clinical benefit [89]. In a phase II trial (see below), the combined use of Upadacitinib (JAK inhibitor) and Elsubrutinib (BTK inhibitor), as well as the Upadacitinib monotherapy, met the primary endpoint of SRI-4 but it was unclear whether there was any benefit of adding the BTK inhibitor to the JAK inhibitor [90].

Preliminary results from a phase I/II study (NCT04305197) showed that another BTK inhibitor, Orelabrutinib (ICP-02), may be an effective and tolerable treatment for SLE. Orelabrutinib showed higher SRI-4 response at 12 weeks, 50.0% (50 mg, n = 14), 61.5% (80 mg, $n = 13$), and 64.3% (100 mg, n = 14) compared to the placebo's group 35.7% (n = 14). The difference in SRI-4 response between placebo and Orelabrutinib groups was even higher when only patients with SLEDAI-2 K $\geq$ 8 were analyzed [91]. This paved the way for further evaluating Orelabrutinib in a phase II trial (NCT05688696) recruiting primarily in China.

Several other BTK inhibitors have been (BIIB068, NCT02829541) or are being evaluated (AC0058TA, NCT03878303) for use in SLE, but their efficacy remains uncertain. A phase II trial is recruiting to evaluate Zanubrutinib, another BTK inhibitor, in proliferative LN (NCT04643470). Moreover, a phase II trial which has recently been completed, evaluated the efficacy of Branebrutinib, followed by Abatacept (see below) (NCT04186871) in Cutaneous Lupus Erythematosus, with a primary endpoint $\geq$50% reduction of the modified CLASI. The results have not been published yet. Overall, results from BTK inhibition have been mixed at best making the further development of these agents

especially as monotherapy highly unlikely.

3.2. Cereblon Modulators

Cereblon modulators such as Iberdomide (CC-220) and KPG-818 are novel oral immunomodulatory agents with a unique mechanism of action. They bind with high-affinity to cereblon (CRBN) E3 ubiquitin ligase complex leading to the ubiquitination and subsequent degradation of the transcriptor factors Aiolos (IKZF3) and Ikaros (IKZF1), which both are involved in immune cell development, autoantibody production and SLE pathology [92,93].

Iberdomide was first evaluated in SLE, in a phase IIa 12-week, placebo-controlled, dose-escalation study, in which 17/33 patients were followed in a 2-year open-label active treatment extension phase with a favorable benefit/risk ratio [92]. In another phase II trial involving 288 patients with SLE, the highest dose of Iberdomide (0.45 mg) was shown to have a significantly greater SRI-4 response rate at 24 weeks compared to placebo (54% vs 35%; $p = 0.01$). However, many secondary endpoints were not met. It is worth noting that the trial excluded patients with high-risk thromboembolic events and administered mandatory thromboprophylaxis, as cereblon-modulating agents are associated with thromboembolic effects. The adverse events associated with Iberdomide administration were neutropenia, upper respiratory and urinary tract infections [94]. Currently, there are no registered trials underway to evaluate Iberdomide in SLE.

On the other hand, KPG-818, another novel CRL4-CRBN E3 ubiquitin ligase modulator, following its evaluation in a phase I trial including healthy individuals (NCT03949426), is being investigated in a phase Ib/IIa trial (NCT04643067) to further assess its safety in patients with SLE. According to an abstract presentation of the study, KPG-818 demonstrated a manageable profile and robust dose-dependent modulatory effects, which support clinical development of the agent in SLE [95]. Cereblon modulators results may be beneficial but their toxicity profile may be limiting their eventual adoption as an SLE therapy.

3.3. Calcineurin Inhibitors (CNI)

Calcineurin plays a crucial role in the pathogenesis of SLE. T cell hyperactivation in SLE is mediated by aberrant T cell receptor (TCR) signaling, resulting in an increase in calcium levels that activates calcineurin [96]. Calcineurin then dephosphorylates nuclear factors of activated T-cells (NFAT), leading to the expression of inflammatory mediators such as Interleukin (IL)-2, tumor necrosis factor (TNF), CD40 ligand (CD40-L), interferon-gamma (IFN-γ), and IL-17, which contribute to the development of SLE. Moreover, calcineurin activation leads to the destabilization of the podocyte cytoskeleton and triggers apoptosis, causing destabilization of the glomerular filtration membrane, proteinuria, and kidney damage. While CNI are used as immunosuppressants in transplant patients, their ability to decrease T cell activation and the subsequent inflammation, as well as their ability to promote podocyte cytoskeleton stabilization and reduce proteinuria which are important aspects of LN pathogenesis, makes them a promising treatment option for LN [97].

Tacrolimus more than Cyclosporine, the two traditional CNI, has been extensively studied as a treatment option for LN primarily in patients of Asian descent. In a Phase III trial, the addition of tacrolimus to standard therapy achieved significant change in the LN disease activity index [98]. Positive results have also been demonstrated with the combination of low-dose MMF and Tacrolimus for refractory LN in a phase IV trial [99].

In open-label phase III and/or IV and prospective randomized controlled trials, Tacrolimus was found to be non-inferior to Cyclophosphamide [100,101] or to MMF [102,103] as an induction therapy. In a phase IV trial comparing tacrolimus to MMF as an induction therapy, Tacrolimus showed a similar CRR rate and sustained similar efficacy in terms of flare rate, renal function decline, and mortality over around 10 years. A urine protein to creatinine ratio (uPCR) ≤ 0.75 and eGFR of $\geq$80 mL/min at month 18 were suggested as targets for induction as they best predicted a positive 10-year outcome [103]. However, the trial revealed a trend towards increased incidence of proteinuric renal relapses while patients were on Azathioprine maintenance therapy in the Tacrolimus group (proteinuric and nephritic renal flares: MMF 34% and 37%, Tacrolimus 53% and 30%, respectively, $p = 0.49$). In addition, in a phase III trial that showed similar efficacy between MMF and tacrolimus in achieving renal remission, the MMF group presented a higher decrease in disease activity SLEDAI-2 K score [102]. Moreover, combination therapy with MMF, tacrolimus, and steroids demonstrated a higher rate of complete response compared to the cyclophosphamide-based regimen at both 6 and 9 months (50% vs 5% and 65% vs 15%, respectively), [104]. Similarly, the combination of MMF and Tacrolimus was superior to Cyclophosphamide in another study at 24 weeks (45.9% vs 25.6%, $p < 0.001$) [105].

Small studies focusing on pure class V LN showed that Tacrolimus favorably compares to MMF ($n = 16$) [106] and oral Cyclophosphamide/Azathioprine ($n = 37$) [107]. The Tacrolimus group achieved a significantly higher rate of CRR compared to MMF (57.1% vs. 11.1%, $p = 0.049$), and a faster resolution of proteinuria ($p = 0.032$), and a lower risk of lupus flare within 1 year ($p = 0.027$) compared to Cyclophosphamide/Azathioprine [106,107].

The use of Tacrolimus was also found beneficial as a maintenance therapy in LN. In an open-label phase III trial in China tacrolimus was found to be non-inferior to azathioprine as a maintenance therapy [108]. Moreover, in a 5-year interim post-marketing surveillance study in Japan (TRUST) including 1355 patients with LN receiving Tacrolimus as a maintenance treatment [109], showed a significant improvement as early as in 4 weeks, in urine protein-to-creatinine ratio, steroid-sparing effects, anti-dsDNA antibody, and complement C3 levels ($p < 0.001$); this improvement was sustained for the full 5 years. In addition, the cumulative rate of progression to renal failure (year 1: 0.8%, year 5: 6.6%) and relapse rate (year 1: 7.8%, year 5: 30.6%) improved, while the agent was well tolerated. Post hoc analysis of this study suggested that Tacrolimus may be a safe therapeutic option during pregnancy, with further insights awaited from TRUST PM trial results [110].

In January 2021, the FDA approved a new oral calcineurin inhibitor called Voclosporin, for the treatment of LN. The approval of Voclosporin was based on the results of AURA-LV phase II [111], and AURORA-1 phase III [8] studies. In both trials, patients with LN received Voclosporin or a placebo, with a background MMF therapy and relatively low-dose steroids. In AURA-LV, a higher CRR rate was achieved at 24 weeks (high dose Voclosporin 32.6%, $p = 0.204$; low dose Voclosporin 27.3%, $p = 0.046$; placebo: 19.3%) and at 48 weeks (high dose Voclosporin: 49.4%, $p < 0.001$; low dose Voclosporin: 39.8%, $p = 0.026$ vs placebo: 23.9%), but no dose-response was observed [111]. In AURORA-1 Voclosporin achieved a higher CRR rate at 52 weeks (41% vs 23%, $p < 0{\cdot}0001$) vs MMF alone [8].

From a safety standpoint, the Voclosporin low-dose group in AURA-LV was associated with higher rates of serious adverse events including death (low dose Voclosporin:11.2%, high dose Voclosporin: 2.3% vs placebo: 1.1%). 13 reported deaths in this study raised serious questions about the safety of this agent but in the larger AURORA-1 study, the adverse events profile was similar between groups; serious adverse events occurred in 21% of patients in each group. During the study follow-up period, there were 6 deaths; <1% of Voclosporin-treated patients, 3% of placebo-treated patients, but none was attributed to the studied therapy [8,111]. The 2-year AURORA-2 study that enrolled the patients who finished the one-year AURORA-1 trial, showed that Voclosporin maintained its clinical benefits (decreasing proteinuria and stabilizing eGFR), with an acceptable safety profile [112].

Compared to its predecessors in CNIs class, Voclosporin has a more predictable pharmacokinetic (PK)-pharmacodynamic (PD) relationship, which requires less monitoring and an improved metabolic effect. Voclosporin permits the concomitant use of MMF without dose

modifications. However, Voclosporin nevertheless is can cause classic CNI-related effects such as GFR decrease (26.2% vs placebo 9.4%) and hypertension (19.1% vs placebo 8.6%) [113]. The promising data for Voclosporin in combination with MMF, have moved it up in the treatment algorithm of LN, especially in cases of severe proteinuria and patients at high risk for corticosteroid-related morbidity. As less than half the patients attain CRR in most LN trials, the question remains of whether multimodal therapy combining Belimumab, Voclosporin and MMF may further improve outcomes.

CNI use in LN is currently being evaluated in several studies: a phase IV trial (NCT02630628) compares Tacrolimus to MMF in achieving a sustained renal response in active LN; an observational study (NCT05337124) will evaluate Voclosporin patterns of use and effectiveness in LN; a phase III study (NCT05288855) will evaluate the efficacy of Voclosporin in adolescents with LN.

3.4. Mammalian Target of Rapamycin (mTOR) Signaling Inhibitor

The mammalian target of rapamycin (mTOR) is a ubiquitous serine/threonine kinase with an important role in the regulation of cellular, growth, survival, and proliferation, and it is influenced by metabolic cues. It is composed of two interacting complexes, mTORC1 and mTORC2, which have been linked to SLE pathogenesis. Activation of mTORC1 precedes the onset and flares of SLE [114,115]. The mTORC1 drives the pro-inflammatory expansion of Th1, Th17, and CD4 − CD8− (double-negative) T cells, while both mTORC1 and mTORC2 inhibit the development of CD4 + CD25 + FoxP3+ Treg cells. In addition, mTORC2 indirectly promotes the expansion of T follicular helper (Tfh) cells, which similarly to double-negative T cells, promote B-cell activation and autoantibody production. Therefore, mTOR inhibition may help reprogram the aberrant immune response in SLE.

The mTOR inhibitor, Rapamycin, directly and rapidly inhibits mTORC1 and with some delay indirectly inhibits mTORC2, resulting in a significant impact on immune cells [114]. A meta-analysis of 9 studies has shown that rapamycin is a well-tolerable and promising treatment option for SLE. It appeared to have a clinical benefit in reducing disease activity, particularly musculoskeletal and mucocutaneous manifestations. In addition, it has shown encouraging results in sustaining remission of LN. Its side effects were mainly hematological, mucocutaneous, and dyslipidemia, resulting in early withdrawals in 9.28% of the cases [116]. In a 21-year follow-up study of 73 patients with renal and non-renal SLE, Rapamycin resulted in a significant reduction of proteinuria, hematuria, steroid use, and anti-dsDNA levels [117]. Clinical trials that evaluate Rapamycin efficacy and safety in patients with active SLE (NCT04582136, NCT04736953) and proteinuric flares of LN (NCT04892212) are currently registered.

N-acetylcysteine (NAC) is an antioxidant that reverses the depletion of reduced glutathione (GSH), and inhibits mTORC1 [114]. Results from two randomized placebo-control studies in patients with SLE, showed that NAC can significantly reduce disease activity, serological markers [118,119] and fatigue [118]. It is noteworthy that NAC caused a significant decrease of complications in all organs except hematological, based on BILAG scoring. NAC was overall well-tolerated, and primary adverse effect observed being reversible nausea at the high-dose group (4.8 g/day) [118]. A phase II study (NCT00775476) is underway to evaluate the role of NAC in SLE.

Finally, Metformin, a traditional antidiabetic agent, inhibits multiple metabolic pathways in the immune system, including oxidative phosphorylation and mTOR [120,121]. It was found to be safe but with questionable efficacy in patients with SLE [122,123]. A post hoc analysis of these studies showed some promise that can reduce disease flares in patients with low SLE activity, particularly if they were serologically quiescent [122]. Currently, a phase IV trial (NCT04145687) evaluating Metformin in patients with LN is ongoing.

3.5. JAK/STAT Inhibitors

The Janus kinase (JAK) family (including JAK-1, 2, 3 and Tyrosine Kinase 2, TYK2) are intracellular protein tyrosine kinases that mediate signals from various cytokines, growth factors, and hormones. They combine in a homodimeric or heterodimeric fashion, bind to the receptor, and activate one or more of the STAT (Signal Transducers and Activators of Transcription) transcription factors. Several cytokines that have been linked to SLE pathogenesis, including the Interferons, IL-2 and IL-23, signal through this pathway [124]. In a murine model of SLE, inhibition of STAT3 led to improvement of nephritis [125–127] suggesting that the JAK/STAT pathway may be a good treatment target in SLE. Theoretically targeting different JAK/STAT combinations, different cytokine signals can be blocked: Inhibition of JAK-1 inhibits cytokines that are members of the IL-6, IL-2, Interferon, and IL-10 families, while inhibition of JAK-2 affects IL-12/23, Interferon-γ as well as trophic factors such as Erythropoietin. JAK-3 transduces the signal from the IL-2 family of cytokines. Finally, TYK2 is responsible for the transduction of signal from IL-12/23, IL-4/13, IL-10 family and Interferon-α, β, κ, ω, λ.

Tofacitinib, a JAK-1/3 inhibitor, was the first JAK inhibitor to be approved for use in patients with Rheumatoid Arthritis (RA). In a phase I study in SLE, Tofacitinib demonstrated a safe profile in a phase I study in SLE and exhibited beneficial cardiometabolic and immunologic effects [128]. Case reports have suggested that Tofacitinib can be helpful in cutaneous lupus [129]. A study in cutaneous SLE in young adults (NCT03288324) has been completed but results are not yet available.

Baricitinib, a selective inhibitor of JAK 1/2, already FDA-approved for rheumatoid arthritis, showed promising results in a phase II 24-week trial [130] at a high dose (4 mg a day). In two phase III trials, BRAVE-I and II [131,132], assessing the SRI-4 response at 52 weeks, Baricitinib showed inconsistent efficacy. Only the 4 mg dose in BRAVE-I achieved the primary outcome SRI-4 at 52 weeks (56.7% vs. placebo 45.9%, $p = 0.016$), while neither study met any of the key secondary endpoints. Further development of Baricitinib in SLE is therefore not pursued, although a phase III trial (NCT05432531) to assess the use of Baricitinib in LN is still registered.

Deucravacitinib, an oral selective inhibitor of TYK2, which is already approved for Psoriasis, demonstrated promising results in a phase II trial [133]. Deucravacitinib achieved a significantly higher SRI-4 response rate, and greater response in the secondary points like BICLA, CLASI-50, LLDAS, and joint counts compared to placebo. Although infections and cutaneous events occurred more frequently with Deucravacitinib than with placebo, the safety profile was deemed acceptable. These promising results have led to further studies of Deucravacitinib's safety and efficacy, including a long-term assessment phase II trial (NCT03920267), a phase II trial including patients with active discoid and/or subacute cutaneous lupus erythematosus (NCT04857034), and two phase III-trials, POETYK SLE-1 and 2 (NCT05617677; NCT05620407). A study evaluating Deucravacitinib for the treatment of LN was also planned, but this was terminated due to insufficient enrollment.

A phase II randomized control trial investigated the use of the combination of 30 mg Upadacitinib, a JAK inhibitor with 60 mg of Elsubrutinib, a selective BTK inhibitor (ABBV-599HD), as well as the monotherapies of the respective medications compared to placebo. The combination of the two drugs as well as the monotherapy with Upadacitinib 30 mg met the primary endpoint as a significantly higher proportion of patients vs. placebo achieved SRI-4 and steroid dose $\leq$10 mg QD at week 24[90]. These groups also demonstrated significant improvements in SLE disease activity and flares with acceptable safety through 48 weeks. Patients who completed this study continued in a long-term extension study (NCT04451772), evaluating the same agents up to week 108. A phase III trial, known as SELECT-SLE, (NCT05843643) is now recruiting to further evaluate the safety and efficacy of Upadacitinib in SLE with the primary outcome being the BICLA response at 52 weeks.

The JAK-1 inhibitor, Filgotinib or Lanraplenib (a spleen tyrosine kinase, Syk inhibitor), was evaluated in patients with lupus associated membranous nephropathy. Figlotinib was tolerable and reduced proteinuria (median reduction 50.7%) in the four patients who completed 16 weeks of treatment [134]. These two treatments though did not show an effect in patients with cutaneous lupus [135]. Solcitinib (GSK2586184), another JAK-1 inhibitor, was evaluated in phase I studies (NCT01953835, NCT01687309) in SLE, but the phase II study (NCT01777256) recruitment was terminated due to lack of efficacy and significant side-effects [136]. R333, a topical JAK-1/3/SYK inhibitor was evaluated in skin involvement in SLE, but failed to demonstrate efficacy [137]. A phase IIb trial (NCT03845517) to evaluate the safety and efficacy of Brepocitinib (PF06700841), an oral selective TYK2/JAK-1 inhibitor that previously demonstrated positive results in plaque psoriasis [138] failed to show meaningful effect and further development of this medication for SLE was stopped.

Overall, JAK inhibitors remain an attractive option in SLE given that target relevant inflammatory pathways in SLE such as the interferon, are administered orally, and have long been used in autoimmune diseases such as RA. The efficacy in treating patients with SLE remains still unclear given lack of positive data in large phase III trials. The safety of these medications has also been questioned after the results of the ORAL surveillance study: Tofacitinib increases the risk of both cancer and major cardiovascular events in older patients with RA [139]. Whether this is true for inhibitors of JAK-1 (Upadacitinib) and TYK2 (Deucravacitinib) remains unclear. Moreover, the exact risk from JAK inhibition in SLE patients who may be at higher risk than RA patients for thromboembolic events due presence of antiphospholipid antibodies has not been established. All these questions will need to be addressed not only in the ongoing phase III trials but also in long-term real-world studies.

3.6. Rho Kinase (ROCK) Inhibitors

ROCK1 and ROCK2 are serine/threonine kinases that act by binding to RhoA, regulating several biological functions such as cytoskeletal reorganization, proliferation, and differentiation. The abnormal activation of RhoA-ROCK pathway is implicated in autoimmunity, including SLE. Murine experiments showed that ROCK activation is linked to enhanced phosphorylation of the interferon regulatory factor (IRF)-4, and subsequently in the increased production of IL-17 and IL-21, which are key players in SLE pathogenesis [140]. Fasudil, a ROCK inhibitor, can significantly alleviate murine lupus [141]. Similarly, the administration of different Rho inhibitors, including Y27632 (pan-ROCK inhibitor), KD025 (a selective ROCK2 inhibitor) or simvastatin (which inhibits RhoA, a major ROCK activator) in purified SLE T cells led to reduction of IL-17 and IL-21 [142]. However, KD025 (Belumosudil) has been approved for use in chronic graft-versus-host-disease, received an orphan drug status by the FDA in 2020 for the treatment of systemic sclerosis, and has been evaluated for psoriasis vulgaris, idiopathic pulmonary fibrosis and hepatic impairment [143]. Fasudil, which has vasodilatory effect, has been evaluated with positive results in cerebrovascular cardiovascular conditions [144]. Currently there are no clinical trials investigating the use of these agents in SLE.

4. Co-Stimulation

T cell activation is triggered by a primary signal transmitted by the MHC-Antigen complex on the antigen-presenting cell (APC) and the T-cell receptor on the T cell. However, the simultaneous engagement between co-stimulatory molecules on both cells may potentiate or abrogate the effect of the primary signal on T cells. Interference of these co-stimulatory interactions has proven to be effective in RA and has been the focus of research in SLE for at least three decades as well. Below we discuss targeting several co-stimulatory pairs as a potential treatment approach for SLE. It has to be noted though that these agents have not been proven to date to be efficacious in either SLE or LN.

4.1. CD28/B7

Abatacept, a selective modulator of the T-cell CD80/CD86:CD28 costimulatory pathway that is required for T-cell activation. Abatacept has long been used for the treatment of RA [145]. The molecule is a fusion of the extracellular domain of cytotoxic T-lymphocyte–associated protein (CTLA)-4 and the modified Fc portion of human IgG1 and does not activate complement. CTLA-4 shares a similar structure to CD28, but has a higher affinity for CD80/86, resulting in the inhibition of T cell activation and a reduction in subsequent inflammatory reactions [146]. Despite strong rationale for the use Abatacept in patients with SLE, clinical trials have been disappointing: Phase II and III trials in SLE [147] and LN [148,149] did not demonstrate a significant clinical benefit, or were terminated ((NCT00430677, NCT01714817, NCT02429934).

A different modulator of this pathway, Lulizumab is a polyethylene glycol conjugated anti-CD28 domain antibody. While Abatacept binds to CD80 and CD86 on APCs with different affinities, inhibiting T cell stimulation, Lulizumab can block T cell proliferation by inhibiting with equal potency both CD80 and CD86 molecules [150]. In a phase II study, Lulizumab pegol, was administered to patients with non-renal SLE, but no clinical improvement was observed compared to placebo [151].

4.2. CD154/CD40

CD154 (CD40L), which is primarily expressed on activated T cells and its ligand CD40 primarily expressed on B cells, regulate various aspects of T cell-dependent humoral immunity: activation of B cells, immunoglobulin class switching, formation of germinal centers and memory cells. It is not surprising therefore that the CD154/CD40 interaction is implicated in autoimmune diseases, including SLE and LN [152]. Three CD154/CD40 blocking agents, Dapirolizumab, BI 655064 and Iscalimab (CFZ533) are currently being tested in SLE.

Dapirolizumab pegol is a polyethylene glycol-conjugated antigen-binding (Fab') fragment that targets CD154. The design of Dapirolizumab pegol excluded the functional Fc domain, which significantly reduced the potential for platelet activation and aggregation, to mitigate safety concerns that resulted in the halting of previous trials that investigated anti-human CD154 IgG Ab in SLE. In two phase I trials in SLE, Dapirolizumab was well tolerated without reports of thromboembolic events. In a phase II trial enrolling 182 patients with moderate to severe SLE, the incidence of thromboembolic events was lower in the Dapirolizumab-treated patients compared to placebo-treated patients (0.7%vs 6.7%), confirming the low risk of this agent. Although the primary endpoint of the phase II trial was not met (achieving dose-response relationship based on BICLA at week 24, $p = 0.07$), there were consistent numerical improvements across multiple clinical and immunological measures of disease activity [153,154]. Currently there are two phase III trials on the way to determine the efficacy of Dapirolizumab on a larger scale (NCT04294667) and to evaluate its long-term safety and tolerability (NCT04976322).

BI 655064, a humanized anti-CD40 monoclonal antibody with a modified Fc region, was tested in a phase II trial in LN. BI 655064 did not show a difference from placebo in terms of CRR rates at week 52. This may have been in part due to the very high placebo response (48.3%); a post hoc analysis using confirmed CRR (CRR at weeks 48 and 52) showed that at the dose of 180 mg, BI 655064 may be superior to placebo [155]. Finally, Iscalimab (CFZ533), a Fc-silent, blocking, non-depleting anti-CD40 Ab is also being evaluated in two phase II trials, NCT03610516 and NCT03656562 in LN and non-renal SLE respectively. The latter trial is also evaluating VAY736, an anti-BLyS Ab (see 2.1).

4.3. ICOS/ICOSL

ICOS and its ICOSL is another important pair of co-stimulatory molecules involved in the T cell dependent humoral response. The highest expression of ICOS is seen on T follicular helper (Tfh) cells in

germinal centers, where it regulates the humoral response and promotes the differentiation and maintenance of Tfh cells. ICOS is also associated also with the differentiation of Th1 and Th17 [156]. Tfh are thought to play an outsize role in SLE potentially through the help they provide to pathogenic autoantibody producing B cells [156–158].

Preluzumab (AMG 557), is a human anti-ICOSL monoclonal antibody that has been investigated in patients with SLE in three phase I studies, demonstrating an acceptable safety profile [159,160]. Preluzumab demonstrated a remarkable pharmacodynamic effect but no improvement in clinical features was observed [159]. In a placebo-controlled phase Ib study including 20 patients with active lupus arthritis, Preluzumab resulted in numerical improvements in the clinical measurements, suggesting potential efficacy [160]. However, no further studies have been registered to investigate this agent in SLE, while a phase I trial (NCT01389895) in subacute cutaneous lupus erythematosus was terminated due to slow enrollment.

Rozibafusp alfa (AMG 570) [161] and Acazicolcept (ALPN-101) [162] are dual inhibitors targeting both ICOSL and other co-stimulatory molecules. Rozibafusp alfa is a bispecific antibody that targets ICOSL and BLyS, while Acazicolcept is a Fc fusion protein of ICOSL variant immunoglobulin domain that inhibits both ICOS and CD28. In the results from a phase I trial, presented in an abstract, Rozibafusp alfa was found to be safe, with no serious drug-related or fatal adverse events reported in healthy participants, and evident PD activity [161]. A phase II trial (NCT04058028) to further assess the safety and efficacy of Rozibafusp alfa in patients with active SLE was terminated prematurely due to futility. In a trial including healthy participants, Acazicolcept demonstrated a tolerable profile and a dose-dependent PK and PD consistent with the CD28 and ICOS costimulatory pathways' known biology [162]. A phase II trial (NCT04835441) is currently recruiting to evaluate safety, tolerability, efficacy, immunogenicity, PK, and PD of Acazicolcept in patients with moderate to severe SLE.

Bispecific antibodies represent a promising approach to treat autoimmune disorders. However there have been reports of increased immunogenicity compared to monoclonal antibodies, highlighting the need for further research to optimize their development [156].

4.4. CD6/ALCAM

Effector T cells express CD6 on their surface, a receptor that can colocalize with the T cell receptor (TCR) and act as a modulator of TCR delivered activation signals[163]. CD6 binds to the adhesion molecule CD166/ALCAM (Activated Leukocyte Cell Adhesion Molecule): this interaction may be important for T effector cell activation as ALCAM is expressed on Antigen Presenting Cells but also T cell trafficking as Endothelial and Epithelial Cells also express ALCAM. Preclinical work showed that blocking CD6 can improve nephritis in lupus prone mice [164]. Inhibition of CD6/ALCAM interaction using the monoclonal antibody Itolizumab improved lupus nephritis in an open label single arm phase Ib (EQUALISE) study. In preliminary results presented at the ACR Convergence Meeting, 15/17 subjects who received Itolizumab plus standard of care reached 28 weeks of therapy with 6/15 achieving complete response [165]. The main safety concern with this medication was lymphopenia that was not though associated with serious infections in this small study. Longer placebo-controlled trials are needed to assess the efficacy of this intervention and address whether the observed lymphopenia results in increased infection rates.

5. Cytokines

Various cytokines have been linked to SLE disease activity, and it is believed that different SLE phenotypes or symptom presentations may be associated with distinct cytokine networks and patterns. Therefore, a broad range of cytokines are currently under investigation as potential therapeutic targets for treating SLE [166,167].

5.1. Interleukin-2 (IL-2)

Interleukin-2 has regained interest due to its potential to maintain CD4 T cells homeostasis and redirect immune responses towards tolerance. The immune dysregulation and loss of immune tolerance observed in SLE have been linked to deficient IL-2 production [166]. The low IL-2 environment in SLE fails to properly empower Tregs and indeed promotes Tfh differentiation leading to generation of high-affinity autoantibodies. Although high dose IL-2 is immunostimulatory and long used in cancer treatment, low-dose IL-2 facilitates the expansion of Tregs and promotes reversion of the Treg:Tfh imbalance acting as an immune suppressant or rather an immune modulator. Following successful trials in chronic Graft versus Host disease [168], low dose IL-2 has been evaluated in patients with SLE [169]. The low dose IL-2 was well tolerated without evidence of over-activation of effector T cells but it does cause a skin rash at the site of injection that may lead to unblinding of studies.

In an open label phase I/II trial involving 38 patients with SLE, the administration of three cycles of human recombinant low dose IL-2 led to significant changes in the proportions of Tfh, Treg, and Th17 cells leading to a significant reduction of the (Tfh + Th17) cells/Treg cells ratio ($p < 0.001$) and a significant decrease in disease activity. The SELENA-SLEDAI score was significantly reduced as early as two weeks and sustained over 12 weeks, with the SRI-4 response rate reaching 89.5% of the patients. Furthermore, a high percentage of patients (67.6%) achieved a $\geq$ 50% reduction in their steroids dose [170].

Building on the findings of the open-label study, the same investigators conducted a placebo-controlled Phase II trial including 60 patients with SLE and using the same regimen. Although the study did not achieve its primary endpoint of SRI-4 response rate at 12 weeks (55.17% vs 30.00%, $p = 0.052$), it demonstrated a significantly higher SRI-4 response rate at 24 weeks (65.52% vs 36.67%, $p = 0.027$) with the use of low dose IL-2, as well as significantly higher rate of complete LN remission [53.85% (7/13) vs 16.67% (2/12), $p = 0.036$]. The safety profile was acceptable with most frequent side effect being injection-site reactions (31.0% vs 6.7% in placebo). Notably, the treatment was associated with the promotion of anti-infection immunity. The rIL-2 led to significant expansion of Tregs and Natural Killer cells ($p < 0.05$, both), which was reflected in a decrease of viral titers without the use of antiviral treatment and a lower incidence of infections (6.9% vs 20.0%, NS) observed in the low dose IL-2 group [171].

Subsequently, more trials evaluated different IL-2 preparations and dosing schedules including recombinant IL-2 s, Aldesleukin (TRANSREG) [172] or ILT-101, [173] AMG 592, a novel long-acting IL-2 mutein Fc fusion protein with greater Treg selectivity [174], and Rezpegaldesleukin (LY3471851 or NKTR-358) a PEGylated form of rIL-2 that targets the IL-2 receptor alpha (ISLAND-SLE, NCT04433585). The AMG 592 program has been terminated due to futility. Similarly, Rezpegaldesleukin treatment despite showing numeric improvement at the mid dose vs. placebo in SRI-4, failed to reach meaningful statistical significance and no further development of this formulation in SLE is planned.

Aldesleukin was evaluated in small phase II trials: a. TRANSREG, which included patients with different rheumatic diseases (SLE $n = 6$) [172], and b. Charact-IL-2 (NCT03312335) in SLE only patients ($n = 16$). In TRANSREG, Aldesleukin demonstrated a significant increase in Tregs at day 8 (mean of 11.1% $\pm$ 4.6%, ($p < 0.0001$), while the results of Charact-IL-2 are not published yet.

ILT-101 was evaluated in the LUPIL-2 trial, a placebo-controlled phase II study ($n = 100$) and demonstrated the effectiveness in reducing disease activity in SLE. While this trial did not meet its primary endpoint of SRI-4 response, a post hoc analysis that excluded patients from two sites with a 100% placebo response revealed a significantly higher SRI-4 response rate among patients treated with ILT-101 (83.3% vs 51.7%, $p = 0.017$) [173].

Despite most of the trials not meeting their primary endpoint, there

are indications that IL-2 treatment may be effective, and as such, different IL-2 formulations are being investigated. Phase II studies are registered to further assess Efavaleukin alfa, and recombinant IL-2 (NCT04680637, NCT04077684 respectively). CUG252, a long-lasting variant of IL-2 with high Treg specificity and low toxicity, is also currently under evaluation in a phase I trial (NCT05328557) in healthy adults for prospective use in SLE. Moreover, phase III studies will investigate the combination of IL-2 with Belimumab (NCT05262686) or Telitacicept (NCT05339217) in SLE while another study will compare IL-2 treatment to umbilical cord mesenchymal stem cells as LN therapy (NCT05631717).

Moving forward, low dose IL-2 may be a useful therapy in restoring the immune system balance in SLE but its efficacy and its place in the treatment armamentarium is yet to be defined.

5.2. The IL-17/23 Axis

IL-12 and IL-23 are cytokines with a partially common structure but different functions, have been involved in SLE pathogenesis. IL-12 induces Th1 differentiation, while IL-23 promotes Th17 cell differentiation. IL-12 and IL-23 levels are elevated in SLE, while their shared subunit p40 levels has been positively correlated with the disease activity (SLEDAI) and negatively with C3 complement levels [175]. IL-23 levels correlate with the skin and renal manifestations as well as arthritis [176]. IL-17, which lays downstream of IL-23, has also been intensely studied in SLE. Patients with SLE have high levels of IL-17 levels, as the DN T cells which are a major source of IL-17 are expanded in SLE, while SLE CD4+ T cells as well produce more IL-17 than in healthy individuals [177,178]. Studies in lupus prone mice showed that IL-17 A and IL-23 receptor mRNA increased as the disease severity worsened [179], while genetic deficiency of IL-23 receptor prevents the development of LN [180].

Ustekinumab, a fully human IgG1κ monoclonal antibody directed towards the p40 shared subunit of IL-12 and IL-23, showed promising results in a phase II trial in SLE: Ustekinumab-treated patients with SLE achieved a higher SRI-4 response rate at 24 weeks compared to placebo-treated patients (62% vs 33%, difference: p = 0·006) [181]. However, these outcomes were not replicated in Phase III trials. Of the two planned phase III trials, one was terminated early (NCT03517722) as in the pre-planned interim analysis the primary endpoint was not met, with the placebo group demonstrating a higher SRI-4 response rate than the experimental group at week 52 (56% vs 44%) [182]. The other phase III trial (NCT04060888) was stopped. Currently, no further studies are investigating Ustekinumab in SLE, while it has not been evaluated in LN.

The IL-23/IL-17 axis has also been targeted in LN. Guselkumab, an anti-IL-23 antibody, was investigated in a phase II trial, ORCHID-LN, but the results have not been published yet (NCT04376827). Secukinumab, an anti-IL-17 A monoclonal antibody, on the other hand was evaluated in two phase III trials in LN, the SELUNE two year trial and its open-label extension study (NCT04181762 and NCT05232864, respectively), but the clinical trial was halted due to futility.

Overall, despite strong pre-clinical data, targeting the IL-23/IL-17 pathway has not proven to be of value in the treatment of SLE or LN to date.

5.3. IL-10

IL-10 plays a dual role in the development of systemic lupus erythematosus (SLE). Basic research indicates that IL-10 promotes the generation of autoantibodies by supporting the proliferation and differentiation of autoreactive B cells into plasma cells. However, several murine lupus studies demonstrated that IL-10 also has a protective, anti-inflammatory role. For example, continuous low-level IL-10 overexpression in B6.Sle1.Sle2.Sle3 mice delayed autoantibody production and reduced IgG and C3 deposition in the glomeruli [183]. In B6.NZM mice though, genetic deletion of IL-10 reduced autoantibody production [184]. This dual effect of IL-10 make it difficult to target it in SLE [185]. A small trial (total 6 patients) more than two decades ago, addressed the usefulness of murine anti-IL-10 antibodies as a treatment in SLE. Despite reactions to the murine antibodies, their patients SLE disease activity significantly decreased. Improvement in cutaneous and joint symptoms was observed, and the dose of corticosteroids was reduced. Notably, after six months, five out of the six patients achieved remission; however, only one patient had a reduction in anti-dsDNA antibodies [186]. This study provided a foundation for a randomized placebo-controlled phase II clinical trial (NCT02554019), evaluating the safety and efficacy of humanized anti-IL-10 antibodies (BT063) in SLE. The results of this small trial (12 patients on low dose of BT063, 12 patients on high dose and 12 on placebo), have not been published in a peer-reviewed journal yet, but showed a potential effect on skin lupus.

5.4. IL-6

IL-6 is a proinflammatory multifunctional cytokine which is significantly increased in patients with SLE and its levels correlate with disease activity as measured by the SLEDAI-2 K score [187]. IL-6 induces B cell differentiation, increases T cells differentiation to Th17 cells and Tfh cells, and inhibits TGF-induced Treg differentiation [188,189]. Studies have shown that IL-6 polymorphism is associated with the risk of SLE [190]. Animal studies have linked IL-6 with LN, as IL-6 deficiency can diminish disease activity, resulting in delayed onset of LN, reduced kidney pathology and increased survival [191].

Several drugs have been tested in clinical trials targeting IL-6 in SLE. Tocilizumab, a monoclonal antibody against the IL-6 receptor approved for use in RA, was evaluated in SLE in a phase I trial (NCT00046774) which showed promising serological and clinical responses, warranting further studies evaluating the agent. Main adverse event of tocilizumab use was dose-related neutropenia, which was not associated with occurrence of infections [192]. While these results were published in 2010, no other studies investigating this agent in SLE have been planned since then. A recent phase II trial (STEADY, NCT02437890), evaluated Vobarilizumab (ALX-0061), a bispecific nanobody that targets IL-6R, as well as human serum albumin which extends its half-life. However, this trial did not meet its primary endpoint of mBICLA at 24 weeks.

PF-04236921, an anti-IL-6 monoclonal antibody, was evaluated in a phase II trial, in which 183 patients with SLE received SC placebo or 10, 50 or 200 mg of the drug. There was increased incidence of serious adverse events, including four deaths (200 mg $n = 3$, 10 mg n = 1) due to serious infections and thromboembolic events, which led to the discontinuation of the 200 mg group and its exclusion from the efficacy analysis. The trial did not meet the SRI-4 response rate endpoint, but significant differences compared to placebo, were observed in BICLA response rate of the 10 mg group ($p = 0.026$) and in the incidence of severe flares with 10 mg ($n = 0$) and 50 mg ($n = 2$) combined (vs placebo $n = 8$, $p < 0.01$). In addition, subgroup analysis of patients with high disease activity [SLEDAI-2 K score $\geq$ 10, corticosteroids $\geq$7.5 mg/day, anti-dsDNA $\geq$28 IU/mL or hypocomplementaemia (C3 and C4)], revealed a significant greater SRI-4 ($p = 0.004$) and BICLA ($p = 0.012$) response rates with 10 mg compared to placebo [193]. Sirukumab, another anti-IL-6 monoclonal antibody, in a phase II trial including patients with LN, did not demonstrate a significant therapeutic benefit or a favorable safety profile for the population studied [194].

In general, IL-6 targeting in SLE does not appear to be very efficacious and may be associated with severe side effects.

6. The Interferons (IFNs)

Abundant evidence from both human and animal studies supporting the hypothesis that IFNs, specifically type I IFN, play a crucial role in SLE development [195]. One of the most consistent findings in SLE is the upregulation of type I interferon-responsive genes in peripheral blood mononuclear cells, known as the “IFN signature”. The IFN signature has

been associated with cutaneous, joint, renal and CNS manifestations, as well as with the presence of autoantibodies and low complement [195,196]. Since type I IFNs can initiate or enhance immune responses that lead to organ damage in lupus, this cytokine system has become a promising therapeutic target in SLE [195].

IFN-α was the first type I IFN that was associated with SLE disease manifestations and therefore the first one to be targeted. Rontalizumab, a humanized antibody that can block all known subtypes of interferon alpha, did not meet the primary endpoint in a phase II trial (ROSE study) comparing it to placebo using the BILAG score [197,198]. However, the exploratory analysis revealed somewhat surprisingly benefits for patients with low IFN signature, including a significantly higher SRI-4 response rate at week 24 (72.7 vs. 41.7% placebo, $p = 0.03$), reduced SELENA-SLEDAI flare index rates ($p = 0.004$), and reduced prednisone requirements (average dose of ≤10 mg daily during weeks 8 to 24). Rontalizumab was well tolerated without increased serious adverse events (10.1% vs placebo: 11.4%) [198]. Given the results of these studies further development of this molecule stopped.

Sifalimumab (MEDI 545), a monoclonal antibody targeting most of the IFN-α subtypes showed significant improvements in several measures at a phase II trial [199], but was associated with a notable incidence of treatment emergent adverse events in a following trial [200]. These results led to the discontinuation of this program for SLE. Additional monoclonal antibodies have been developed to target IFN-α, including JNJ-55920839, an IgG1κ against IFNα/ω [200], and AGS-009, an IgG4 against IFN-α. Results from Phase I trials supported the further development of both of these antibodies, but no further studies have been conducted to date.

6.1. IFN Receptor Blockers

An alternative strategy to block the interferon pathway is to target the IFN receptor. Anifrolumab, is a humanized monoclonal antibody that targets the type-I IFN receptor subunit 1. The binding to the receptor drives the receptor's internalization into the cell, which prevents potential binding by IFNs and subsequent IFN-mediated signaling by Type-I IFNs, including IFN-α, IFN-β, and INF-ω [199].

Anifrolumab (as an intravenous formulation) has received approval from the US Food and Drug Administration (FDA) as an adjunct to standard care of SLE treatment, based on the positive results from the MUSE, TULIP-1, and TULIP-2 trials. Anifrolumab decreased disease activity, reduced the need for steroids, and improved musculoskeletal and cutaneous manifestations while having a manageable safety profile [201].

In the MUSE trial, a placebo-controlled phase IIb study, patients with SLE received either 300 mg or 1000 mg of Anifrolumab successfully met its primary endpoint of SRI-4 response rate at 24 weeks while maintaining a reduction in steroid dose. Significant responses were observed in the 300 mg (34.3%) and 1000 mg (28.8%) groups, particularly in patients with a high baseline IFN gene signature. Anifrolumab also demonstrated significant reduction in disease activity and across multiple endpoints such as CLASI, BILAG, SLEDAI-2 K, and PGA [202].

In light of the positive results from the MUSE trial, two phase III trials, namely TULIP-1[203] and TULIP-2 [204], were conducted to further evaluate the efficacy of Anifrolumab in SLE. TULIP-1 comparing the effects of Anifrolumab 300 mg, Anifrolumab 150 mg, and placebo did not meet its primary endpoint of SRI-4 response rate at week 52 (300 mg: 36% vs placebo: 40%) over a follow-up period of 52 weeks. However, the Anifrolumab 300 mg group showed a higher incidence of sustained steroid tapering (49% vs 32%), BICLA response (46% vs 30%), CLASI reduction ≥50% (44% vs 25%), and ≥ 50% reduction in active joint count (53% vs 32%) compared to the placebo group.

In TULIP-2, using a protocol similar to TULIP-1, Anifrolumab 300 mg was compared to placebo, with a modified primary endpoint of BICLA response at week 52, which would enable the detection of partial improvements in disease activity. The Anifrolumab group demonstrated a significantly higher BICLA response rate at week 52 (47.8% vs 31.5%, $p = 0.001$), and significant differences in secondary endpoints, including sustained steroid dose reduction (51.5% vs 30.2%, $p = 0.01$) and CLASI improvement ≥50% (49.0% vs 25.0%, $p = 0.04$) [204]. The promising effects of Anifrolumab in ameliorating cutaneous manifestations of SLE have also been demonstrated in a case series of three patients with refractory cutaneous SLE, including one with discoid lupus and cicatricial alopecia and two with acute cutaneous lupus erythematosus, demonstrated improvement following treatment with Anifrolumab [205]. However, neither in TULIP-2 the reduction in tender and swollen joint count reached a significant level [204]. The 3-year placebo-controlled long-term extension study of the TULIP trials, TULIP LTE, showed that Anifrolumab has an acceptable long-term safety profile and was well tolerated and presented favorable outcomes including maintained decrease in disease activity and glucocorticoid usage. [206]

To add clarity to the divergent findings of the TULIP trials, a pooled analysis of data from the MUSE, TULIP-1, and TULIP-2 trials revealed that the outcomes of BICLA and SRI-4 were concordant in the majority of cases (78–85%). A subgroup of patients with discordance (BICLA non-responders/SRI-4 responders) was found in all three trials, but particularly in the placebo group of TULIP-1. These patients had lower disease activity, joint counts and glucocorticoid tapering rates which favored the placebo group in the TULIP-1 trial disproportionately [207]. In addition, a post hoc analysis revealed that BICLA response, irrespective of treatment assignment, was linked with clinically significant improvements, including quality of life measures such as Functional Assessment of Chronic Illness Therapy– Fatigue, Short Form 36 Health Survey, as well as a reduction in flares rate, and emergency department visits or hospitalizations (all $p < 0.001$) [208]. According to a meta-analysis, despite the lack of improvement in certain outcomes such as SRI-4, SRI-6, and CLASI score, Anifrolumab was still linked to improved BICLA response, steroid reduction, and SRI-7 and SRI-8 response while swollen and tender joint counts were not assessed due to insufficient data [209].

Additional analyses of the data from the TULIP trials revealed that Anifrolumab was linked with a significantly higher rate of sustained steroid tapering response (51% vs. 32%, $p < 0.001$), and a higher proportion of patients achieved the combination of BICLA response and sustained glucocorticoid taper response at week 52 compared to placebo (38% vs. 23%, $p = 0.002$) [210]. Overall, these studies support the use of Anifrolumab, especially in cutaneous lupus and its usefulness as a steroid sparing agent. Notably though the presence of the IFN signature did not predict response to Anifrolumab in the late phase studies as opposed to the phase II trial.

The MUSE trial, as well as the subsequent TULIP-1 and -2 trials, were conducted exclusively to patients without lupus LN or central nervous system involvement. To assess the efficacy of Anifrolumab in patients with LN, a phase II randomized controlled trial was undertaken, which enrolled participants diagnosed with biopsy-confirmed proliferative LN within three months. This trial compared two treatment groups: Anifrolumab 300 mg every four weeks, and Anifrolumab with a loading dose of 900 mg for the first three doses, followed by 300 mg every four weeks, against placebo. The primary endpoint was the mean change in urine protein creatinine ratio (UPCR) at week 52, which was not achieved, as both groups demonstrated similar improvements in UPCR (69% vs 70%). However, the secondary and exploratory endpoints showed that particularly the loading dose of Anifrolumab was beneficial compared to placebo, demonstrating numerically greater rates of CRR (45% vs 31%) and its components which were achieving 24 h-UPCR ≤0.7 mg/mg (50% vs 36% at week 52) and eGFR ≥60 mL/min/1.73 m2 or no reduction ≥20% from baseline (82% vs 73.3% at week 52) as well as a numerical benefit in the sustained steroid dose reduction rate (≤7.5 mg/day, week 24 to week 52, in patients oral glucocorticoid dosage ≥20 mg/day at baseline, 56% vs 33%) [211]. Although the primary end point was not met, a phase III trial (IRIS, NCT05138133) evaluating Anifrolumab's efficacy in patients with active proliferative nephritis has

been initiated.

The incidence of adverse events was comparable between patients who received placebo or Anifrolumab (85–96% vs 84–90%). The most frequently reported adverse events included infections (23–41%), upper respiratory tract infection (12–29%), headaches (5–21%), diarrhea (4–18%), herpes zoster (5–17%), and infusion reactions (1–14%). It is noteworthy that the incidence of herpes zoster infections was higher in the TULIP-LN trial at 17% compared to 5–7% in the MUSE, TULIP-1, and TULIP-2 trials [201]. The placebo-controlled TULIP-LTE study demonstrated that herpes zoster infection rate was lower after the first year of treatment and that the placebo group had a similar malignancy rate. More specifically, during the 3-year LTE period, the incidence rates per 100 patient-years for herpes zoster were 3.4 in the Anifrolumab 300 mg group and 2.8 in the placebo group, while the incidence decreased each year of the study [206].

Current phase III trials are investigating the efficacy of Anifrolumab subcutaneous formulation (Tulip SC, NCT04877691) or in the Asian population (NCT04931563). Considering that Following early investigations into the effect of Anifrolumab on cardiovascular health of SLE patients [212], a phase I trial (NCT05440422) will investigate the role of Anifrolumab in modulating vascular risk markers in SLE.

6.2. IFNα Kinoid (IFNα-K)

An intriguing alternative immunotherapeutic agent designed to block the IFN pathway is the IFN-α Kinoid, a vaccine composed of inactivated recombinant human IFN-α2b coupled to a T-helper carrier protein. This combination induces antibody production targeting various IFN-α subtypes [213], with promising results in SLE clinical trials. In a phase I/IIa dose-escalation placebo-controlled study of 28 patients with mild-to-moderate SLE, the IFNα-K injection (30 μg, 60 μg,120 μg, or 240 μg vs placebo) was well-tolerated and induced high titers of neutralizing antibodies against IFN-α, particularly in patients with a type I IFN signature. In addition, high anti-IFNα antibody titers (≥1:25,600) were associated with increase of the complement C3 levels [214]. Follow-up analyses showed that the anti-IFN-α antibodies persisted and were linked to downregulation of the IFN signature and reduced expression of activated B cell-associated transcripts [215].

In a 36-week phase IIb randomized double-blind placebo-controlled trial involving 185 patients with positive IFN gene signature and active SLE despite standard of care, IFNα-K (5 injections on days 0, 7, 28, and weeks 12, 24) induced neutralizing anti-IFN-α2b serum antibodies in the majority of patients (91%) and decreased significantly the IFN gene signature ($p < 0.0001$). Although the study did not achieve its clinical co-primary endpoint of modified BICLA response, (41% vs placebo: 34%) IFNα-K treatment resulted in a significantly greater steroid sparing effect and attainment of low lupus disease activity state (LLDAS) at week 36 (53% vs 30%, $p = 0.0022$). This is a noteworthy effect as LLDAS has been associated with decreased organ damage accumulation, improved quality of life, and lower healthcare expenses [213].

The safety profile of IFNα-K was acceptable, and adverse events were evenly distributed between the two groups. Of note, seronegativity for certain viruses (herpes simplex virus, varicella-zoster virus, cytomegalovirus, and Epstein-Barr virus) was an exclusion criterion from the trial [213]. Although the phase IIb trial (NCT02665364) described was terminated due to reorganization proceedings of the sponsor according to clinicaltrial.gov, the promising results of IFNα-K suggest its potential efficacy as a treatment for SLE and warrant further investigation.

6.3. Interferon-γ (IFN-γ)

Although IFN-α has been widely recognized as a critical player in the pathogenesis of SLE, emerging evidence indicates that the IFN-γ gene signature is also implicated in the early stages of the disease, LN pathogenesis and disease activity. Preclinical studies have shown that targeting IFN-γ may represent a potential therapeutic approach for SLE and LN [216]. In phase I clinical trials, the anti-IFN-γ antibody AMG811 effectively normalized interferon-regulated gene expression and reduced IFN-γ-induced protein 10 in patients with SLE [217,218]. However, subsequent phase I trials using AMG811in patients with discoid lupus [219] or SLE ± LN [220] failed to demonstrate significant therapeutic efficacy, despite a safe profile and reduction of IFN-γ-associated biomarkers. As a result, further development of this agent was discontinued.

6.4. Plasmatocytoid Dendritic Cells (pDC)

Another approach to modulate the IFNs, is to target plasmacytoid DCs, which are known to generate substantial quantities of type I IFN [221]. BIIB059 (Litifilimab), a humanized monoclonal antibody, specifically targets the blood pDC antigen 2 (BDCA2), a receptor found exclusively on pDCs. Litifilimab leads to the rapid internalization of BDCA2, which suppresses the generation of IFN-I and other inflammatory mediators [221].

In a phase I trial, Litifilimab demonstrated a safe and tolerable profile in patients with SLE and promising efficacy in cutaneous disease activity [222]. A two-part phase II trial, the LILAC study, enrolling 132 patients with SLE, arthritis, and active skin disease, showed that Litifilimab is beneficial for joint and cutaneous involvement. In part A the primary analysis included 102 participants who received either 450-mg Litifilimab or placebo and had ≥4 tender as well as ≥4 swollen joints. The study showed a significant improvement in the primary endpoint which was the reduction of active joint count at week 24 (mean difference −3.4, $p = 0.04$) [223]. In the part B of the LILAC study, 132 participants with histologically confirmed cutaneous lupus, regardless of the presence of systemic manifestations, were administered different doses of Litifilimab or placebo. Litifilimab was superior to placebo in reducing skin disease activity as measured by CLASI-A score at 16 weeks.[268] While the agent met the primary endpoints of this two-parts study, most of the secondary end points did not support these results. Noteworthy adverse effects presented with Litifilimab were hypersensitivity reactions and viral infections, including influenza and herpetic viruses, such as oral herpes infection, herpes keratitis and herpes zoster of which one case presented as meningitis 4 months after the drug administration [223,224].

The safety and efficacy of Litifilimab in SLE will be further evaluated in phase III trials (NCT04895241, TOPAZ-1; NCT04961567, TOPAZ-2; NCT05352919, EMERALD) while a phase II/III trial (NCT05531565, AMETHYST) is planned to evaluate Litifilimab specifically in refractory cutaneous lupus erythematosus with or without systemic manifestations.

Another approach to deplete pDC is through targeting the pDC specific marker Immunoglobulin-Like Transcript 7 (ILT7) using the monoclonal antibody Daxdilimab. Daxdilimab showed early clinical effectiveness in cutaneous lupus, including systemic and skin pDC depletion, decreased type I IFN activity locally and improvement of the lesions. A larger though phase II trial in SLE failed to reach its primary endpoint (BICLA) and development for SLE is on hold. The drug is currently under evaluation in a phase II study for primary cutaneous (discoid) lupus (NCT05591222).

Based on the hypothesis that neutralizing auto reactive IgE would limit basophil and plasmacytoid DC activation and, therefore, reduce IFN production, omalizumab, a monoclonal antibody targeting IgE, was assessed as a potential treatment for SLE in a phase I trial [225]. The trial found that omalizumab use resulted in a significant improvement in SLE disease activity at week 16, as measured by the SLEDAI 2 K score ($p = 0.038$), potentially due to modulation of the type-I IFN response. Further development of this treatment for SLE is not pursued at this point.

Overall, targeting the type I IFNs is effective in limiting disease activity, especially cutaneous, and reducing the need for corticosteroids, a major goal of modern lupus therapeutic regimens.

7. Miscellaneous

Iguratimod is a small-molecule interfering with B cell differentiation, used for the treatment of RA in Northeast Asia, and is currently under evaluation for the treatment of SLE [226]. In an observational study, Iguratimod add-on therapy showed promising results in 26 patients with refractory LN, resulting in 42.3% CRR by 6 months without any increase in steroid dose or the escalation of co-administered immunosuppressants [227]. A 52-week phase II study (IGeLu, NCT02936375) with a primary outcome of renal remission rate is underway to evaluate the superiority of Iguratimod over cyclophosphamide for induction therapy and Azathioprine for maintenance therapy in LN [226].

Lupuzor (Regiremod or IPP-201101 or P140), is a 21-mer peptide designed to selectively stimulate Treg cells and restore immune tolerance in patients with SLE. The peptide contains an amino acid sequence from the U1-70K small nuclear RNP, which is an autoantibody-target in SLE. The phosphorylation of the peptide at the serine position 140 selectively stimulates Treg cells while it prevents the activation of the autoreactive Th2 cells following the antigen presentation by the APC.

As a result, the downstream B cell expansion is reduced and the Treg response is upregulated [228].

Small phase II studies Lupuzor at the dose of 200 μg demonstrated a safe profile and resulted in SLE clinical improvement [229]. A study in Bulgaria focused on the effect on anti-dsDNA Abs levels, demonstrating a time-dependent and significant decrease with the use of Lupuzor (24% reduction on day 43, $p = 0.0014$) [229], while a placebo-controlled study in Europe and Latin America showed a significantly higher SRI-4 response rate at 12 weeks with the subcutaneous administration of 200 μg of Lupuzor every four weeks compared to placebo (53.1 vs 36.2%, $p = 0.048$) [230]. However, subsequent studies, including a phase II trial in the United States with 183 patients (NCT01135459), did not support the initial enthusiasm, as it did not meet its primary outcome of SRI response rate at week 24.

Similarly, a phase III trial, Lupuzor (NCT02504645, clinicaltrials.gov), did not meet its primary endpoint of SRI-4 response rate at 52 weeks (52.5% vs 44.6%, $p = 0.26$). Nevertheless, in patients with anti-dsDNA Ab positivity, Lupuzor demonstrated numerical superiority over placebo in achieving SRI-4 response (61.5% vs 47.3%, $p = 0.0967$) and full remission (7.6% vs 0%). However, the interpretation of these results is limited as they have not been subject of a peer-review in a scientific publication. The same applies for another phase III trial (NCT01240694) evaluating Lupuzor long-term safety and tolerability, which was terminated due to business decision, not for safety issues, and the results are posted in clinicaltrials.gov. From the 136 patients analyzed over the period of 64 weeks, 86.0% presented adverse events, while 100% received concomitant medications which were the two co-primary outcomes of the study. Another phase III trial (NCT03427151, IP-006) conducted evaluating the safety and efficacy of Lupuzor 200 mg every four weeks in the timeframe of seven months, but the results have not been published to date.

Cenerimod is a potent oral selective sphingosine 1-phosphate (S1P) receptor 1 modulator, a G protein-coupled receptor, resulting in inhibition of lymphocyte migration from the lymphoid organs to the inflammation site. In a phase I/II trial in SLE Cenerimod administration for 12 weeks reduced significantly the circulating lymphocytes in a dose-dependent manner. Further analysis revealed that 4 mg resulted in reduction in the modified SLEDAI-2 K score which excluded lymphopenia (4 mg: −2.420, $p = 0.0306$), in the anti-dsDNA Abs levels (4 mg: −64.55 U/mL, $p = 0.0082$) as well as the mucocutaneous SLEDAI-2 K subscore [231]. Compared to other SIP modulators, Cenerimod exhibits a moderate first-dose decrease in heart rate, a slow accumulation which leads to a gradual desensitization without the need for uptitration. However, cardiac abnormalities should still be considered before imitating the agent. A phase IIb study (NCT03742037) evaluated the efficacy and safety of Cenerimod with primary outcome the change in the modified SLEDAI-2 K score after 6 months of treatment. The results of this trial are awaiting publication while two phase III trials, the OPUS-1 and OPUS-2 (NCT05672576, NCT05648500) are currently recruiting to evaluate Cenerimod in SLE with primary outcome the modified SLEDAI-2 K change in 12 months.

Mesenchymal stem cells have immunomodulatory effects in a range of cells, including B cells, T cells dendritic and NK cells [232]. While the mechanism by which MSCs exert their effects in SLE is not fully understood, it has been shown that in patients with SLE the allogeneic mesenchymal stem cells (MSCs) inhibit T cell proliferation. Specifically, the high levels of IFN-γ that are produced particularly by CD8+ T cells, stimulate the MSCs to secrete indoleamine 2,3-dioxygenase (IDO), which inhibits the T cell proliferation through the IFNGR1/JAK-2/STAT signaling pathways. Notably, bone marrow MSCs from patients with SLE presented defective IFN-γ driven IDO production and allogeneic CD8+ T cell stimulation, suggesting that the transplantation of allogenic rather than to autologous MSCs, may be more suitable for treating SLE [233]. A phase I/II study evaluated the administration of two IV infusions of umbilical cord-derived MSCs at a 7-day interval in patients with active refractory SLE ($n = 45$). The treatment was well tolerated and resulted in satisfactory clinical response, but several patients after 6 months had a relapse, suggesting the need for repeated MSC infusions [233]. Another phase I open label study evaluated umbilical cord derived MSCs in refractory SLE showing tolerability and suggesting that they may also be efficacious [234]. However, in a placebo-controlled double-blind phase II trial in LN ($n = 18$) the allogenic umbilical MSCs did not differ from placebo in renal efficacy, and the trial was abandoned [235]. Despite the setbacks, phase I and II trials are registered to evaluate the safety and/or efficacy of MSCs in SLE (NCT05018858, NCT02633163, NCT03562065, NCT04835883) and LN (NCT03917797, NCT03580291, NCT03673748). Finally, a phase III trial (NCT05631717) is comparing low dose IL-2 to allogenic human umbilical cord MSCs in LN.

One other mechanism that has drawn a lot of attention for the treatment of LN in particular, is the inhibition of complement activation. Following deposition of immune complexes, the complement cascade is activated primarily through the classical and leptin pathways. This activation contributes directly and indirectly through chemotaxis to the damage of target-organs in SLE. Ravulizumab, a monoclonal antibody against complement C5 already approved for Myasthenia Gravis, Paroxysmal Nocturnal Hemoglobinuria and Atypical Hemolytic Uremic Syndrome [236], is currently being evaluated in a proof-of-concept study in patients with LN and IgA nephropathy (NCT04564339). Similarly, ALXN2050 or Vemircopan, an oral factor D inhibitor is evaluated in a phase II trial of patients with proliferative LN or IgA nephropathy (NCT05097989). These agents promise to improve outcomes in LN and to limit the reliance on corticosteroids similar to the successful use of the C5a receptor inhibitor Avacopan in ANCA associated vasculitis [237].

8. Conclusion

Recent positive developments in lupus therapeutics include the approval of Belimumab and Voclosporine for LN, and Anifrolumab for SLE. While these agents are gradually being incorporated into the standard of treatment paradigm, they have shown efficacy in different areas and should be considered accordingly: Anifrolumab has specifically demonstrated efficacy in managing cutaneous manifestations while also sparing the use of steroids; Belimumab has shown promise in preventing future disease flares and improve LN outcomes; and Voclosporin has shown efficacy in addressing LN. A wide range of agents is currently under evaluation for potential use in SLE, including the promising B cell targeting drug Telitacicept, which has shown positive results in a phase III trial and received fast track designation from the FDA (see Table 1 and Fig. 1). However, despite these important advancements, the need for further development of treatments that can prevent long-term damage and reduce overreliance on corticosteroids remains.

CRediT authorship contribution statement

Eleni Papachristodoulou: Writing – review & editing, Writing – original draft. **Vasileios C. Kyttaris:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Data curation.

Data availability

No data was used for the research described in the article.

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