Treatment evolution of Systemic Lupus Erythematosus

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Abstract

Systemic Lupus Erythematosus (SLE) is a chronic multisystem autoimmune disease with diverse clinical manifestations ranging from mild to severe or even life-threatening. The purpose of this review is to summarize data on SLE management that have emerged over the last few years. Regimens that have been investigated target B cells, plasma cells, T cells and plasmacytoid dendritic cells. Additionally, treatments that affect B cell survival and specific intracellular pathways such as the JAK STAT pathway, the IFN pathway and mTOR or cytokines have also been used in the treatment of SLE or are currently being evaluated. Despite the existence of several therapeutic regimens in SLE, there are still unmet needs in patients with persistent disease activity, disease flares, decreased health-related quality of life, organ damage development, intolerance to standard treatment and comorbidities. It is encouraging that a plethora of therapeutic agents are currently under evaluation, although there are occasional clinical trial failures.

Key words: *Systemic lupus erythematosus; treatment; B cell; clinical trial*

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic heterogeneous multisystem autoimmune disease. Patients with SLE are typically treated with corticosteroids and immunosuppressants. Novel developments in the treatment of patients with SLE have been recently reviewed [1]. The U.S Food and Drug Administration (FDA) has approved belimumab and anifrolumab for the treatment of patients with SLE who are receiving standard therapy, and voclosporin and the intravenous form of belimumab for the treatment of lupus nephritis. Telitacicept has been also approved for the treatment of SLE in China. Rituximab, a B cell depletion treatment, may also be administered according to the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) guidelines in refractory lupus nephritis despite the fact that the two large clinical trials failed to meet their primary endpoints and is also often administered off-label for other manifestations, based on the encouraging results of a plethora of studies [2,3]. Failure to achieve remission of lupus nephritis may lead to end-stage renal disease due to irreversible damage of the kidneys. Measurement of proteinuria using the urine protein to creatinine ratio (UPCR) is a tool to assess disease activity in patients with lupus nephritis. Improvement of proteinuria at 12 months of treatment is associated with a favorable long-term renal outcome. Despite advantages, a complete renal response is infeasible in more than 40% of patients with renal involvement. Thus, there is a need to introduce and evaluate additional or new regimens that are summarized in Table 1.

Targeting cells

B cells

B cells play a central role in the pathogenesis of SLE. B cells are able to produce autoantibodies after their differentiation into plasma cells, secrete cytokines, and present autoantigens to T cells as well. Thus, targeting B cells in the treatment of SLE seems a reasonable strategy.

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Table 1. *Trials of agents demonstrating favorable results in the treatment of patients with SLE.*

Regimen	Phase of the study / Indication	Primary endpoint	Result	
Obinutuzumab	II / lupus nephritis	Complete renal response at week 52	35% (Obinutuzumab) vs 23% (placebo), p=0.115	
Obexelimab	II / SLE	Loss of improvement at day 225	42% (obexelimab) vs 28.6% (placebo), p=0,18	
Lupuzor	III / SLE	SRI response at week 52	52.5% (lupuzor) vs 44.65% (placebo), p=0.26	
Daratumumab	Case report / SLE and lupus nephritis			
Belimumab	FDA approved / lupus nephritis	Primary efficacy renal response at week 104	43% (belimumab) vs 32% (placebo), p=0.03	
Telitacicept	2b / SLE	SRI-4 response at week 48	71.0% (80mg), 68.3% (160mg), 75.8% (240mg) vs 33.9% (placebo), p<0.001, p<0.001, p<0.001, respectively	
Anifrolumab	FDA approved / SLE	BICLA response at week 52	47.8% (anifrolumab) vs 31.5% (placebo), p=0.001	
Voclosporin	FDA approved / lupus nephritis	Complete renal response at week 52	40.8% (voclosporin) vs 22.5% (placebo), p<0.0001	
Sirolimus		1/2 / SLE	Decreases of BILAG and SLEDAI scores at each visit (months 1-12)	BILAG: 28.4 (baseline) vs 17.4 (month 12), p<0.001 SLEDAI: 10.2 (baseline) vs 4.8 (month 12), p<0.001
		Retrospective / lupus nephritis		Proteinuria: 2.8±1.9 at baseline vs 0.1±0.1 at month 36
VIB7734		I / SLE, Sjogren's and CLE		Median change in CLASI-A from baseline to month 3: -5 (50mg), -9.5 (150mg), -5 (placebo)
BIIB059		II / SLE (part A)	Change of total joint count from baseline to week 24 CLASI-A at week 16	-15.0 (450mg) vs -11,6 (placebo), p=0.037
		CLE (part B)		-38.78 (50mg), -47.91 (150mg), -42.48 (450mg) vs -14.49 (placebo), p=0.015, p<0.001, p=0.001

Obinutuzumab is a type II humanized anti-CD20 monoclonal antibody (mAb) causing a greater B cell elimination than rituximab which is a type I anti-CD20 monoclonal antibody. Contrary to rituximab that failed to demonstrate a clinically significant difference compared to placebo in the primary endpoint of complete renal response, obinutuzumab was tested in patients with lupus nephritis with encouraging results. A total of more than 100 patients with Class III or Class IV lupus nephritis was randomized to receive obinutuzumab or placebo along with corticosteroids and mycophenolate mofetil (MMF) [4]. Complete renal response was achieved in 35% of the patients in the obinutuzumab group and in 23% of the patients in the placebo group (p=0.115) at week 52. This favorable response was sustained in 41% of the patients in the obinutuzumab group and in 23% of the patients in the placebo group through week 104 (p=0.026). Serious infections were observed in 8% in the obinutuzumab group and in 18% in the placebo group. It was also noticed that patients who had achieved sustained B cell depletion had a more favorable outcome of their renal disease at week 76, emphasizing the important effect of B cell elimination in the disease progress [5]. A phase III study aims to demonstrate that obinutuzumab and MMF without oral corticosteroids is non-inferior to treatment with MMF and oral corticosteroids in achieving the primary outcome of complete renal response at week 52 [6].

Obexelimab is a mAb against the CD19 molecule expressed on the surface of B cells, but it also binds to the Fcγ receptor IIb (FcγRIIB) the only inhibitory Fcγ receptor on the surface of B cells. Thus, obexelimab suppresses the activation of B cells without depleting them. In a phase II study, 104 patients were randomly assigned to receive obexelimab or placebo after achieving low disease activity by intramuscular (IM) steroids and after discontinuing previous immunosuppression [7]. Maintenance of improvement was observed through day 225 in 42% of patients in the obexelimab group and in 28.6% of patients in placebo group (p=0.18). However, patients in the obexelimab group had a significantly longer time to loss-of-improvement (median: 230 vs 131 days for patients in the placebo group, p=0.025).

T cells

T cells also participate in the pathogenesis of SLE. Lulizumab is a mAb against CD28, the T cell co-stimulatory molecule that is essential for T cell activation. In a phase II 24-week study, lulizumab was administered in a dose of 12.5 mg/week or at doses of 1.25, 5 mg, 12,5 mg every other week or placebo along with standard treatment in 349 patients with SLE [8]. Disease activity indices, such as the British Isles Lupus Assessment Group Based Composite Lupus Assessment (BICLA) response rate, the CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index), and the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) did not show significant changes between groups during treatment.

Rigerimod or Lupuzor is a peptide, a fragment of the small nuclear ribonucleoprotein U1-70K. It may act as an immunomodulator by binding to major histocompatibility complex (MHC) class II and hence inhibiting T-cell reactivity, resulting in a partial restoration of the immune tolerance. In a phase III study rigerimod was introduced subcutaneously at a dose of 200 mg every 4 weeks for 48 weeks in combination to standard treatment [9]. A small and without statistical significance better response rate was noticed over placebo (52.5% vs 44.6%, p=0.26). Obviously, approaches targeting T cells seem less effective. Co-stimulation blockade has not been efficacious in the treatment of SLE, pointing perhaps to different pathway targets.

Plasma cells

Daratumumab that has been approved for the treatment of multiple myeloma, is an IgG1k mAb against CD38 causing depletion of plasma cells. Long-lived plasma cells are residents in niches in the bone marrow or in inflamed tissue and they do not respond to immunosuppressants, including B-cell-targeting treatments. Two patients with severe manifestations of SLE received daratumumab at a dose of 16 mg/kg of body weight once a week for 4 weeks followed by maintenance treatment with I.V. belimumab [10]. Daratumumab treatment resulted in remarkable clinical outcomes including improvement not only of severe manifestations such as lupus nephritis, autoimmune hemolytic anemia and autoimmune thrombocytopenia but also of less severe manifestations such as arthritis, skin rashes, pericarditis, cutaneous vasculitis, alopecia and mucosal ulcers. Favorable serologic responses were also observed. Importantly, previous therapeutic interventions with a variety of agents such as bortezomib, mycophenolate mofetil, and cyclophosphamide were ineffective. Despite the extremely small number of patients, data are encouraging supporting the further evaluation of daratumumab in adequately powered trials of patients with SLE. Of note, the clinical efficacy

of daratumumab was not associated exclusively to plasma cell depletion. Other circulating cells also express CD38 and their numbers were decreased after treatment with daratumumab. These include B cell subsets, plasmacytoid dendritic cells and an expanded CD38+ T cell subpopulation.

Plasmacytoid dendritic cells

Plasmacytoid dendritic cells have the ability to secrete massive amounts of type 1 interferons when activated contributing, thereby, to SLE pathogenesis. VIB7734 is a mAb that binds to ILT7, a surface molecule of pDCs, resulting in their elimination and also in the reduction of other cytokines such as IL-6 and TNF-α. A phase I, randomized, placebo-controlled trial evaluated VIB7734 in 3 cohorts [11]. Cohort 1 included 6 patients with SLE or Sjogren's syndrome with or without active disease. Cohorts 2 and 3 included patients with SLE or cutaneous lupus erythematosus (CLE) with a CLE Disease Area and Severity Index Activity Score (CLASI-A) ≥ 8. The median change of CLASI-A from baseline to month 3 was -5 in the 50mg, -9.5 in the 150mg group and -5 in the placebo group. Additionally, a ≥50% improvement in CLASI-A was observed in 56% of the patients treated with VIB7734 and in 29% of the patients in the placebo group at month 3. Treatment with VIB7734 was generally safe.

BIIB059 is a humanized IgG1 mAb that binds to the specific receptor of pDC BDCA2 (blood dendritic cell antigen 2) and suppresses the production of IFN-I. A 2-part phase II study assessed the effect of BIIB059 in patients with SLE (part A) and in patients with CLE (part B) [12]. The study achieved its primary endpoint which was the change in totally inflamed joints (tender and swollen joints) between baseline and week 24. Total active joint count significantly decreased in the BIIB059 450mg group [-15.0 vs -11.6 in the placebo group (p=0.037)]. A non-statistically significant increased CLASI-50 response was noticed in the BIIB059 group vs placebo. Adverse events were recorded in 67.9% in the placebo group and in 59.2% in the BIIB059 group. A further evaluation of part B illustrated a statistically significant change of CLASI-A score from baseline to week 16. Patients with severe SLE manifestations were not included in the study [13].

Treatments that affect B cell survival

Belimumab is a specific inhibitor of the soluble BLyS (B lymphocyte stimulator). The large belimumab's approval clinical trials had excluded patients with severe lupus nephritis. Of note, we had previously reported two patients in which lupus nephritis manifested shortly after the initiation of belimumab treatment [14]. Both these patients improved immediately after withdrawal of belimumab and before the initiation of standard therapy. Furthermore, a retrospective study showed that introducing belimumab into a standard treatment regimen of patients with SLE without renal involvement resulted in development of lupus nephritis with an increased frequency compared to patients with non-renal SLE who did not receive belimumab (hazard ratio, HR: 10.7, p=0.012) [15]. It was proposed that concomitant treatment with antimalarials was protective over this "nephritogenic" effect of belimumab ((HR: 0.2, p=0.046).

An international phase III, 104-week, randomized, double-blind, placebo-controlled trial of intravenous belimumab along with standard treatment formally addressed the question of its efficacy and safety in lupus nephritis [16]. A total of 448 patients were randomized to receive belimumab or placebo (1:1). The primary endpoint was primary efficacy renal response at week 104, an endpoint that was defined as a urinary protein to creatinine ratio (UPCR) ≤ 0.7, an estimated glomerular filtration rate (eGFR) that had not declined more than 20% below the levels before the flare of the disease or was >60ml/min/1.73 m^2, as well as no use of rescue treatment in cases of treatment failure. Primary efficacy renal response was noticed in 43% of the patients that were treated with belimumab along with standard therapy and in 32% of the patients that were treated with placebo in combination with standard treatment at week 104 (p=0.03). Regarding safety, no differences were observed between the two groups of patients. Although a significant number of patients with lupus nephritis was enrolled in each arm of the study, no subgroups of patients that could have a greater benefit from belimumab treatment were identified. Despite the fact that a better outcome was noticed in 11% more patients, the percentages of patients with renal response are not sufficient satisfying. The FDA has approved intravenous belimumab for the treatment of patients with lupus nephritis. Treatment with belimumab at the time that circulating BLyS peaks following rituximab treatment in order to sustain B cell depletion seems reasonable. However, a phase II study that examined the effect of induction therapy with rituximab followed by maintenance therapy with belimumab did not demonstrate a significant improvement of patients with lupus nephritis [17].

A randomized trial currently investigates the long-term efficacy of combination B cell targeting by initiation treatment with belimumab followed by rituximab in patients with lupus nephritis. The primary outcome is treatment failure rate at week 104 [18].

Bruton's tyrosine kinase (BTK) is an intracellular signaling molecule that plays an essential role in the activation, differentiation and survival of B cells. Fenebrutinib is a highly selective inhibitor of Bruton's tyrosine kinase (BTK). A phase II study that enrolled 260 SLE patients from 12 countries was conducted [19]. The SRI-4 response rates at week 48 were 51% in the fenebrutinib 150mg once daily group (p=0.37 vs placebo), 52% in the fenebrutinib 200mg twice daily group (p=0.34 vs placebo) and 44% in the placebo group. Although fenebrutinib illustrated an acceptable safety profile, it failed to improve disease activity.

Targeting other signals of B cell survival

Telitacicept (RC18) is a novel recombinant TACI-Fc (transmembrane activator and calcium modulator and cyclophilin ligand interactor) fusion protein that binds to soluble BLyS and APRIL (A proliferation inducing ligand) suppressing thereby their biological activities, that also affect the plasma cells. Therefore, telitacicept does not affect early and memory B cells. In a phase 2b study, patients with a Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA)-SLEDAI score ≥ 8, consistent with active disease, received telitacicept at doses of 80mg, 160mg and 240mg or placebo along with standard treatment [20]. The primary endpoint was an SRI-4 at week 48. The SRI-4 was achieved in 71.0%, 68.3% and 75.8% of the patients who received the 80mg, 160mg and 240mg doses, respectively, at week 48 and in 33.9% of the patients in the placebo group. The proportion of patients achieving at least a 4-point reduction in their SELENA-SLEDAI score at week 48 was 75.8%, 77.8% and 79.0% in the telitacicept groups and 50.0% in the placebo group. Adverse events were observed in 90.3%, 92.1%, 93.5% and 82.3% of the patients in the 80mg, 160mg, 240mg telitacicept and placebo groups, respectively. Adverse events included mainly reactions at the injection site and infections of the upper respiratory tract. In March 2021, telitacicept was firstly approved in China for the treatment of patients with active SLE. Telitacicept is also evaluated in a phase III placebo-controlled study along with standard treatment. The primary outcome is SRI response rate at week 52 [21].

Targeting the IFN pathway

Anifrolumab is a fully human mAb that binds to the type I interferon receptor, blocking the activity of type I interferons such as interferon-α and interferon-β. A phase III, randomized, double-blind, placebo-controlled study included 362 patients with SLE [22]. They were randomized to receive anifrolumab (n=180) or placebo (n=182). A BICLA response was achieved in 47.8% of the patients in the anifrolumab group and in 31.5% of the patients in the placebo group at week 52. For patients with a high interferon gene signature, the percentages were 48.0% in the anifrolumab group and 30.7% in the placebo group. For patients with a low interferon gene signature, the percentages were almost similar to those with a high interferon gene signature (46.7% and 35.5%, respectively). Anifrolumab treatment also resulted in a reduction of glucocorticoid dosages and an improvement of skin involvement. Anifrolumab did not illustrate significant effects in arthritis or in annualized flare rates. Serious adverse events including pneumonia and deterioration of SLE were reported in 8.3% of the patients in the anifrolumab group and in 17% of the patients in the placebo group. Herpes zoster infection developed in 7.2% in the anifrolumab group and in 1.1% in the placebo group. Anifrolumab (Saphnelo) has been approved by the FDA for the treatment of adult patients with moderate to severe SLE who are receiving standard treatment. An ongoing phase III randomized, placebo-controlled trial currently evaluates the efficacy and safety of anifrolumab compared to placebo as added to standard treatment in patients with lupus nephritis. The primary outcome is complete renal response at week 52 [23].

Targeting specific intracellular pathways

Calcineurin inhibitors suppress the rapid ionized calcium infux that induces calcineurin activation in T cells following activation of BCR and TCR. Voclosporin is a novel cyclosporine analog, the most potent and least toxic among all known calcineurin inhibitors. A phase 3 study demonstrated that the addition of voclosporin to mycophenolate mofetil and low-dose corticosteroids was superior to standard treatment in patients with lupus nephritis. The AURORA study included 357 patients with active lupus nephritis [24]. Renal response was achieved in 40.8% of the patients in the voclosporin group and 22.5% of those in the control group and therefore the study met its primary endpoint. Patients receiving voclosporin had a 50% reduction in

the UPCR more rapidly than the control group. Serious adverse events, mainly infections were recorded in 20.8% of the patients in the voclosporin group and in 21.3% in the control group. Renal response at week 24, partial renal response at weeks 24 and 52, time to achieve UPCR ≤ 0.5, and time for 50% reduction of UPCR were the secondary endpoints and they all displayed a statistical significance in favor of voclosporin compared to standard treatment alone. There was no significant reduction of the eGFR at week 52 in the voclosporin group or increases of glucose, lipid levels or in blood pressure, which constitute common side effects of calcineurin inhibitors. A 2-year, controlled extension trial (AURORA 2) with a follow-up of 30 months included 90 patients in the voclosporin group and 78 patients in the control group [25]. According to these results, there were sustained meaningful reductions in proteinuria and no fluctuations of renal function through month 30. Voclosporin has been approved by the FDA as the first orally administered treatment for patients with lupus nephritis.

Targeting mTOR

Sirolimus is an immunosuppressive macrolide. It blocks the activation of T cells and B cells through mTOR (mammalian target of rapamycin) suppression, decreasing thereby their sensitivity to IL-2. In a prospective, open-label, single-arm clinical trial sirolimus was administered in 40 patients with SLE for 12 months [26]. Patients with severe or life-threatening manifestations of SLE, proteinuria (an UPCR more than 0.5) and hematological abnormalities had been excluded. Eleven patients discontinued the study due to lack of tolerance or lack of compliance. SLEDAI and BILAG scores were reduced in 16 out of 29 patients that completed treatment. Mean SLEDAI score was decreased from 10.2 at enrollment to 4.8 at 12 months after treatment ($p<0.001$). Mean BILAG score was decreased from 28.4 at enrollment to 17.4 at 12 months after treatment ($p<0.001$). The mean daily dose of prednisone was decreased from 23.7mg to 7.2mg ($p<0.001$) at 12 months after sirolimus initiation.

A retrospective study included 16 patients with class III and/or V or IV and/or V or pure class V lupus nephritis who received sirolimus [27]. Nine patients had intolerance to standard treatment (MMF and calcineurin inhibitors), and 7 patients had a history of cancer. Sirolimus was introduced as an induction treatment in 5 and as maintenance therapy in 11 patients. Proteinuria was diminished from 2.8±1.9 g/d at baseline to 0.1±0.1 g/d ($p=0.011$) at 36 months after treatment in the first group. A stable renal function was achieved in the second group. one patient experienced a renal flare and another one developed end-stage renal disease at 27 months after sirolimus treatment.

A meta-analysis was conducted to determine the overall efficacy of sirolimus in patients with SLE [28]. The overall reduction of SLEDAI and BILAG scores and that of corticosteroid dosages was 4.85, 1.98 and 13.17mg/d respectively in 111 patients with active disease. Remission was observed in 74% of the patients who received sirolimus for their active disease and maintenance of remission was achieved in 95.5% of the patients with lupus nephritis. Side effects were mild; only 9.3% of the patients discontinued treatment. It is therefore plausible that mTOR suppression may represent a promising novel therapeutic approach for patients with SLE.

Targeting the JAK-STAT pathway

The activation of the JAK-STAT pathway participates in the differentiation of pathogenic effector T cells and in the dysregulation of Treg cels. Baricitinib is an oral inhibitor of Janus kinase (JAK), blocking the subtypes JAK1 and JAK2. In a phase 2, double-blind, randomized, placebo-controlled, multicenter, 24-week study, 314 patients with active SLE involving skin or joints were randomized to receive baricitinib 4mg/d (n=104), baricitinib 2mg/d (n=105), or placebo (n=105) [29]. At week 24, reductions of SLEDAI scores were noticed in 67% of the patients in the baricitinib 4mg/d arm and in 58% of the patients in the baricitinib 2 mg/d arm. The higher dose of baricitinib (4mg/d) appeared to be more effective in the management of patients with SLE refractory standard treatment. Severe infections were recorded in 6% of the patients in the baricitinib 4 mg/d group, in 2% of the patients in the baricitinib 2 mg/d group and in 1% of the patients in the placebo group. Of note, deep vein thrombosis was observed in 1 patient receiving the 4 mg dosage regimen; this patient was positive for antiphospholipid antibodies.

In the phase III (SLE-BRAVE-I) study, the baricitinib 4mg regimen met the primary endpoint, illustrating a statistically significant reduction in disease activity as measured by the proportion of adult patients with active SLE who had an SRI-4 response at week 52 compared to placebo. However, the SLE-BRAVE-II study failed to meet the primary endpoint of SRI-4 response. In addition, important secondary endpoints were not met in either study. Based on top-line efficacy results from

the above phase-3 studies, the manufacturer decided to discontinue the phase-3 development program for baricitinib in patients with SLE [30]. Notably, safety that represented a major issue for JAK-inhibitors in rheumatoid arthritis patients with cardiovascular risk factors did not influence the manufacturer's decision.

Targeting cytokines interleukin 12 and 23

Ustekinumab is a mAb that binds to the p40 subunit of IL-12 and IL-23 preventing their binding to their receptors. A multicenter, randomized, double-blind, placebo-controlled study included 102 patients with active SLE. These patients were randomized to receive either ustekinumab or placebo along with standard treatment. SRI-4 response rates were significantly greater in the ustekinumab group (62%) compared to the placebo group (33%) at week 24 and were sustained through week 48. Ustekinumab was generally safe, since no opportunistic infections or deaths were recorded. The encouraging results of the phase II trial led investigators to design a phase III study. The manufacturer announced discontinuation of this study due to lack of efficacy resulting in the exclusion of ustekinumab from the therapeutic alternative approaches of SLE. The safety profile of ustekinumab was consistent with that of previous studies and did not impact the decision to discontinue the clinical trial.

Ongoing clinical trials

Apart from trials that were mentioned above, other ongoing studies are described below.

Treatments against T cells

Acazicolcept (ALPN-101) is a dual inhibitor of the CD28 and ICOS T cell co-stimulatory receptors that regulate the activation, proliferation and differentiation of T cells. It was created by engineering a single protein domain, or vIgD (Variant Ig Domain) based on a human inducible T cell co-stimulatory ligand (ICOSL) that is able to bind to CD28 and ICOS. A first-in-human study assessed the tolerability, safety, pharmacokinetics and pharmacodynamics of ALPN-101 in healthy adults [31]. According to the results, ALPN-101 seems to be well-tolerated with no clinically significant immunogenicity, evidence of cytokine release or severe side effects. A phase 2, randomized, blinded study aims to evaluate the safety and efficacy of ALPN-101 in patients with moderate to severe SLE [32].

Dapirolizumab pegol is an anti-CD40L pegylated Fab fragment that blocks co-stimulatory interactions between T cells and antigen presenting cells expressing CD40. A phase 2b study of dapirolizumab pegol in patients with SLE failed to meet the primary endpoint which was the dose-response at week 24, despite the fact that it was well-tolerated and showed improvements in disease activity [33]. However, investigators continue their research in order to determine the efficacy of dapirolizumab in a phase III study [34]. The primary outcome is BICLA response at week 48.

Itolizumab (EQ001) is a monoclonal antibody targeting the CD6 receptor on the surface of T cells. It blocks the binding of CD6 on ICAM (activated leukocyte cell adhesion molecule) ligand, inhibiting therefore immune responses mediated by T cells. CD6 and ALCAM positive cells were found to be increased in patients with lupus nephritis and to be associated with SLE activity [35]. Itolizumab improved renal disease in murine models, reduced the migration of T cells to inflamed tissues and also increased the levels of IL-10. Based on previous animal model data, the manufacturer was granted a U.S. FDA fast-track designation for itolizumab for the treatment of patients with lupus nephritis.

LY3471851 (NKTR-358) targets the IL-2 receptor complex and represents a novel Treg cell stimulator. It is designed to correct specifically this immune system dysregulation without affecting the entire immune system. The primary outcome of a phase II study is the percentage of patients that will achieve a ≥4-point reduction in SLEDAI-2K score at week 24 [36].

Abatacept is a fusion protein of the extracellular domain of CTLA4 and human IgG1-Fc, constructed to suppress B cell/T cell co-stimulation. Previous studies of abatacept failed to demonstrate benefit, even after withdrawal of background treatments. Nevertheless, a phase 2 study will evaluate the efficacy of abatacept in patients with SLE and the primary endpoint is BICLA response at 6 months [37].

Treatments against mainly (but not only) B cells

ALPN-303 inhibits B cell cytokines BLyS and APRIL, which play an important role in B cell survival, with higher than fivefold potency in vitro. In a mouse model of lupus, ALPN-303 treatment significantly decreased anti-dsDNA autoantibody levels and glomerulonephritis, whereas renal function remained stable and overall survival was improved [38]. Patients are currently enrolled in a phase 1 healthy volunteer clinical trial [39].

Iberdomide (CC220) is a cereblon modulator causing

potent degradation of the transcriptional factors Ikaros and Aiolos leading to suppressed B cell proliferation and cytokine secretion. A phase II, placebo-controlled study aims to evaluate the efficacy and safety of CC220 in patients with active SLE and the primary outcome is an SRI-4 at week 24 [40]. B cell and T cell collaboration plays a central role in the pathogenesis of SLE. Thus, AMG 570, an ICOSL and BAFF bispecific inhibitory molecule, has been employed in a phase 2b study [41]. The primary outcome is the percentage of patients achieving an SR-4 at week 52. Based on the same concept, VAY736 or lanalumab, a mAb that blocks the FAFF receptor and CFZ533 or iscalimab, a mAb that blocks CD40 pathway signaling are under investigation in a phase 2 study in patients with SLE and the primary outcome is an SRI-4 response at week 29 [42].

A phase Ib/IIa of orelabrutinib (ICP-022) aims to assess the safety, preliminary efficacy and tolerability in patients with mild to moderate SLE [43]. A phase 2 study aims to evaluate the safety and effectiveness of branebrutinib in patients with autoimmune diseases including SLE [44]. Elsubrutinib and upadacitinib treatments that are given alone or in combination are currently evaluated in patients with moderate to severe SLE [45]. The primary outcome of this phase 2 study is the achievement of SRI-4 and steroid dose ≤ 10mg prednisone equivalent once a day at week 24.

A 76-week, 3-part 1b/2 study aims to assess the pharmacological properties, safety and preliminary efficacy of tofacitinib in young adults with moderate to severe skin involvement due to lupus [46]. Brepocitinib (JAK1 and TYK2 inhibitor) is currently under evaluation in a dose-ranging phase 2 study in patients with SLE refractory to standard treatment [47]. The primary endpoint is SRI-4 at week 52. Deucravacitinib (TYK2 inhibitor) is under investigation in a phase 2 study in patients with lupus nephritis [48].

Secukinumab is a human IgG1 monoclonal antibody that selectively binds to interleukin-17A (IL-17A). A phase III study evaluates the efficacy and safety of secukinumab in combination with standard treatment in patients with active lupus nephritis. The primary outcome is the proportion of patients achieving complete renal response at week 52 [49].

Other potential treatments

Low-dose IL-2 might also be effective in patients with SLE. A randomized, placebo-controlled study showed that the SRI-4 response rate was 65.2% of the patients in the IL-2 group and 36.7% in the placebo group (p=0.027) at week 24 [50]. The primary endpoint which was the SRI-4 response at week 12 was not met. Regarding lupus nephritis, complete renal response was achieved in 53.85% of the patients in the IL-2 group compared to 16.67% in the placebo group (p=0.036). A multicenter, double-blind, placebo-controlled trial will establish which of the three different dosages of IL-2 would be more efficacious and safer for patients with SLE [51].

Lenabasum is a synthetic endocannabinoid receptor type 2 agonist that activates innate immunity without immunosuppression. A phase 2 study evaluates the efficacy and safety of lenabasum in SLE patients with active joint disease and at least moderate pain [52]. It has been found that a single nucleotide polymorphism in the gene for the N2A subunit of the N-methyl-D-aspartate (NMDA) receptor, GRIN2A, encodes augmented NMDA receptor activity. Memantine is an NMDA receptor antagonist and is currently evaluated in a phase 2 study in patients with cognitive dysfunction [53]. A phase 1b/2 study aims to evaluate KZR-616 (a selective immunoproteasome inhibitor) in SLE patients with and without renal involvement [54].

Cenerimod is a selective agonist for the G-protein-coupled sphingosine-1-phosphate receptor 1 (S1P receptor 1 or S1P1), also known as endothelial differentiation gene 1 (EDG1). It seems to be a potent immunomodulator due to its effects in the number of circulating and infiltrating T- and B-cells. In a phase II study cenerimod was introduced at different doses in patients with SLE [55]. T- and B-cells were measured by flow cytometry before and at 12 weeks after treatment. There was a reduction of CD4+T cells (95%) and CD19+B cells (90%) and also a reduction of antibody-secreting cells (85%). The safety profile of this agent is unknown. The purpose of a phase 2 study is to evaluate the efficacy and safety of 4 doses of cenerimod in patients with SLE [56]. The primary outcome is change of the modified SLEDAI from baseline to month 6.

Other potential therapeutic approaches such as Epstein Barr Virus-specific cytotoxic T lymphocytes [57], mesenchymal stem cells [58,59] and curcumin are also currently under investigation in patients with SLE [60].

DISCUSSION

This review demonstrates the continuous efforts in order to achieve a sufficient control of the manifestations of SLE. The trials that have been conducted or are currently under way, include a variety of regimens due

to the plethora of the disturbances implicated in SLE pathogenesis.

Lupus nephritis is an aspect of the disease often difficult to treat. Fortunately, two drugs, the orally administered voclosporin and the intravenous form of belimumab, have been recently approved by the FDA for the treatment of patients with lupus nephritis on top of standard of care. Regarding voclosporin, besides its efficacy persisting at 30 months, no drug interaction with MMF has been observed, while it is also associated with a more favorable effect on glucose and lipid levels than other calcineurin inhibitors. On the other hand, belimumab prevents time-to-organ damage progression, while it is not associated with arterial hypertension. A report suggests daratumumab that targets plasma cells as well as other immune cells, as an alternative therapeutic approach for patients with SLE. However, studies with greater numbers of patients are necessary to determine the efficacy and safety of daratumumab in patients with SLE. A pilot study suggests that the mTOR inhibitor sirolimus could also be a generally safe and well tolerated alternative therapeutic approach in the management of lupus nephritis in patients who are intolerant to standard treatment or in cases of a history of malignancy. Treatment options for other aspects of the disease such as neuropsychiatric involvement are quite limited. A common symptom that dramatically decreases the quality of patients' lives is fatigue and cannot be managed sufficiently so far.

Sometimes a combination of treatments might be necessary to be introduced, since lupus is a multifactorial disease. Generalized immunosuppression should be minimized with the administration of novel agents, because infections that are potentially life threatening are always an important issue.

CONCLUSIONS

SLE is a multifactorial disease often difficult to manage. Occasionally, combination therapy is mandatory to control disease activity. Due to the extreme heterogeneity of the disease, personalized approaches might also be important. Apart from the efficacy of a treatment, the safety profile is another important issue.

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