ImmunoTargets and Therapy

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REVIEW

Immunotargets and Therapy for Systemic Lupus Erythematosus

Chi Chiu Mok

Department of Medicine and Geriatrics, Tuen Mun Hospital, Hong Kong

Correspondence: Chi Chiu Mok, Department of Medicine & Geriatrics, Tuen Mun Hospital, Tsing Chung Koon Road, New Territories, Hong Kong, SAR, People's Republic of China, Tel +85224685386, Fax +852245691100, Email ccmok2005@yahoo.com

Abstract: The pathophysiology of systemic lupus erythematosus (SLE) is complex and involves most cell types of the innate and adaptive immune system. Impaired clearance of apoptotic bodies and self-antigens, dysregulated cytokine network and aberrated functions of the immune cells lead to overproduction of autoantibodies, activation of complements, immune complex deposition and tissue injury. Novel biological and newer generation immunosuppressive agents have been developed to target the B cells, T cells, T/B cell interaction, plasmacytoid dendritic cells and the cytokines. With the advances in the knowledge about the intracellular pathways, small molecules that inhibit the downstream signal transduction from surface receptors and intracellular protein degradation by the ubiquitin-proteasome system are being developed in the pipeline. This article summarizes the evidence of various immunotargets for the treatment of SLE. These novel agents target specific cellular mechanisms, and further works are necessary to stratify patients according to biomarkers to receive individualized therapies that could help maximize the clinical response. With the availability of more therapeutic choices, a combination approach to achieve synergistic effects while reducing adverse events by dosage reduction of individual drugs is being explored for SLE patients at risk of disease progression or refractory to conventional therapies.

Keywords: target, immune, therapeutics, novel, biologics, small molecules, lupus

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that predominantly affects women in their childbearing age. The illness is characterized by periods of quiescence and flares, which are notoriously unpredictable The onset of SLE cannot be prevented and there is no cure. Despite the availability of new drugs and improvement in adjunctive therapies, the survival of SLE patients fails to improve further after the mid-1990s'.[1] Conventional immunomodulatory drugs, except for hydroxychloroquine, have not been shown to confer survival benefit in SLE,[2] probably related to their adverse effects, such as infective complications, which still account for more than 50% of the mortality in more recent cohorts of SLE patients.[3] This calls for the development of novel therapeutic approaches with a better efficacy-to-toxicity balance.[4]

The pathogenesis of SLE remains obscure.[5] A plethora of genetic, epigenetic and environmental factors, including infective agents, hormonal factors and ultraviolet light, are involved and lead to dysregulation of the innate and adaptive immune responses.[6] Genome- wide association studies (GWAS) have identified more than 200 risk loci in SLE,[7] many of which are related to antigen presentation, immune regulation and interferon (IFN) signalling.[8] Abnormal epigenetic mechanisms such as DNA methylation, histone modification, noncoding RNAs and RNA methylation also contribute to the modification of gene expression.[9] Pathological processes that are probably involved in the initiation and perpetuation of the immune perturbations in SLE include: (1) loss of self-tolerance and generation of autoreactive B cells and T cells, leading to the production of antinuclear (ANA) and other autoantibodies[10] (2) defective clearance of apoptotic materials, nuclear antigens, nucleosomes and immune complexes (ICs) by macrophages and complements[6,11,12] (3) impaired neutrophil apoptosis and degradation of DNA, histones, cytoplasmic granules and other mediators inside the neutrophil extracellular traps (NETs).[13–16] These antigens activate the plasmacytoid dendritic cells (pDCs) via the toll-like receptors (TLR7/9) to produce type I interferons (IFNs) and interleukin (IL)-6, which in turn accelerate monocyte maturation,

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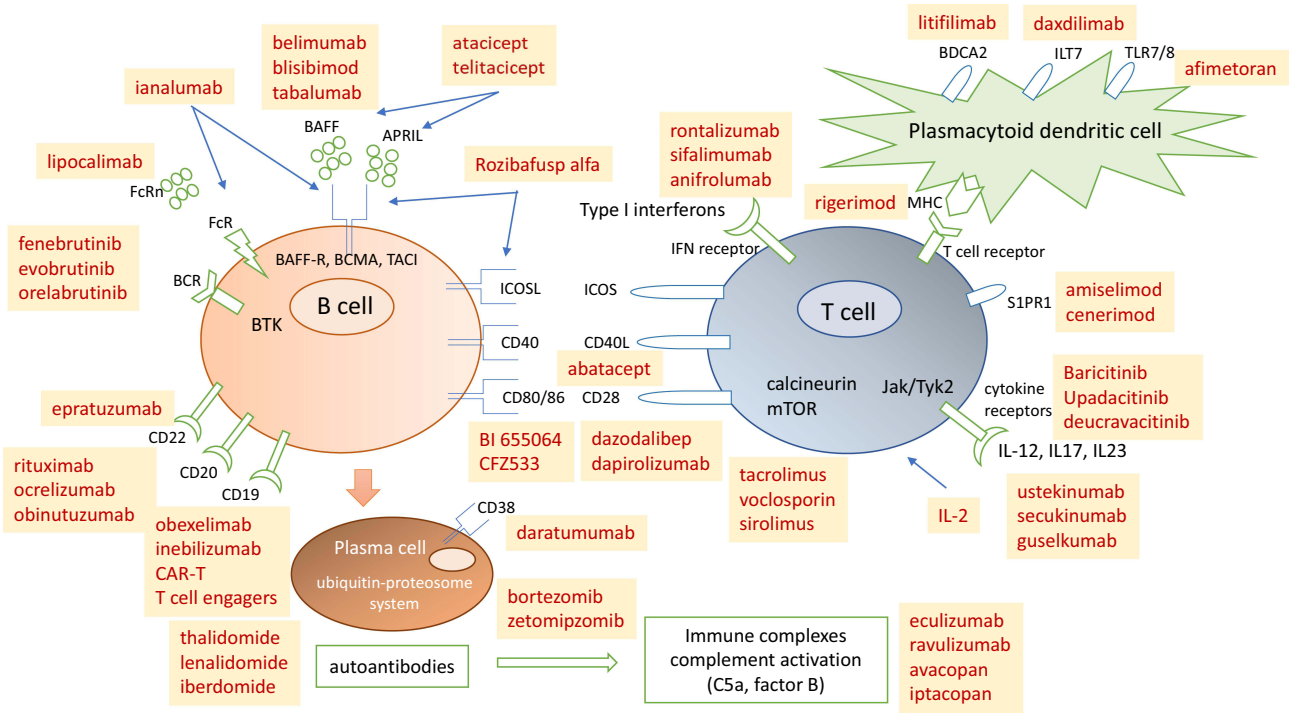

Figure 1 Immune targets of SLE therapies: (1) B cells (CD19, CD20, CD22, BAFF, April, BAFF receptors [BAFF-R, BCMA, TACI], BCR, BTK, FcR, FcRn, ICOSL, CD40, CD80/86); (2) Plasma cells (immunoproteasomes, CD38, CAR-T, T cell engagers); (3) T cells (CD40L, CD28, calcineurin, mTOR, JAK/TYK-2, S1PR1, TCR, low-dose IL-2); (4) plasmacytoid dendritic cells (BDCA2, ILT7, TLR7/8); (5) cytokines (IFN, IL-12, IL-17, IL-23); and (6) complements (C5a, factor B).

Abbreviations: BAFF, B cell activation factor; APRIL, a proliferation-inducing ligand; BCMA, B-cell maturation antigen; TACI, transmembrane activator and CAML interactor; BCR, B cell receptor; BTK, Bruton's tyrosine kinase; FcR, Fc receptor; FcRn, neonatal Fc receptor; ICOSL, inducible T cell costimulator ligand; CAR-T, chimeric antigen receptor T-cell immunotherapy; mTOR, mammalian target of rapamycin; JAK, Janus kinase; TYK2, tyrosine kinase 2; S1PR1, sphingosine-1-phosphate receptor 1; TCR, T cell receptor; IL, interleukin; BDCA2, blood dendritic cell antigen 2; ILT7, immunoglobulin-like transcript 7; TLR, toll-like receptor; IFN, interferon.

inhibit T cell apoptosis, increase proliferation and autoantibody production by B cells.[10,12] Increased activity of the myeloid dendritic cells[17] and defective functions of the regulatory B (Bregs) and T cells (Tregs)[18–20] polarizes the T cells to differentiate into the proinflammatory phenotypes (Th1/Th17). The augmented autoantibody production and IC formation mediates tissue inflammation and organ damage in patients with SLE.

Despite the negative results from multiple clinical trials of SLE drugs, newer biologic and targeted small molecules continue to emerge from the pipeline[21] (Table 1). This article reviews the various immune targets for novel SLE therapies (Figure 1).

Table 1 Immunotargets and Therapy of Systemic Lupus Erythematosus

Targets	Agents	Stage of Development	Results	Targets	Agents	Stage of Development	Results
B Cells				**T Cells**			
CD20	Rituximab	P3	N	calcineurin	Tacrolimus	P3; P4	P
	Ocrelizumab	P3	T (safety)		Voclosporin	P3	P
	Obinutuzumab	P3	P	mTOR	Sirolimus	P2	P
CD22	Epratuzumab	P3	N	CTLA-4	Abatacept	P2	N
CD19	Obexelimab	P2	N	CD40L	Dapirolizumab	P2	N

(*Continued*)

Table 1 (Continued).

Targets	Agents	Stage of Development	Results	Targets	Agents	Stage of Development	Results
	Inebilizumab	P1/2	-	**Dendritic cells**			
CD3/BCMA	Teclistamab	Case report	P	BDCA2	Litifilimab	P2	P
CD3/CD19	Blinatumomab	P1/2	-	ILT7	Daxdilimab	P2 (CLE)	In progress
	CAR-T	Case series	P	TLR7/8	Afimetoran	P2	P
Proteasomes	Bortezomib	Case series	P but toxic	**Cytokines**			
	Zetomipzomib	P2	T (safety)	Type I IFNs	Rontalizumab	P2	N
Celebron E3 ligase	Thalidomide; Lenalidomide	Case series	P but toxic		Sifalimumab	P2	P
	Iberdomide	P2, including CLE	P		Anifrolumab	P3	P (licensed for non-renal SLE)
CD38	Daratumumab	Case series	P		IFN-kinoid	P2	P
	Felzartamab	P1	-	IL-6	Tocilizumab	P1	P (safety)
BAFF	Belimumab	P3; P4	Approved for SLE/LN		Sirukumab	P2	N
	Tabalumab	P3	N	IL12/23	Ustekinumab	P3	T (futility)
	Blisibimod	P3	N	IL23	Guselkumab	P2	N
BAFF/APRIL	Atacicept	P3	T (safety)	Low-dose IL-2	Efavaleukin alpha	P2	T (futility)
	Telitacicept	P2/3	P (licensed in China)	JAK	Baricitinib	P3	N
BAFF + CD20	Belimumab/ Rituximab	P2; P3	N		Upadacitinib	P2	P
Dual mechanism anti-BAFF	Ianalumab	P3	In progress		Deucravacitinib	P2	P
	Rozibafusp	P2	T (futility)		Deucravacitinib	P3	In progress
BTK	Evobrutinib	P2	N	**Complements**			
	Fenebrutinib	P2	N	C5	Eculizumab	P12	P (safety)
	Orelabrutinib	P2 (in China)	P	C5aR	Avacopan	-	-
FcRn	Lipocalimab	P2	-	Factor B	Iptacopan	P2	Registered
				Other targets			
				S1PR1	Amiselimod	P1	P (safety)
					Cenerimod	P2	N
					Cenerimod	P3	In progress
				Synthetic peptides	Abetimus sodium	P3	N
					Edratide	P2	T (futility)
					Rigerimod	P3	N

(*Continued*)

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Table 1 (Continued).

Targets	Agents	Stage of Development	Results	Targets	Agents	Stage of Development	Results
					Laquinimod	P2	P
				PML/RAR-alpha	Arsenic trioxide	P2	P

Abbreviations: P1, phase I study; P2, phase II study; P3, phase III study; P4, phase IV study; P, positive results; N, negative results; T, termination (premature); BCMA, B-cell maturation antigen; BAFF, B cell activating factor; APRIL, a proliferation-inducing ligand; BTK, Bruton's tyrosine kinase; FcRn, neonatal Fc receptor; mTOR, mammalian target of rapamycin; BDCA2, blood dendritic cell antigen-2; ILT7, immunoglobulin-like transcript 7; TLR, toll-like receptor; IFN, interferon; IFN, interferon; JAK, Janus kinase; S1PR1, Sphingosine 1-phosphate receptor 1; PML, promyelocytic leukemia; RAR-alpha, retinoic acid receptor alpha; CLE, cutaneous lupus erythematosus.

Targeting the B Cells

B cells are central in the pathophysiology of SLE because they produce pathogenic antibodies. In addition, they are capable of presenting self-antigens to activate the autoreactive T cells[22,23] and produce cytokines that amplify the inflammatory response.[20] A subset of IL-10 secreting Bregs that suppresses the inflammatory response are altered in SLE, which is coupled with an expansion of transitional B cells which are dependent on B cell activating factor (BAFF) for maturation and a subpopulation of autoreactive age-associated B cells (ABCs).[23,24]

B cells can be targeted by direct depletion with monoclonal antibodies (anti-CD19, anti-CD20), engineered T cells (Chimeric Antigen Receptor T cells [CAR-T]) and dual action monoclonal antibodies, or indirect modulation via inhibition of growth factors (eg BAFF), costimulatory molecules and intracellular signalling pathways (eg Bruton's tyrosine kinase [BTK]).[25]

B-Cell Depletion

Anti-CD20

The chimeric anti-CD20 monoclonal antibody, rituximab, was first studied in SLE. In the pivotal randomized controlled trial (RCT) of active non-renal SLE, two courses of rituximab (1gm for 2 doses) on background standard of care (SOC) did not report benefit in disease activity reduction at week 52 compared with placebo (PBO).[26] Another RCT (LUNAR) of rituximab in lupus nephritis (LN) also failed to meet its primary end point of renal response at week 52 when added to glucocorticoid (GC) and mycophenolate mofetil (MMF).[27] While rituximab was more effective than PBO in improving anti-dsDNA and complement levels, neutropenia, leukopenia, hypotension, infusion reactions, herpes zoster, and opportunistic infections were more common. Despite the futility of these RCTs, rituximab continued to be used off-label to treat refractory SLE and LN, with clinical responses reported in 67–86% of patients.[28]

Ocrelizumab is a fully humanized anti-CD20 biologic that was subsequently studied in SLE.[29,30] In two RCTs of non-renal SLE and LN, patients were randomly assigned to receive two courses of ocrelizumab (400 mg or 1000 mg for 2 doses 2-weekly and after 4 months) or PBO. Patients in the LN trial received the SOC with GC combined with either MMF (3g/day) or low-dose cyclophosphamide (CYC) followed by azathioprine (AZA). Both studies were terminated prematurely because of severe serious infections. An analysis of the data from patients who received study drug for ≥32 weeks showed that the overall renal response rate of the combined ocrelizumab groups was non-significantly higher than that of PBO.[30] The effect size was higher with ocrelizumab combining with CYC than MMF whereas serious infections were more common in the MMF/ocrelizumab group.

As the serious infections in the ocrelizumab studies were potentially related to the protocol-based high-dose of MMF being used in Asian patients, subsequent RCTs of anti-CD20 biologics in SLE adopted a lower dose of MMF and less intense background immunosuppression.[31] Obinutuzumab is a recombinant humanized type II anti-CD20 monoclonal antibody that is glyco-engineered for greater affinity for the FcγRIII on effector cells, leading to enhanced antibody dependent cellular cytotoxicity (ADCC), direct B-cell killing, and less reliance on complement dependent cytotoxicity (CDC).[32] Obinutuzumab is more effective than rituximab in depleting B cells and ameliorating LN in the lupus mice.[33]

A Phase II RCT (NOBILITY) of 125 patients with active proliferative LN who were receiving a SOC of GC and MMF showed that the complete renal response (CRR) rate at week 52 through week 104 in the obinutuzumab arm was superior to PBO.[31] Obinutuzumab was not associated with an increase in serious adverse events (SAEs), serious infections or deaths. Post-hoc analyses demonstrated that the anti-CD20 agent reduced the incidence of LN flares, first estimated glomerular filtration rate (eGFR) decline by 30% or 40%, and a composite outcome of treatment failure, doubling of serum creatinine, or death.[34] The Phase III RCT of obinutuzumab in 271 patients with active LN (REGENCY) confirmed its efficacy compared to PBO, in conjunction with GC and MMF, at week 76 in terms of CRR or CRR together with a maintenance prednisone dose of ≤7.5mg/day.[35] Despite the absence of unexpected safety signals, SAEs and infections were more frequent in obinutuzumab-treated patients. Greater adjusted between-group differences in the rate of CRR were observed in those patients with higher serological SLE activity, uP/Cr>3.0 and histological class IV±V disease.

A GC-free regimen consisting of rituximab (1 gram for 2 doses) and MMF (dosage adjusted by drug level) has been explored in a single arm prospective study of 50 patients with LN.[36] Complete or partial renal response was reported in 90% of patients treated with this regimen (RITUXILUP regimen) without concomitant oral prednisone over a median time of 37 weeks. As a planned RCT of this regimen was aborted (NCT01773616), it is hoped that the ongoing RCT of obinutuzumab/MMF versus GC/MMF in LN (OBILUP; NCT04702256) would provide new insights on the efficacy of this GC-free regimen in LN.

Anti-CD22

Epratuzumab is a human monoclonal antibody that targets the CD22 antigen on mature B cells, which is involved in the modulation of B-cell receptor (BCR) signalling, cellular activation and survival.[37] Compared to CD20, CD22 blockade is less cytotoxic. Epratuzumab diminished B cell proliferation, migration and production of inflammatory cytokines.[38] Early clinical trials showed that epratuzumab induced a modest depletion of peripheral B cells without significant effects on T cells, autoantibody or immunoglobulin levels.[39,40] Following a phase IIb PBO-controlled RCT of epratuzumab (ENBLEM) demonstrating safety and preliminary efficacy in SLE,[41,42] two subsequent phase III RCTs were conducted (EMBODY 1/2).[43] Unfortunately, the primary clinical improvement end point, BILAG-based combined lupus assessment [BICLA] at week 48, was not met, although adverse events (AEs) and treatment-emergent AEs (TEAEs) were not increased with treatment.

Anti-CD19 and T-Cell Engagers

Obexelimab is dual function, non-cytolytic monoclonal antibody that binds to CD19 and FcγRIIb to inhibit B cells and plasmablasts.[44] A phase II PBO-controlled RCT of obexelimab in 104 SLE patients with non-organ-threatening manifestations did not meet the primary end point of reaching week 32 without loss of improvement, although the time to this end point was prolonged with obexelimab compared to PBO.[45] B cells decreased by approximately 50% after anti-CD19 treatment and the presence of gene expression clusters with high B cell pathway modules were associated with longer time to loss of improvement. Another anti-CD19 monoclonal, inebilizumab, approved for treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients, is registered for a study in refractory SLE (NCT06570798).

The anti-CD3/anti-CD19 bispecific T cell engager (BiTE), blinatumomab, instigates CD3-positive T cells to target CD19-positive B cells,[46] leading to B cell elimination and concomitant reduction of T cells. Blinatumomab is effective against acute lymphoblastic leukemia and other B cell malignancies. As the drug targets both malignant and non-malignant lymphocytes, it may potentially cause the cytokine release syndrome and neurotoxicity similar to CAR-T therapy. Blinatumomab has been shown to be effective in refractory rheumatoid arthritis[47] and systemic sclerosis.[48] As the effect of blinatumomab mimics CAR-T but does not require preconditioning with lymphodepletion and chemotherapy, it is a more acceptable option in younger SLE patients.[49] Two studies of blinatumomab in refractory SLE have been registered (NCT06789107 and NCT06570798).

Teclistamab is a CD3/B-cell maturation antigen (BCMA) BiTE that is used to treat refractory myeloma.[50] Unlike CD3/CD19 BiTE, it has a capacity to deplete the long-lived plasma cells. Successful use of teclistamab has been reported

in a patient with refractory SLE.[51] Teclistamab led to a rapid depletion of peripheral-blood B cells by week 1 and eradication of marrow B cells and plasma cells by week 8. However, no clinical trials in SLE have been registered yet.

Car-t

CAR-T therapy involves the use of engineered T cells to target CD19 on B cells or BCMA on myeloma cells.[25,52] CAR-T depletes B cells profoundly, including the memory B cells, plasmablasts and plasma cells. Pilot studies of CD19-targeted CAR-T therapy showed good response in patients with severe or refractory SLE.[53] However, the procedure involves pre-conditioning with cyclophosphamide and fludarabine, which is undesirable for fertility and oncogenicity reasons. Moreover, it carries the risk of cytokine release and immune effector cell-associated neurotoxicity syndromes. Publication bias, relatively small number of SLE patients treated with CAR-T, lack of long-term data on safety and efficacy, and the general unavailability of this procedure are the major limitations of CAR-T in SLE.[5]

Long-Lived Plasma Cells

Long-lived plasma cells are capable of generating autoreactive immunologic memory and autoantibodies that are relevant for the pathogenesis of SLE.[54] In contrast to short-lived plasmablasts, they are resistant to conventional immunosuppressive and B cell depletion therapies because of the lack of CD19 and CD20 expression.[55] However, these plasma cells have upregulation of the autophagy pathways and the unfolded protein response, leading to the susceptibility to proteasome inhibition.[25] Targeting the immunoproteasomes and the cereblon E3 ligase in the ubiquitin-proteasome system (UPS), which is a major pathway for intracellular protein degradation, is a novel therapeutic approach in SLE.[56,57]

Bortezomib is a non-selective inhibitor of both the constitutive and immune proteasomes. Case series have reported efficacy of bortezomib in conjunction with GCs for the treatment of refractory SLE manifestations, including LN.[58–62] Bortezomib depleted both short-lived and long-lived plasma cells in the peripheral blood and bone marrow, which was associated with improvement of anti-dsDNA level and proteinuria in LN.[58,60–62] However, the drug is limited by gastrointestinal toxicities, peripheral neuropathy and drug resistance on prolonged use.[63]

Zetomipzomib is a highly selective immunoproteasome inhibitor with enhanced safety.[64] A phase Ib/II open study in 33 patients with active SLE despite stable background immunosuppression showed that subcutaneous zetomipzomib for 13 weeks improved disease activity, which was maintained for 12 weeks in 94% patients.[65] The drug was well tolerated and no neuropathy, prolonged gastrointestinal AEs were reported. Patients with LN recruited in this study also showed improvement in proteinuria after treatment for 24 weeks.[66] Unfortunately, a PBO-controlled phase IIb RCT (NCT05781750) to evaluate the efficacy and safety of zetomipzomib with SOC in LN was prematurely terminated for safety signals.

The protein cereblon is a substrate receptor of the cullin-ring ligase-4 E3 ubiquitin ligase complex, which tags polyubiquitin chains to degrade neo-substrate proteins that are disease promoting, such as transcription factors and tumor promoting proteins.[67] Cereblon E3 ligase modulators (CELMoDs) such as thalidomide, lenalidomide and pomalidomide synergize with the UPS to degrade Ikaros and Aiolos, which are transcriptional factors that regulate differentiation of lymphocytes, plasma cells and pDCs.[57,68] Moreover, as Ikaros and Aiolos are transcriptional suppressors of IL-2, their degradation leads to enhanced IL-2 and NK cell activity.[69]

Thalidomide and lenalidomide have been used to treat refractory cutaneous lupus erythematosus (CLE), particularly subacute and chronic lesions.[70] Most published studies were small, retrospective and uncontrolled.[70–75] Moreover, thalidomide is limited by its poor intestinal absorption and the risk of peripheral polyneuropathy, which was reported in 15–80% of patients with no clear dose relationship.[70] Lenalidomide appeared to be less neurotoxic, but disease flares were common after drug discontinuation. Teratogenicity, potential cardiovascular AEs and thromboembolism,[76] are major deterrent of CELMoD use in SLE.

Iberdomide is a high affinity CELMoD. In a phase IIb RCT,[77] iberdomide treatment for 24 weeks in SLE patients significantly reduced the number of peripheral B cells and pDCs but increased Tregs and IL-2 production in a dose-dependent manner.[78] However, reduction in type I IFN gene signature occurred only in patients with high expression at

baseline. These findings are consistent with the known immunomodulatory effects of iberdomide through enhanced degradation of Ikaros and Aiolos.

In a phase IIa PBO-controlled dose-escalating RCT of iberdomide in 42 patients with active SLE,[79] improvement in physicians' global assessment (PGA) and Cutaneous Lupus Area and Severity Index Activity (CLASI-A) scores were observed with treatment. Safety was established and a subsequent phase II RCT of 288 active SLE patients confirmed efficacy of iberdomide 0.45mg compared to PBO in terms of SRI-4 response at week 24.[80] Subgroup analyses revealed higher effectiveness in patients with baseline SLEDAI ≥10, high Aiolos and IFN gene signature.[78,80] However, meaningful differences in most secondary end points, including CLASI-A score and joint counts, were not observed between iberdomide and PBO. AEs and SAEs were non-significantly higher in iberdomide-treated patients, with neutropenia and infections being the commonest. No peripheral neuropathy was reported. In patients with active CLE who participated in the above RCT,[80] significantly more iberdomide-treated (0.45mg) patients achieved ≥50% CLASI-A improvement from baseline to week 24 compared with PBO for subacute and chronic but not acute CLE lesions.[81] Further clinical trials are necessary to confirm the efficacy of iberdomide in SLE, particularly for different subtypes of CLE.

There are alternative ways of targeting the plasma cells. Daratumumab is a monoclonal antibody that binds to CD38 expressed on plasma cells and plasmablasts. It depletes plasma cells and is approved for upfront combination therapy of myeloma.[82] Successful treatment of refractory SLE by daratumumab has been reported.[83,84] However, there are no controlled trials in SLE yet. Felzartamab is another anti-CD38 monoclonal antibody that is being studied in primary membranous nephropathy.[85] A phase Ib study of felzartamab in LN has been registered (NCT06064929).

Targeting B-Cell Growth Factor

BAFF Inhibition

BAFF binds to three receptors on B cell surface, namely transmembrane activator and calcium modulator ligand interactor (TACI), BCMA and BAFF-R, which is essential for B cell maturation, survival, proliferation and immunoglobulin class switching.[86] BAFF mRNA and serum levels were elevated in SLE and correlated with disease activity.[87,88] APRIL (a proliferation-inducing ligand), a homolog of BAFF, is also important factor for survival and activation of B cells.[89] APRIL binds to TACI and BCMA receptors with a higher affinity than BAFF. Inhibition of the BAFF and/or APRIL promotes apoptosis and prevents maturation of the B cells.[90]

Belimumab is a monoclonal antibody against BAFF that is approved for the treatment of SLE and LN. Pivotal RCTs in non-renal SLE confirmed benefit of belimumab when added to SOC in achieving the SRI-4 response.[91–94] Extension of the BLISS-52 and BLISS-72 RCTs[91,92] for up to 8 years showed sustained efficacy of belimumab and stable organ damage score in 88% of these patients.[95] Pooled data from RCTs confirmed superiority of belimumab to PBO when combined with SOC in the treatment of SLE[96] and a GC-sparing effect.[97] However, the efficacy of belimumab in reducing renal flare in patients treated for extra-renal activity appeared to be dependent on concomitant anti-malarial therapy.[98] For the treatment of LN, a large RCT reported significantly higher rate of primary end point renal response (PERR) when belimumab was combined to the SOC of either MMF or low-dose CYC when compared to PBO.[99] Efficacy was consistent in the Asian subpopulation[100] and across patients with newly diagnosed or relapsed LN.[101] Open-label extension of this study for 28 weeks showed maintenance of the treatment response without new safety signals.[102] A secondary analysis of the BLISS-LN trial showed that belimumab significantly reduced the risk of kidney-related events or death, renal flares and a sustained 30% or 40% decline in eGFR versus SOC alone.[103] However, kidney response to belimumab was not observed in patients with sub-epithelial deposits or a baseline uP/Cr of ≥3.0.

Tabalumab is a human monoclonal antibody against both soluble and membrane-bound BAFF.[104] Two identical PBO-controlled phase III RCTs of tabalumab in SLE with moderate to severe activity were conducted.[105,106] In the ILLUMINATE-1 study, the primary end point (SRI-5 rate) was not met at week 52, although significant improvement in anti-dsDNA and complements, reduction in total B cells, immunoglobulins and BAFF levels were achieved with tabalumab treatment.[105] In ILLUMINATE-2 study, the primary end point (SRI-5 at week 52) was met in the 120 mg (every 2 week) tabalumab arm.[106] In both RCTs, none of the secondary end points, which included time to first severe SLE flare and GC-sparing effect, supported efficacy of tabalumab. SAEs, TEAEs and

mortality were not increased across the tabalumab arms, although depression and suicidal ideation was more common. A pooling of data of the two RCTs did not reveal significant benefit of tabalumab on various renal parameters.[107] Although the primary end point could have been met if SRI-4 had been used, further development of the drug was not pursued.

Blisibimod is a fusion protein comprising four BAFF binding domains linked to the N-terminus of the fragment crystallizable region (Fc) of a human antibody.[108] Following a phase II RCT showing efficacy of blisibimod at week 24 in terms of the SRI-5 response and a significant improvement in SLE serology and reduction in B cell count,[109] a phase III PBO-controlled RCT were performed (CHABLIS-SC1).[110] This study recruited 442 SLE patients with high disease activity despite GCs and SOC. Unfortunately, the primary outcome, SRI-6 response at week 52, was not met. Exploratory end points that included SRI-4 and SRI-8 were also not significantly different between the blisibimod and PBO arms, including AEs and SAEs.

Atacicept (TACI-Ig) is a fusion protein that blocks the activity of both BAFF (soluble and membrane-bound) and APRIL.[111] Atacicept treatment in SLE patients reduced peripheral mature B cells and immunoglobulin levels in a dose-dependent manner.[112] A phase II/III PBO-controlled RCT of atacicept in patients with active LN was prematurely terminated for safety concerns.[113] Another 52-week phase II/III PBO-controlled RCT of atacicept in 461 patients with active SLE did not meet the primary outcome of reduction in the incidence of a new BILAG A or B flare.[114] The atacicept 150 mg arm was terminated prematurely because of increased serious infections. Atacicept reduced immunoglobulin levels and improved lupus serology. Patients with elevated serum levels of BAFF and APRIL showed a greater response in the reduction of SLE flares.[115] Another 24-week phase IIb PBO-controlled RCT (ADDRESS II) involving 306 active SLE patients was repeated and did not show an increased incidence of TEAEs or SAEs as compared to PBO.[116] Although the primary end point (SRI-4 at week 24) was not met, subgroups of patients with higher disease activity at baseline showed a significantly higher SRI-4 rates than PBO. However, further studies of atacicept were not pursued.

Telitacicept is another fusion protein that inhibits the binding of BAFF and APRIL to the TACI receptor.[117] A multicenter phase II RCT involving 249 patients with active SLE conducted in China met the primary end point of having a significantly higher SRI-4 response at week 48 in all the 3 doses of telitacicept studied as compared to PBO. The drug was well tolerated with no increase in the incidence of AEs or SAEs.[118] Telitacicept is currently licensed for SLE treatment in mainland China.

Anti-BAFF/Anti-CD20 Combination

The rebound increase in serum BAFF level after B cell depletion promotes reconstitution of autoreactive B cells that may be associated with SLE flares.[119] Administration of a BAFF inhibitor after anti-CD20 therapy may retard full B-cell repopulation and production of SLE-specific autoantibodies.[120] A phase II open RCT (CALIBRATE) of 43 patients with recurrent or refractory LN showed that the addition of belimumab to the background GC/CYC/rituximab regimen caused a greater reduction in autoreactive naive B cells from baseline to week 48 compared to the no belimumab group without increasing AEs.[121] However, the renal response rates were not significantly improved with belimumab/rituximab combination. Another phase II PBO-controlled RCT (Beat-Lupus) confirmed safety of rituximab and belimumab combination in 52 patients with refractory SLE manifestations (38% with LN).[122] Belimumab-rituximab combination resulted in greater suppression of B-cell repopulation, anti-dsDNA levels, and reduced frequency of severe flares at week 52 compared to PBO.

In a more recent RCT (BLISS-BELIEVE) which recruited 263 patients with active SLE, combining rituximab with a background of SC belimumab while stopping concomitant immunosuppression led to a more profound drop in most B cell subsets, including memory B cells, and anti-dsDNA levels compared to PBO at week 52.[123] However, there was no significant difference between the combination group and the belimumab only group in the proportion of patients who achieved disease control at this time point, defined as a SLEDAI-2K ≤ 2 without immunosuppressants and a prednisone-equivalent dose of ≤ 5 mg/day. Of concern was an increased incidence of serious infections in the biologic combination group.

As the efficacy and safety of rituximab/belimumab combination is conflicting, further works are needed to re-evaluate this approach in different patient subgroups. A phase III open-label 2-year RCT (Synbiose-2) of rituximab/belimumab in patients with severe SLE, including LN, is in progress (NCT03747159).

Dual Mechanism Anti-BAFF

Ianalumab (VAY-736) is a human, decarboxylated antibody against the BAFF receptor (BAFF-R). It eliminates B cells via a dual mechanism of actions through enhancing ADCC and induction of B cell apoptosis via blockade of the BAFF/BAFF-R interaction.[124] A phase III PBO-controlled RCT of ianalumab in LN (SIRIUS-LN) is in progress (NCT05126277).

Rozibafusp alfa is a bispecific IgG2-peptide fusion designed to inhibit both BAFF and inducible T-cell costimulator ligand (ICOSL). A phase Ib RCT in rheumatoid arthritis showed safety and efficacy of rozibafusp as compared to PBO.[125] However, a phase IIb RCT in SLE was terminated because of futility of the interim results (NCT04058028).

Targeting B-Cell Signalling Pathway

The BTK is expressed in most hematopoietic cells, including the B cells and terminally differentiated plasma cells.[126] In B cells, BTK plays an essential role in the downstream signal pathways through the B-cell receptor[127] and enhances the sensitivity of the B cells to the toll-like TLR-mediated events that include cytokine and autoantibody production.[128] BTK expression was increased in peripheral blood mononuclear cells (PBMCs) of SLE patients and correlated with disease activity, including renal.[129] BTK inhibitors (BTKis) do not deplete B cells and the effects of BTK blockade in other immune cell types may enhance their therapeutic effects in SLE.

Evobrutinib, a highly selective oral BTKi, was studied in a phase II RCT of patients with active SLE despite SOC.[130] However, the study did not meet the primary end points of SRI-4 and SRI-6 at week 52 compared to PBO in the high disease activity subpopulation. No clinically meaningful differences in other secondary outcomes were observed either between evobrutinib and PBO, although the drug was well-tolerated. Another phase II dose-ranging study of fenebrutinib, a second-generation highly selective, reversible oral BTKi, was conducted in 260 SLE patients with moderate/severe activity who were receiving SOC.[131] Although fenebrutinib reduced the BTK-dependent plasmablast RNA signature, anti-dsDNA, and IgG/IgM levels relative to PBO, the proportion of patients who achieved the SRI-4 and BICLA responses was not significantly higher in the treatment groups at week 48. However, SAEs were numerically more common in BTKi users. Orelabrutinib is a highly selective, irreversible oral BTKi that has been studied in a phase Ib/II RCT of 60 SLE patients in China.[132] The primary outcome, SRI-4 response rate at week 12, was significantly higher in the treatment than PBO groups. Overall, AEs were mild to moderate and the majority of TEAEs were not severe. As the results of these three RCTs are discrepant, further phase III RCTs of the BTKis in SLE are needed.

Lipocalimab is a monoclonal antibody that binds with high affinity to block the neonatal Fc receptor (FcRn). It inhibits IgG recycling and reduces circulating IgG levels, including autoantibodies in a dose-dependent manner.[133] The biologic agent is being studied in primary Sjogren's syndrome (NCT04969812),[134] rheumatoid arthritis, autoimmune hemolytic anemia, myasthenia gravis,[135] chronic inflammatory demyelinating polyneuropathy and severe hemolytic disease of the fetus and newborn.[136] Two studies of lipocalimab in SLE and LN have been registered (NCT04882878; NCT04883619).

Targeting T Cells

Calcineurin Inhibitors

The calcineurin inhibitors (CNIs) block T-cell activation through suppression of the calcium/calmodulin-dependent phosphatase calcineurin.[137] Cyclosporin A (CSA) and tacrolimus (TAC) have long been used in the treatment of SLE and LN.[138,139] TAC is preferred to CSA for SLE treatment because of fewer cosmetic, hypertensive and dyslipidemic AEs. Recent RCTs have established non-inferiority of TAC to MMF or intravenous pulse CYC as initial therapy of LN in terms of renal response at 6 months.[140,141] Moreover, low-dose combination of TAC and MMF has been shown to be more effective than intravenous CYC as initial therapy of LN at 6 months.[142] Over 18 months, the rate of renal flares was similar between the MMF-TAC and CYC-AZA groups but the former was associated with a lower

withdrawal rate due to AEs.[143] Addition of low-dose TAC to background MMF has also been shown to be effective in reducing proteinuria in refractory LN.[144,145] TAC does not affect the cell counts and is relatively safe during pregnancy.[146] Although long-term data on CNI nephrotoxicity are awaiting, TAC is commonly used for initial or maintenance treatment of SLE and LN in Asian countries.[147,148] In the latest 2024 Asia Pacific League of Association for Rheumatology (APLAR) consensus, CNI is one of the first-line agents recommended for initial treatment of LN.[149]

Voclosporin is a chemical analog of CSA that has a stronger binding capacity to cyclophilin A, leading to a higher potency of calcineurin inhibition, faster elimination and less variability in plasma concentration.[150] A phase III PBO-controlled RCT of voclosporin in active LN showed efficacy of voclosporin in enhancing the CRR rate at week 52 when used in conjunction with MMF and GCs.[151] SAE, serious infection and mortality was not significantly different between the voclosporin and PBO groups of patients. The results of this RCT corroborates that of the multi-target regimen in China in which upfront combination of CNI (TAC) with MMF was more effective than CYC in LN.[142] While the cost-effectiveness of combined MMF and voclosporin for upfront combination therapy of LN has to be further evaluated,[152] it is recommended for patients at risk of renal progression,[149,153] including refractory and frequently relapsing disease. Moreover, the CNIs may be more effective in ameliorating LN patients with heavy proteinuria and/or podocytopathy in kidney biopsy.[154]

The mTOR Inhibitors

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that is essential for cell metabolism, growth and survival. Activation of the mTOR pathway in kidney tissues is reported in patients with active LN.[155] Inhibitors of mTOR, such as sirolimus and everolimus, are newer immunosuppressive agents that are used in kidney transplantation to prevent allograft rejection to facilitate sparing of the CNIs.[156] An open single-arm phase I/II study demonstrated efficacy of sirolimus in 40 patients with active SLE who were unresponsive or intolerant to SOC therapies in reducing disease activity and the dosage requirement of GCs at month 12.[157] Sirolimus was well tolerated, with only mild reduction in hemoglobin, neutrophil count and HDL-cholesterol level reported. Other case series of Caucasian and Asian patients with SLE also demonstrated efficacy and tolerability of sirolimus.[158,159] Meta-analysis of observational studies showed that sirolimus (1–3mg/day) treatment led to remission of SLE manifestations in 74% of patients.[160] Discontinuation of sirolimus occurred in 9.3% of patients due to reversible and mild AEs.

Inhibition of B/T Cell Co-Stimulation

Abatacept (CTLA4-Ig) is a recombinant fusion protein consisting of the extracellular domain of CTLA4 and a fragment of Fc domain of human IgG1. It binds to CD80 or CD86 with a higher affinity than CD28, thus hindering the co-stimulatory signal for T cell activation.[161] In a phase IIb exploratory RCT, 175 patients with active non-renal SLE were randomized to receive abatacept or PBO,[162] in addition to prednisone. The primary outcome of absence of new BILAG A or B flare at month 12 was not met, although treatment difference was greatest in patients with polyarthritis. Another PBO-controlled phase II/III multicenter RCT of abatacept in active proliferative LN on a background of GC and MMF also did not meet the primary end point of CRR at week 52.[163] In both RCTs, serious AEs and AEs such as herpes zoster and gastroenteritis, and withdrawal due to SAEs, were numerically more frequent in abatacept users. Another phase II RCT of active proliferative LN (ACCESS) also did not show benefit of abatacept over PBO in the CRR rate at week 24 when combined with prednisone and low-dose CYC as initial treatment.[164] However, the incidence of AEs and SAEs was not significantly increased with abatacept.

Interaction between CD40 ligand (CD40L or CD154) on activated T cells and CD40 on B cells is important for maintaining B cell functions such as B cell differentiation, germinal center formation, and antibody isotype switching.[165] Abnormal expression of CD40L in SLE patients might be associated with the generation of autoantibodies.[166,167] An anti-CD40L antibody, BG9588, has halted development because of increased risk of thromboembolism related to platelet activation.[168] Dapirolizumab pegol, a polyethylene glycol-conjugated antigen-binding (Fab0) fragment that lacks a functional Fc domain to reduce the risk of platelet activation, was developed to target the CD40L.[169] A phase IIb, PBO-

controlled RCT of dapirolizumab in 182 SLE patients moderate-to-severe disease activity (RISE)[170] did not meet the primary end point of a dose-responsive BICLA responder rates at week 24, although the drug was well tolerated.

Targeting Dendritic Cells

The pDCs are the main producers of type I interferons (IFNs) which are important for the pathogenesis of SLE. Although pDCs constitute a small population of leukocytes in the peripheral blood, they accumulate in lesions of skin and other organs in patients with SLE.[171,172] Litifilimab is a monoclonal antibody that directs against blood dendritic cell antigen-2 (BDCA2) uniquely expressed on pDCs.[173] This interaction results in suppression of TLR-7/9-induced production of type I IFNs, other cytokines and chemokine by the pDCs.[173,174] Litifilimab also exhibits a dual effect on pDCs by internalization of surface low-affinity Fc gamma receptor (CD32a), thus preventing stimulation of the pDCs by DNA or RNA-containing immune complexes. A phase II PBO-controlled RCT (LILAC-A) of SLE patients with active arthritis or skin lesions showed a significantly greater reduction in active joint counts in the litifilimab 450mg group compared to PBO at week 24.[175] In the second part of this RCT (LILAC-B) that involved patients with active CLE, litifilimab was shown to be superior to PBO in the reduction of the CLASI-A score.[176] In both studies, most of the secondary end points did not support the results of the primary end point analyses. Litifilimab was associated with increased herpes zoster and other viral infections.

Daxdilimab is an IgG1 monoclonal antibody that binds to immunoglobulin-like transcript 7 (ILT7) on the surface of pDCs, leading to their depletion through the ADCC mechanism.[177] A Phase I study showed that daxdilimab profoundly reduced both circulating and tissue-resident pDCs, which was associated with reduced type I IFN activity and improvement in the CLASI-A score in patients with CLE.[177] No increased viral infection was observed with daxdilimab. A phase II trial in discoid lupus is in progress (NCT05591222).

Afimetoran is an antagonist of TLR7 and 8. A phase Ib study of afimetoran in 13 patients with CLE showed efficacy of the drug in suppressing the CLASI-A score, which was coupled with a reduction in expression of the TLR7/8 and IFN pathway genes and other cytokines.[178]

Targeting Cytokines

Cytokines are secreted by immune cells for mutual communication and orchestration of the immune response.[179] They may exhibit pro-inflammatory or anti-inflammatory properties, or both, depending on the micro-environment. Cytokine production is dysregulated in SLE, which may the primary or secondary to the imbalance of the Th1/Th2 and Th17/Treg pathways.[180] A number of cytokines are over-expressed in patients with SLE, including the IFNs (IFNα, IFNγ), interleukins (IL-6/10/12/17/21/23) and BAFF.[181] Targeting the cytokines by monoclonal antibodies and their downstream intracellular pathway by the Janus kinase inhibitors (JAKis) is an important approach in the treatment of SLE.

Anti-Interferon

IFNα promotes dendritic cell development, T cell activation, and autoantibody production by B cells.[182] Levels of IFN-α, IFN-driven chemokines, and expression of IFN-regulated genes were elevated in SLE patients and correlated with clinical and serological disease activity and serum IL-10 levels.[183–185] Moreover, gain-of-function genetic variants in the type I IFN pathway have been associated with increased susceptibility to SLE.[186]

Rontalizumab is a human monoclonal antibody that neutralizes 12 subtypes of IFNα but does not bind to IFNβ or IFNω.[187] A phase II PBO-controlled RCT did not meet the clinical end points of BILAG improvement and SRI response at week 24 in patients with active SLE.[188] Sifalimumab is another human IgG1κ monoclonal antibody that neutralizes most subtypes of IFNα. A phase II RCT in 431 SLE patients showed that the SRI-4 response rate at week 52 was superior in the 1200mg sifalimumab arm than PBO.[189] Improvement in joint counts and CLASI-A skin scores was also documented with sifalimumab treatment, although no changes in anti-dsDNA or C3/4 levels were observed. AEs were not increased with treatment except herpes zoster. Despite the encouraging results, the drug was not further developed.

Anifrolumab is a human monoclonal antibody that directs against the type I IFN receptor, thus blocking the signals from all type I IFNs, including IFNα, IFNβ, IFNε, IFNκ and IFNω.[190] Following a phase IIb RCT showing promising results and safety of anifrolumab,[191] two pivotal phase III PBO-controlled RCTs were conducted.[192,193] In the TULIP-1

study, 457 patients with active non-renal SLE were randomized to receive two doses of anifrolumab and PBO in addition to the SOC.[192] At week 52, the SRI-4 response rate was similar between anifrolumab and PBO groups. However, a secondary analysis of the BICLA response and the abolition of the treatment failure criterion of new prescription of non-steroidal anti-inflammatory drugs (NSAIDs) during the trial showed benefit of anifrolumab compared to PBO. In the TULIP-2 study, a modified primary end point of BICLA at week 52 was adopted.[193] Results showed a significant higher proportion of SLE patients achieved the BICLA response than PBO. Anifrolumab was subsequently approved for the treatment of moderate to severe SLE in addition to SOC.

Pooled data of the TULIP studies showed that anifrolumab treatment was associated with earlier, more frequent, more prolonged and sustained achievement of the low disease activity state (LLDAS)[194] and a sustained GC tapering effect compared to PBO.[195] Patient subgroups with larger treatment differences relative to PBO included those with baseline high IFN gene signature, abnormal serological markers and Asian ethnicity.[196] A 3-year extension of the TULIP studies revealed sustained efficacy of anifrolumab in the reduction of SLE activity and the cumulative GC doses without new safety signals.[197] However, anifrolumab treatment was associated with an increased incidence of herpes zoster and respiratory tract infections.[198]

Anifrolumab has also been studied in LN. A phase II PBO-controlled RCT of 147 patients with active LN did not meet the primary outcome of improvement in the geometric mean of proteinuria at week 52 with anifrolumab.[199] However, secondary analysis indicated that using an intensified anifrolumab regimen (with loading doses), the CRR rate was significantly higher than that of PBO. While the incidence of SAEs was similar across all groups, herpes zoster was more common in anifrolumab users. An extension of this study for a further of 12 months demonstrated similar efficacy of anifrolumab over PBO without new safety signals.[200] A phase III study of anifrolumab in LN is in progress (NCT05138133).

There are alternative ways of targeting IFNα in SLE. IFN-α-kinoid (IFN-K) is a recombinant human IFNα conjugated to an immunogenic carrier protein.[201] Active immunization of IFN-K disrupts B cell tolerance and generates neutralizing antibodies against all subtypes of IFNα. A phase I/II dose-escalating RCT of IFN-K in 28 patients with active SLE showed safety and immunogenicity of the drug.[202] IFN-K administration induced anti-IFNα antibodies in all subjects, with significantly higher anti-IFNα titers in IFN signature positive than negative patients. IFN-K significantly diminished the expression of IFN-induced genes, which was associated with improvement in C3 levels. A significant correlation was found between the neutralizing anti-IFNα titers and reduction in IFN scores compared to baseline.[203]

On the other hand, IFNα can also be antagonized by targeting the pDCs (Targeting Dendritic Cells above) or the intracellular downstream signal pathway by the JAKis (see below).

Anti-IL6

IL-6 is mainly secreted by activated macrophages and T cells and acts synergistically with the type I IFNs to activate B cells, leading to production of protective and pathogenic antibodies. Serum IL-6 levels were elevated in SLE patients and correlated with disease activity and anti-dsDNA level.[204] A phase I study of tocilizumab in 16 SLE patients showed efficacy in improving disease activity, particularly arthritis, which was associated with reduction in anti-dsDNA,[205] number of activated T and B cells, plasmablasts and post-switched memory B cells.[206] Another anti-IL6 monoclonal antibody (sirukumab) was studied in a phase I PBO-controlled trial of 46 patients with SLE or CLE.[207] Both tocilizumab and sirukumab treatment were associated with a dose-dependent reduction in neutrophil count and increase in infective complications.[205,207] In a phase II proof-of-concept PBO-controlled RCT of 25 patients with refractory LN, the renal response was not found to be superior in the treatment group at week 24.[208] Moreover, in the sirukumab group, SAEs developed in 48% of patients through week 40, most of which were infective complications.

Anti-IL12/23

IL12 and IL23 play an essential role in inflammation and autoimmunity.[209] In patients with SLE, a disease activity-related upregulation of serum IL12, IL-23 and IL-23 receptor levels, as well as the expression of the IL12/23 shared common p40 subunit as compared to healthy subjects has been demonstrated.[210–212] Ustekinumab is a fully human monoclonal antibody that inhibits the IL-12/23 p40 subunit and is approved for patients with skin psoriasis, psoriatic

arthritis and inflammatory bowel disease. Despite the promising results from a phase II PBO-controlled RCT of ustekinumab in SLE,[213,214] a phase III RCT of 516 patients with active SLE was prematurely terminated due futility of the efficacy end point on interim analysis.[215] The AEs were consistent with the known safety profile of ustekinumab.

Guselkumab is a monoclonal antibody that targets IL-23p19 subunit. A phase II RCT in adult patients with active LN (histologic class III/IV) was prematurely terminated due to enrollment challenges.[216] At week 24, no differences in the primary renal efficacy endpoint and other secondary endpoints could be demonstrated between the guselkumab and PBO group of patients.

Low-Dose IL-2

IL-2 is a cytokine produced by activated CD4+ T cells that induces growth and proliferation of the T cells, NK and B cells.[217] High-dose IL-2 augments the anti-tumor effects of the cytotoxic T cells but also lead to undesirable effects due to the activation of other immune cells. However, low-dose IL-2 preferentially activates the Tregs, leading to immune suppression and tolerance.[218] Binding of IL-2 to the IL-2 receptor (IL-2R) triggers several downstream signalling pathways that include the JAK-STAT, phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt) and the mitogen activated protein kinase (MAPK) that increase Treg proliferation and functional activity.[219] In addition, murine studies also indicated low-dose IL-2 could effectively deplete autoreactive follicular T helper cells and abolish the autoantibody response.[220]

A phase II PBO-controlled RCT of low-dose IL-2 in 100 SLE patients who were receiving SOC did not meet the primary outcome of SRI-4 response at week 12.[221] However, efficacy of low-dose IL-2 was shown after excluding 2 centers with 100% SRI-4 rate in the PBO arms. Another RCT of 60 SLE patients in China also did not meet the same primary end point at week 12.[222] However, at week 24, a significantly higher rate of SRI-4 response was observed with IL-2 treatment without increased serious infections. Another phase II PBO-controlled RCT of IL-2 (efavaleukin alfa) in patients with active non-renal SLE was prematurely terminated due to futility (NCT04680637).

The limitations of low-dose IL-2 include the short serum half-life, potential dose-dependent adverse effects, great variability in patients' response at different dosages, as well as the lack of long-term safety data. Future study design should refine the dosage regimens, explore the prospect of combination with other novel agents, and nest the most appropriate patient subsets by biomarkers to receive IL-2 therapy.

Targeting Cytokine Downstream Pathways

Baricitinib

Baricitinib is a JAK1/2 inhibitor that has shown efficacy in a phase II RCT of SLE patients with active joint and/or skin disease.[223] Both the primary efficacy endpoint (resolution of skin disease or arthritis at week 24) and secondary end points that included SRI-4 response and LLDAS were achieved in the baricitinib (4mg) group compared to PBO. Although baricitinib did not lead to a greater improvement in anti-dsDNA and C3,[224] levels of IL-12 p40, IL-6, mRNA expression of STAT1-target, STAT2-target, and STAT4-target and multiple IFN responsive genes were reduced.[225] Serious infections were more frequent in the baricitinib 4mg group relative to PBO. Two identical phase III RCTs of baricitinib in non-renal SLE (BRAVE 1/2) were subsequently performed.[226,227] The primary end point, SRI-4 response at week 52, was met in BRAVE-1 but not in BRAVE-2. All secondary endpoints were not met in both studies. Although the musculoskeletal and mucocutaneous domains on SLEDAI and BILAG improved significantly with baricitinib 4mg in BRAVE-1, result was not reproduced in BRAVE-2. The inconsistent results of these two RCTs render the efficacy of baricitinib in SLE inconclusive.[228] A long-term extension study of baricitinib in SLE is in progress (SLE-BRAVE-X).

Upadacitinib

Upadacitinib is a selective JAK1 inhibitor that has been approved for rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, atopic dermatitis and inflammatory bowel disease.[11] The results of a PBO-controlled phase II RCT comparing the efficacy of two doses of upadacitinib, alone or in combination with elsubrutinib, a BTK inhibitor, was recently published.[229] The low-dose upadacitinib/elsubrutinib and elsubrutinib arms were discontinued after an interim analysis showing lack of efficacy. More patients achieved the primary end point of SRI-4 and GC dose ≤10mg/day at week 24

with upadacitinib (30mg/day) and high-dose upadacitinib/elsubrutinib versus PBO. Secondary end points such as the rates of SRI-4, BICLA, LLDAS at week 24 and 48, and reduction of SLE flares were also in favor of these two treatment arms. No new safety signals were observed for upadacitinib or elsubrutinib.

Deucravacitinib

Deucravacitinib is a selective Tyk-2 inhibitor that blocks the downstream signalling of IL-12, IL-23, IL-10, and the type I IFNs.[230] The phase II PBO-controlled RCT (PAISLEY) of deucravacitinib in 363 patients with active SLE (skin or joint) achieved the end point of SRI-4 at week 32.[231] Secondary endpoints such as SRI-4, BICLA and LLDAS at week 48 were also in favor of the deucravacitinib (3mg twice-daily) group. Moreover, significantly more patients in this group achieved a ≥50% reduction in the CLASI score and combined swollen/tender joint counts. Greater improvement in anti-dsDNA and complement levels was observed in the deucravacitinib groups across all dosages, but not PBO, which were associated with an improvement in IFN signature through 44 weeks. Deucravacitinib was well-tolerated, with no increase in infective complications, including herpes zoster, reported. Two phase III RCTs (POETYK SLE-1/2) are in progress (NCT05617677 and NCT05620407).

Targeting Other Cellular Mechanisms

Targeting the Complements

Complements play an essential role in clearance of immune complexes and apoptotic bodies in SLE. They also regulate the functions of T and B cells.[232] Activation of terminal complement is associated with disease activity and organ damage in SLE, particularly LN. Eculizumab is a monoclonal antibody targeting C5 complement and blocks its cleavage. A phase I study demonstrated safety in SLE patients.[233] Case series have reported efficacy of eculizumab in SLE/LN with thrombotic microangiopathy (TMA) features or part of the atypical hemolytic uremic syndrome.[234,235] Avacopan is a complement 5a receptor (C5aR) antagonist approved as an adjunctive treatment for ANCA-related vasculitis. It is also being investigated for the treatment of C3 glomerulopathy, hidradenitis suppurativa and IgA nephropathy. However, no clinical trial of avacopan in SLE/LN has been registered yet. Iptacopan is an oral inhibitor against complement factor B in the alternative complement pathway. It regulates the cleavage of C3, generation of downstream effectors and the amplification of the terminal complement pathway. The drug is approved for paroxysmal nocturnal haemoglobinuria (PNH) and is being investigated in IgA nephropathy and C3 glomerulopathy.[236] A phase II RCT in active LN has been registered (NCT05268289).

Targeting the S1PR1

Sphingosine 1-phosphate (S1P) is a bioactive metabolite of ceramide that binds to five G protein-coupled S1P receptors (S1PR1-S1PR5) and influences cell proliferation, survival, and migration.[237] Among the S1PR isoforms, S1PR1 is expressed on leukocytes and endothelial cells and mediates lymphocyte trafficking, Treg/Th17 cell homeostasis, and vascular permeability.[238] Four S1PR1 modulators (fingolimod, siponimod, ozanimod, and ponesimod) are approved for multiple sclerosis and two SIPR1 modulators (ozanimod and etrasimod) are approved inflammatory bowel disease.[239] The S1PR1 modulators could be effective in reducing SLE activity by inhibiting the trafficking of autoreactive lymphocytes and Th17 cell differentiation, augmenting the number and function of the Tregs, and reducing production of autoantibodies.[240] Moreover, these modulators could enhance the endothelial cell and blood-brain barrier functions, diminish adhesion molecule expression for leukocyte transmigration, and type I IFN production by pDCs in response to viral or oligonucleotides, which are potentially beneficial for renal, neuropsychiatric disease and atherosclerotic injury in SLE.[241]

An open phase Ib safety trial of amiselimod in 17 SLE patients with mild/moderate activity reported lymphopenia after treatment in all patients but no serious infections, cardiac toxicity or SAEs were observed.[242] A proof-of-concept PBO-controlled RCT of oral cenerimod in 49 SLE patients with active mucocutaneous or musculoskeletal manifestations demonstrated efficacy in reducing serological and clinical activity at week 12 without increasing TEAEs.[243] Reduction in lymphocyte count occurred in a dose-dependent manner and a small but non-clinically relevant drop of heart rate was observed in the first 6 hours of drug administration. A more recent phase II PBO-controlled dose-escalating RCT of cenerimod in 427 SLE patients with moderate/severe activity did not meet the primary end point of mSLEDAI-2K score improvement at month 6.[244] However,

cenerimod 4 mg reduced IFN-associated protein and gene signature biomarkers after treatment.[245] Two phase III RCTs (OPUS-1/2) of cenerimod in SLE are in progress (NCT05648500, NCT05672576).

Synthetic Peptides and Immune Tolerizers

Abetimus sodium, consisting of four dsDNA epitopes conjugated to a non-immunogenic polyethylene glycol platform, crosslinks anti-dsDNA immunoglobulin receptors on B cell surface, triggering signal transduction pathways that result in apoptosis or anergy.[246] However, two large phase III RCTs of SLE failed to show efficacy of this agent in reducing disease flares, although it was well tolerated and reduced anti-dsDNA levels.[247,248]

Edratide is a peptide based on the sequence of the first complementarity-determining (CDR1) region of a pathogenic human anti-DNA monoclonal antibody (16/6 idiotype) that downregulates pathogenic cytokines, apoptosis, IFNα gene expression, but upregulates Tregs in PBMCs of SLE patients.[249,250] A 26-week phase II dose-escalating study of SLE patients with mild/moderate activity was terminated because of lack of efficacy.[251]

Rigerimod (Lupuzor) is a 21-mer linear peptide issued from the small nuclear ribonucleoprotein U1-70K and phosphorylated at the Ser140 position.[252] It tolerizes CD4+T cells to react to self-antigens by binding to the MHC class II molecule on cell surface and through other unknown mechanisms.[253] A phase IIa study demonstrated safety of rigerimod and improved clinical and serological SLE activity [122]. Another phase IIb RCT confirmed higher SRI response rate than PBO at week 12.[254] However, the phase III 52-week RCT of rigerimod in SLE (NCT02504645) did not meet the primary end point.[255]

Laquinimod is a modulator of antigen presenting cells that directs T cells toward an anti-inflammatory phenotype through downregulation of the pro-inflammatory cytokines (IL-6/12/17/23/TNFα) but upregulation of IL-10. A phase IIa PBO-controlled RCT showed efficacy of laquinimod in improving renal function and proteinuria on a background of MMF and GCs.[256] No increase in AEs and SAEs were observed in the laquinimod groups. Another study of laquinimod in lupus arthritis has been completed (NCT01085084).

Arsenic Trioxide

Arsenic trioxide (ATO) is now part of the standard treatment regimen for acute promyelocytic leukemia (PML). ATO binds to the PML-retinoic acid receptor (RAR)α fusion oncoprotein and enhances its proteasomal degradation, leading to senescence of the leukemic cells and restoration of terminal differentiation of the myeloid progenitors.[257] The availability of an oral form of ATO has greatly reduced the incidence of cardiotoxicity compared to the intravenous preparation. Increasing evidence shows that ATO has anti-inflammatory properties that include modulation of Treg activation, Th1/Th2 and Th17/Treg balance, depletion of activated T cells and pDCs, and reduction of differentiation, autoantibody and cytokine production by B cells.[257] A phase IIa open single-arm dose-escalating study of 11 SLE patients with refractory disease showed that 50% of patients could achieve a SRI-4 response after intravenous ATO treatment for 24 weeks.[258] Neutropenia occurred in 20% of the patients. As oral ATO is more convenient and has a reduced toxicity profile, it has a great potential for the treatment of SLE.

Conclusion

Novel therapeutic agents that target different cell types, cytokines, receptors and intracellular pathways of the innate and adaptive immune systems are being developed and tested in patients with SLE. As B cells are pivotal in the production of autoantibodies, targeting B cells is one of the main strategies of SLE therapies in the past two decades. However, the clinical efficacy of B cell modulation in SLE has not been too impressive until the recent data from the newer generation anti-CD20, obinutuzumab, showing benefit in LN when combined with the SOC.[35] Previous RCTs of rituximab in non-renal SLE and LN[26,27] did not show efficacy although this biologic has been widely used to treat refractory SLE. Moreover, sequential or combination therapy of the anti-CD20 and anti-BAFF has not been shown to be effective in increasing the response rate in SLE and LN but carries a risk of increased infection.[259] Clinical trials of anti-CD22, anti-CD19 in SLE are futile, and neither are other anti-BAFF agents such as blisibimod and tabalumab.[260]

The cytokine inhibitors show promise in SLE. Despite the futility of anti-IL6 and IL-12/23 trials,[208,215] belimumab and anifrolumab are anti-cytokine biologics approved for SLE at this juncture. Targeted small molecules have the

advantage of lower production cost, convenience of oral administration and lack of immunogenicity.[21] The oral jakinibs, proteasome inhibitors and cereblon modulators have shown preliminary success in SLE. The results of phase II studies of deucravacitinib and zetomipzomib in human SLE are encouraging. Iberdomide shows favorable phase II results in SLE, in particularly CLE lesions.

The clinical and serological heterogeneity of SLE is a major factor contributing to the failure of new drug trials in SLE. With the improvement in patient stratification by multi-omic approach, adjustment of background immunosuppressive regimens and study end points, the response rate and the effect size of SLE trials could be improved.[260] A new era of SLE therapies is expected in the near future and the treat-to-target approach[261] is increasingly feasible in SLE. With the availability of these novel therapeutics and the improved patient selection, it is hoped that the effectiveness of SLE treatment could be improved so that patients can survive longer with improved quality of life.

Disclosure

The author reports no conflicts of interest in this work.

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