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Chapter

Targeted Therapies for Systemic Lupus Erythematosus (SLE): A Critical Appraisal

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Abstract

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease characterized by a wide range of manifestations from mild to life-threatening. Prognosis has markedly improved in the last decades due to earlier diagnosis, prevention of comorbidities, and the use of more intensive treatment regimens. However, the high rates of morbidity, despite treatment, reflect the presence of numerous unmet medical needs in patients with SLE, calling for new, treat-to-target strategies. To date, only two biological agents, belimumab and recently anifrolumab, have been approved in patients with SLE with several others showing promising results. In this review, we critically review the data, with emphasis on the approved biologics.

Keywords: systemic lupus erythematosus, pathogenesis, biologic therapies, targeted therapies

1. Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with significant morbidity and mortality rates. Hydroxychloroquine remains the hallmark in the management of SLE, exerting beneficial effects not only in mild manifestations but also in serious organ involvement [1]. In 2011, belimumab, a monoclonal antibody antagonizing soluble B-lymphocyte stimulator protein (BLyS) became the first approved biologic treatment in SLE patients with active, extrarenal, seropositive disease [2]. A decade later, in 2021, the US Food and Drug Administration (FDA) approved anifrolumab, a monoclonal antibody antagonist of the type 1 interferon receptor for the treatment of adult patients with moderate to severe SLE who are receiving standard therapy [3].

Despite these advances, corticoid dependence and the high rates of relapse underscore the need for more efficient treatment strategies.

In this chapter, we will review current as well as emerging biological therapies in SLE and provide the mechanistic rationale behind their development (**Table 1**).

- SLE pathogenesis is multifactorial and elusive
- In genetically predisposed humans, epigenetic factors such as DNA methylation, environmental factors including ultraviolet light and hormonal factors, lead to loss of tolerance to self-antigens, and immune responses
- Defective clearance of apoptotic cells plays also a central role to SLE pathogenesis, leading to the accumulation of endogenous nucleic acids, stimulating Toll-like receptors (TLRs), and inducing a strong type I interferon (IFN) production
- Autoimmunity is sustained and amplified by multiple cytokines by multiple immune reactants including immune complexes and cytokines

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Table 1.
Keys to SLE pathogenesis [4–7].

2. Steps to SLE pathogenesis

The pathogenesis of SLE is elusive and multifactorial. Mutations in genes related to toll-like receptors and type 1 interferon (IFN) signaling pathways and apoptotic waste clearance epigenetic factors such as DNA methylation and environmental factors including ultraviolet light, hormones, and viruses contribute to its manifestation [4]. Over 100 genetic loci identified through genome-wide association studies (GWAS) are associated with SLE [5].

Defective clearance of apoptotic cells and the accumulation of apoptotic debris play a key role in SLE pathogenesis [6], by stimulating the production of IFNa and promotion of autoimmunity due to a breakdown of self-tolerance. Neutrophil extracellular traps released by dying neutrophils during a process called NETosis may serve as well as a source of autoantigens [7]. Another key to SLE pathogenesis is Toll-like receptors (TLRs). TLRs are expressed in multiple immune cells including dendritic cells, macrophages, B and T cells are also stimulated by nucleic acids contained in apoptotic cells [4] and inducing a strong type I IFN production and plasmacytoid dendritic cells' activation.

The amplification and maintenance of autoimmunity in SLE patients are driven by multiple immune reactants including immune complexes, type I IFN, and other cytokines including B- cell activating factor (BAFF or BLyS), the target of Belimumab. Loss of T and B cell tolerance, deficient regulatory T cells (Tregs), aberrant development of B cells leading to production of autoantibodies play also a central role in SLE pathogenesis.

3. B-cell targeting treatments

B-cells are key cells in the pathogenesis of SLE, and their targeting has drawn the attention for several decades.

3.1 BAFF/BLyS inhibition

B-cell activating factor (BAFF) is a cytokine responsible for proliferation, survival, and differentiation of B lymphocytes into antibody producing

plasmocytes, playing a crucial role in the pathogenesis of SLE. The presence of anti-BAFF antibodies correlated with disease severity and the presence of IFN signature in SLE patients [8].

These findings led to further research on the use of BAFF as a therapeutic target in SLE patients.

3.2 Belimumab

Belimumab is a human monoclonal anti-BLyS antibody binding to and antagonizing soluble human BLyS and selectively reducing the numbers of subsets of CD20+ B lymphocytes [2]. It was approved by FDA after the results of BLISS-52 and BLISS-76 [2, 9], two multicenter, placebo-controlled studies. In both studies, belimumab was associated with a significantly higher SRI-4 response rate at 52 weeks and reduction of severe SLE flares with an excellent safety profile, in patients with active SLE. Patients with severe active lupus nephritis or severe central nervous system (CNS) manifestations were excluded from the study. In 2020, Belimumab proved its efficacy in patients with active lupus nephritis as an add-on to standard of care therapy, by improving rates of achievement of primary efficacy renal response and a complete renal response at week 104 [10]; these results were though significant only in the mycophenolate group and not in the cyclophosphamide or azathioprine group. Importantly, belimumab was efficient in reducing the risk of flares in patients with refractory SLE after treatment with Rituximab [11]. Belimumab has also proven its efficacy in pediatric SLE patients [12].

3.3 Other BLyS inhibitors

Atacicept is a dual APRIL/BLyS inhibitor, reducing total B cell, plasma cell, and serum immunoglobulin levels, which showed evidence of efficacy in the ADRESS IIB study, with SLE patients with moderate to high disease activity [13]; in this study, patients with severe active renal or CNS involvement were excluded.

Blisibimod is a potent and selective BAFF inhibitor composed of a tetrameric BAFF binding domain fused to a human IgG1 Fc region. Blisibimod failed to meet the SLE responder Index-6 (SRI-6) primary endpoint in the PEARL-SC phase III trial, including SLE patients with seropositive SLE and moderate to high disease activity (SELEnA-SLEdAI) score ≥ 10 despite standard-of-care medications [14]; however, it showed encouraging results in terms of successful steroid reduction, decrease of proteinuria and biomarker responses.

Tabalumab, a human IgG4 monoclonal antibody binding and neutralizing membrane and soluble BAFF versus placebo plus standard of care, failed to prove its efficacy in the ILLUMINATE-1 study, a phase III trial in patients with moderate to severe SLE [15].

3.4 B-cell depletion strategies

B cells play a fundamental role in the pathogenesis of SLE through cytokine and autoantibody production and T cell activation. Multiple B-cell depleting strategies have been studied in patients with SLE, but they are most of the times reserved for the treatment of refractory patients.

3.5 Rituximab

Rituximab is a chimeric anti-CD20 monoclonal antibody, sparing stem cells and plasma cells. Despite the crucial role of lymphocytes B in SLE, there are no large randomized controlled trials confirming its efficacy, probably due to study design problems. In the EXPLORER trial, a multicenter, double-blind, placebo-controlled trial, rituximab failed to achieve major or partial clinical responses, as assessed by the BILAG index score [16]. Rituximab was also evaluated in patients with active proliferative lupus nephritis, in the LUNAR trial [17], in association with mycophenolate mofetil; the primary end point, superior response rate in the rituximab group, was not met, but patients treated with rituximab showed higher improvement in serological activity and proteinuria than those treated with placebo. Rituximab has shown evidence of effectiveness in patients with NPSLE as induction therapy as well as in refractory cases, in case series and non-controlled studies [18], but these results need to be confirmed in larger randomized controlled trials.

3.6 Obinutuzumab

Obinutuzumab is a Type II anti-CD20 monoclonal antibody used in the treatment of B-cell malignancies [19]. In lupus-prone MRL/lpr mice, it showed superiority not only in terms of B-cell depletion but also in clinical and biological parameters such as glomerulonephritis and anti-RNA autoantibody titers [20]. These encouraging results were confirmed in a small case series of nine patients with secondary non-response to rituximab; of note one unvaccinated patient died from Covid-19 [21]. Following these data, obinutuzumab was tested in patients with proliferative lupus nephritis in association with mycophenolate mofetil and steroids, in NOBILITY, a phase 2, randomized, double-blind, placebo-controlled trial. In this study, Obinutuzumab was superior to placebo in the achievement of complete renal response at week 104 (26 (41%) vs. 14 (23%), $p = 0.026$) [22].

3.7 Ofatumumab

Ofatumumab is a human IgG1κ anti-CD20 monoclonal antibody that binds to CD20 with a higher affinity compared with rituximab, used in the treatment of chronic lymphocytic leukemia and relapsing remitting multiple sclerosis, which has been used with success in patients with RA [23]. In SLE, it has mostly been studied in patients with prior allergic reaction to rituximab with a good safety profile [24]. In a case series of four patients with refractory lupus nephritis with good clinical response but the development of adverse effects to rituximab, it led to a reduction albuminuria in all four cases [25]. One patient developed widespread urticaria and the treatment was discontinued. To date, there are no RCTs evaluating its efficacy in SLE patients.

3.8 Ocrelizumab

Ocrelizumab is a recombinant humanized anti-CD20 monoclonal antibody, with higher avidity to CD20 compared with rituximab [26]. There are two RCTs assessing its efficacy in SLE. In the BELONG trial [27], ocrelizumab was evaluated in patients with active proliferative lupus nephritis in two treatment regimens (400 and 1000 mg) in association with mycophenolate mofetil or cyclophosphamide

(eurolupus, followed by maintenance with azathioprine). The study was terminated early due to severe infections in the ocrelizumab group when combined with mycophenolate mofetil; renal response was not superior in the ocrelizumab group.

3.9 Epratuzumab

Epratuzumab is a humanized anti-CD22 antibody that preferentially modulates the exaggerated activation and proliferation of B cells in SLE patients [28]. Epratuzumab was evaluated in multiple RCTs in SLE with mixed results. In the EMBODY 1 and 2 studies, epratuzumab failed to meet the primary endpoint of response rate at week 48 according to BILAG-based Combined Lupus Assessment (BICLA) definition [29]. In the underpowered ALLEVIATE-1 and -2 studies and its extension study [29, 30], epratuzumab showed encouraging though nonstatistically significant results.

3.10 CAR-T-cells

Chimeric antigen receptor (CAR)-modified T cells are genetically engineered cells that recognize CD19 and other B-cell surface antigens, currently used in B-cell malignancies. In SLE murine models, the use of CAR-T-cells led to sustained B-cell depletion [31]. CAR-T-cells were used in a 20-year-old patient with active SLE with active class IIIa lupus nephritis with nephrotic syndrome, pericarditis, pleurisy, rash, and arthritis, non-responding to conventional immunosuppression [32]. CAR-T-cell treatment was preceded by preparatory lymphodepletion with fludarabine and cyclophosphamide. The patient achieved complete clinical and serological remission within 5 weeks without severe adverse effects.

4. Targeting long-lived plasma cells

In SLE-prone mice, long-lived plasma cells (LLPCs) are present in the spleen and bone marrow, before week 4 [33] and contribute to the production of autoantibodies before the onset of symptoms. In SLE patients, long-lived plasma cells play a crucial role not only in the pathogenesis but also in the sustainment of autoimmunity and are unresponsive to standard B-cell depletion treatment by rituximab [34]. Treatment regimens, such as the combination of rituximab and belimumab [35], work toward this direction.

4.1 Daratumumab

Daratumumab is an anti-CD38 monoclonal antibody used in the treatment of multiple myeloma as well as in the treatment of AL amyloidosis [36]. It has been successfully administered in two patients with refractory SLE [37]; belimumab was used as maintenance therapy, and treatment response was sustained during the 12-month follow-up period. The success of daratumumab was due to its pleiotropic effect in SLE patients: it eliminates LLPCs while leading to a reduction to interferon type I activity and reduction of CD19n B-cells. This observation led to the DARALUP study, a monocenter, open-label Phase II trial for refractory SLE patients [38].

5. IFN

5.1 Rationale for INF antagonists use in SLE

Interferon is a key cytokine in the pathogenesis of SLE. Interferon (IFN) signature genes are highly expressed in the peripheral blood of SLE patients [39], and interferon-inducible gene expression is associated with disease activity and lupus nephritis [40, 41]; high levels of ultrasensible IFN-a equally seem to be related with a higher risk of relapse in patients with quiescent SLE [42]. There are multiple biological therapies targeting IFN under investigation.

5.2 Anifrolumab

Anifrolumab is a human monoclonal antibody binding the IFN-I receptor subunit 1, inhibiting IFN-I signaling. It is the second biological therapy to be approved by FDA in SLE patients following the TULIP-1 [43] and TULIP-2 trials [3]. TULIP-1 [3] was a phase 3, double-blind, RCT of adults with moderate to severe SLE despite standard-of-care treatment, where patients were randomized to receive anifrolumab in two treatment regimens or placebo; the primary endpoint of SRI-4 at week 52 was not met, but a clinical benefit was observed in the anifrolumab group in terms of steroid sparing effect, skin lesions (as assessed by Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)) and British Isles Lupus Assessment Group–based Composite Lupus Assessment (BICLA) response. In TULIP 2 [3], patients were assigned to receive anifrolumab at 300 mg every 4 weeks or placebo; the primary endpoint of BICLA response at week 52 was achieved (47.8% in the anifrolumab group and 31.5% in the placebo group, p = 0.001). In a phase II trial assessing anifrolumab in association with mycophenolate mofetil and steroids, in patients with active proliferative LN [44], the primary endpoint of change in baseline 24-hour urine protein-creatinine ratio (UPCR) at week (W) 52 was not met, but there were encouraging though nonstatistically significant results in the anifrolumab group in complete renal response and corticoid sparing effect. Patients with high interferon signature genes were more likely to reach BICLA response at week 52 according to a post-hoc analysis [45]. In terms of safety, there was an increased risk of herpes zoster in the anifrolumab group [3, 44].

6. Other interferon targeting therapies

Rontalizumab is a human anti-IFN-α monoclonal antibody neutralizing all 12 IFN-α subtypes; it was assessed in SLE patients with active SLE in the ROSE trial [46], failing to reach the BILAG and SRI-4 primary and secondary endpoints at week 24. Sifalimumab is a human, IgG1 κ monoclonal antibody that neutralizes the majority of IFN-α subtypes [47]; despite the encouraging results of a phase IIb RCT, meeting the primary endpoint of SRI-4 response at week 52, the clinical trials were halted.

IFN-a kinoid is an immunotherapeutic vaccine composed of inactivated recombinant human IFN-α2b coupled to a T-helper carrier protein (keyhole limpet hemocyanin). Its aim is to induce antibodies against IFN by active immunization, thus reducing the expression of IFN-induced genes [48]. This hypothesis was confirmed

in transgenic mice expressing human IFNα2b [49]. The efficacy and safety of IFN-K were evaluated in a phase IIb, randomized, double-blind, placebo-controlled trial in adults with active systemic lupus erythematosus (SLE) and positive interferon gene signature [44]. The primary endpoints were neutralization of IFN gene signature and the BICLA at week 36 modified by mandatory corticosteroid (Cs) tapering. At week 36, 91% of the patients receiving IFN-K had neutralizing IFN antibodies and reduced IFN signature; on the contrary, the clinical primary endpoint of BICLA at week 36 was not met; of note 53% of the treated patients attained LLDAS at week 36 (vs 30% in the placebo group, p = 0.0022). IFN-K had also a significant corticoid sparing effect.

6.1 JAK inhibitors

Janus kinases (JAKs) and signal transducers and activators of transcription (STATs) are responsible for signal transduction of multiple cytokines and growth factors in different cell types [50]. The JAK/STAT pathway is involved in the maintenance of immune tolerance; thus, JAK/STAT dysregulation is implicated in many autoimmune diseases [51] and is an attractive treatment target. JAK inhibitors are already used in multiple rheumatic diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA). There are many in vitro and in vivo studies supporting the involvement of JAK/STAT pathway in SLE [52]. Of note, the STAT4 gene polymorphism has been associated with SLE susceptibility and renal disease [53].

Tofacitinib a JAK 1 and 3 inhibitor was evaluated in a phase I trial in SLE patients [54]. Tofacitinib was found not only to be safe but also improved cardiometabolic and immunologic parameters associated with the premature atherosclerosis and decreased IFN I gene signature.

Baricitinib is a selective JAK 1 and 2 inhibitor; in a phase II double-blind placebo-controlled RCT, it proved to be safe and effective at the dose of 4 mg in the resolution of arthritis or rash at week 24 [55]. In murine models, baricitinib ameliorated renal inflammation and led to the recovery of the expression of structural proteins in podocytes [56], indicating its potential role in the treatment of LN.

Solcitinib, a selective JAK 1 inhibitor, was evaluated in a phase II study in patients with active, extra renal SLE [57]. The study terminated due to absence of significant effect on mean IFN transcriptional biomarker expression (all panels, 50 patients). Safety data showed elevated liver enzymes in six patients (one confirmed and one suspected case of drug reaction with eosinophilia and systemic symptoms), leading to immediate dosing cessation.

Filgotinib, a Janus kinase 1 inhibitor, and lanraplenib, a spleen kinase inhibitor, have been assessed in patients with cutaneous lupus erythematosus (CLE) [58]. In a phase II trial, the primary endpoint of change from baseline in Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity (CLASI-A) score at week 12 was not met; two serious adverse events (SAE) (one major cardiovascular event and hypersensitivity) were reported in the lanraplenib group and one SAE in the filgotinib group. Filgotinib and lanraplenib were also evaluated in patients with lupus membranous nephropathy [59]. The study included only nine patients, of whom only four in the filgotinib group and one in the lanraplenib group completed week 16; in the filgotinib group, all four patients had a median reduction of 50.7% in 24-hour urine protein. Further research is necessary before drawing any conclusions.

7. Other cytokine-targeted therapies

Cytokine production is distinct in patients with SLE compared with patients with other rheumatic diseases and may change during disease course and different SLE phenotypes [60]. There are multiple cytokines not only inflammatory (interferons type I and II, IL-6) but also immunomodulatory (such as IL-10 and TGF-β), implicated in the pathogenesis of the disease [61].

7.1 Targeting Interleukine-6

Interleukine 6 (IL-6) is a cytokine with pleiotropic effects in different target cells [61, 62]. In SLE patients there is an increased production and increased serum levels of IL-6 [63]. IL-6 seems to be implicated in lupus nephritis [64] and has an active role in mesangial proliferative glomerulonephritis [65]. Studies also suggest that IL-6 is implicated in an autocrine manner in maintaining B-cell hyperactivity [66].

Tocilizumab is a humanized mAb against the IL-6 receptor (IL-6R). In SLE patients, it was assessed in an open-label phase I dosage-escalation study [67] in 16 patients with mild-to-moderate disease activity in three treatment regimens: 2 mg/kg, 4 mg/kg and 8 mg/kg every 2 weeks, with a good clinical and serological response in approximately half of the patients; neutropenia occurred in all three groups with two grade III neutropenia in the 8 mg/kg group.

Sirukumab is a human, anti-IL-6 monoclonal antibody binding to IL-6 with high affinity and specificity. It has been evaluated in a phase I trial in 31 patients (23 treated with sirukumab) with cutaneous lupus erythematosus (CLE) and 15 patients with SLE (10 treated with sirukumab), with a good tolerance, but with some cases of neutro-, lympho-, or thrombocytopenia in the sirukumab group [68]. Its efficacy was also assessed in a phase II trial in patients with active proliferative lupus nephritis with persistent proteinuria despite standard of care [69], with disappointing results.

PF-04236921, a fully human immunoglobulin G2 monoclonal antibody, failed to prove its efficacy in lupus in phase II trials [70].

7.2 Interleukin 17

Interleukin 17 is a pro-inflammatory cytokine implicated in the pathogenesis of various RMDs. In SLE, the IL-17 axis seems to promote autoantibody production, immune complex deposition, and complement activation leading to tissue damage [71]. In patients with SLE, there is an increased number of Th17 cells as well as high serum levels of IL-17A, correlated with disease activity [72]. IL-17 seems to be implicated in lupus nephritis [73].

Secukinumab, a human IgG1κ monoclonal antibody, is actually assessed in a phase III trial in combination with standard of care in patients with proliferative LN [74].

7.3 Interleukin 12/23 axis

The IL23/L17 axis plays a fundamental role in multiple autoimmune diseases. In patients with active SLE, there is an upregulation of serum IL-23 and IL-23 receptor compared with healthy controls, and IL-23 seems to limit in vitro IL-2 production, leading to the promotion of autoimmunity [75]. On the other hand, IL-12 through the ILL-12-STAT4 axis is also involved in lupus pathogenesis inducing both IFN-γ and IL-21 by human CD4 + T cells [76]; of note, STAT4 is one of the most dominant risk alleles in SLE [77].

Ustekinumab is a fully human monoclonal antibody directed at the p40 subunit shared by the cytokines IL12 and IL23; in a phase 2 RCT in patients with active SLE, it resulted in higher rates of SRI-4 response in addition to standard of care at week 24 compared with placebo (p = 0•006) [78].

7.4 Low-dose IL-2

Regulatory T-cells (Tregs) under the influence of interleukin 2 (IL-2) play a crucial role in the maintenance of immune tolerance; in SLE patients there is an acquired deficiency in IL-2 leading to defects of Tregs [79]. Low-dose IL-2 corrects defects in Tregs in patients with SLE leading to restoration of immune tolerance [80]. Its potential role in clinical practice has been evaluated in two RCTs [81, 82] with a good safety profile and clinical response resulting to complete remission in seven patients with LN (53.85%, compared with 16.67% in the placebo group, p = 0.036).

7.5 T-cell strategies

In SLE, T cells are chronically active due to T-cell receptor rewiring, hypomethylation of genes related to cell activation, and mTORC1 activation [83] and are implicated in SLE pathogenesis through interaction with B-cells by enhancing the production of autoantibodies, promotion of B-cell differentiation, proliferation, and maturation [84]. Multiple T-cell strategies have already been evaluated in SLE patients.

8. CD28-CD80/86 pathway

8.1 Abatacept

Abatacept is a fusion protein of cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) with the Fc part of immunoglobulin G (IgG), selectively modulating CD80/CD86:CD28 costimulatory signal, approved for patients with RA [85]. Its results have been evaluated in multiple RCTs in SLE. Abatacept failed to prove its efficacy in a phase 2 RCT of 118 patients with SLE with non-life-threatening manifestations, but with some encouraging results in some domains such as polyarthritis [86]. Abatacept has also been evaluated in patients with proliferative LN [87], failing to meet the primary endpoint of time to confirmed complete response but was associated with greater improvements of serological activity and 20–30% greater reduction of in mean urinary protein-to-creatinine ratio compared with placebo. In the phase 2 ACCESS trial [88], patients with LN received cyclophosphamide (Eurolupus) in monotherapy or in association with abatacept; no difference was observed in the primary endpoint of frequency of complete response at week 24 (33% in the placebo arm versus 31% in the abatacept group). Abatacept has also been assessed in a phase III trial in association with MMF [89], not reaching the primary endpoint of complete renal response at W52, but with a favorable effect in proteinuria and biomarkers.

8.2 Lulizumab and theralizumab

Lulizumab pegol is an anti-CD28 domain antagonist antibody, evaluated in a Phase 2 study in patients with active SLE, not reaching the primary endpoint of the

proportion of responders using the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) at Week 24 [90]. Theralizumab, a CD28 superagonist [91], was evaluated in a phase II study; the trial was terminated for administrative reasons.

8.3 CD40-CD40L

CD40 ligand (CD40L) is expressed on naïve and activated CD4+ T cells and platelets [92]. Its receptor, CD40, is expressed on a wide range of cells including B cells. CD40L-CD40 interaction can contribute to autoreactive B cell survival [93], making it an attractive treatment target. In a phase 1 trial [94], dapirolizumab pegol, an anti-CD40L Fab' antibody fragment conjugated to polyethylene glycol (PEG), was safe and effective in patients with active SLE. Changes in the gene expression within the plasma cell and B-cell domains were also observed. These promising results were not confirmed in the phase 2 study [95] including patients with moderately to severely active SLE. BI 655064, another humanized anti-CD40 monoclonal antibody, was evaluated in patients with proliferative lupus nephritis in combination with mycophenolate mofetil [96]; the primary endpoint of complete renal response at W52 was not met. VAY736 and CFZ533, another 2 mAb blocking the CD40 pathway, are under investigation in patients with active SLE [97]. Finally, ruplizumab, another anti-CD40 ligand mAb, was evaluated in patients with LN leading to a decrease in hematuria, proteinuria, and biomarkers [98]; the trial was prematurely terminated due to thromboembolic complications.

8.4 ICOS pathway

Targeting inducible costimulator (ICOS) is a member of the CD28 superfamily, expressed on activated T cells and binding to B7RP1, present on B cells, dendritic cells, and monocytes [99], and playing a crucial role in humoral immunity, T-cell function, and differentiation to T follicular helper cells [100]. Two ICOSL antibodies (AMG557, MEDI-570) and one ICOSL and BAFF bispecific (AMG570) have been evaluated in phase 1 trials [101–104] with a good safety profile.

9. Other molecules

9.1 Rigerimod

Rigerimod is a spliceosomal peptide recognized by lupus CD4+ T cells [105]. In a phase 2 trial, rigerimod was safe and efficient in the achievement of SRI-4 response at W12, in the group receiving 200 μg subcutaneously every 4 weeks (61.9% versus 38.6 in the placebo group ($p = 0.016$)).

9.2 Abetimus

Abetimus sodium is a tetrameric oligonucleotide conjugate reducing antidouble-stranded DNA [106]. Due to the anti-ds DNA antibodies' role in the pathogenesis of LN, abetimus was evaluated in phase 2 and phase 3 trials in a cohort of patients at high risk of nephritic flare [107, 108]. The primary endpoint of prolongation of time to renal flare was not met, despite the reduction of anti-ds DNA.

9.3 SM101

SM1O1 is a human soluble non-glycosylated version of the Fcγ receptor IIB, inhibiting the binding of immune complexes to cell-standing Fcg receptors [109] that has already been evaluated in a phase I/II trial in patients with immune thrombocytopenia with a good safety profile and clinical response [110]. In a phase 2a trial in 51 patients with SLE, it proved to be well tolerated and efficient, mostly in terms of improvement in arthritis and in skin rash (present in 75% and 50% patients, respectively) assessed by the BILAG scale [109].

10. Targeting B-cell intracellular functions

10.1 Targeting Bruton's tyrosine kinases

Bruton's tyrosine kinase (BTK) is implicated in both B-cell and Fcγ-R-mediated myeloid cell activation, playing a crucial role in B-cell survival and proliferation. BTK represents a treatment target in patients with hematological malignancies [111]. BI-BTK-1, an irreversible BTK inhibitor, ameliorated multiple pathological endpoints associated with kidney disease in two distinct murine models of spontaneous lupus nephritis [112]. Fenebrutinib (GDC-0853) a noncovalent, oral, selective BTK inhibitor was evaluated in a phase 2 trial [113], in patients with active SLE; although februtinib significantly reduced levels of CD19-positive B cells, anti- double-stranded DNA autoantibodies, and a BTK-dependent RNA signature expressed in plasmablasts compared with placebo, it failed to achieve SRI-4 response at W48. Ibrutinib, another BTK inhibitor used in B-cell malignancies, resulted in reduced levels of autoantibodies and less severe nephritis in SLE murine models [114].

10.2 Proteasome inhibitors

Long-lived plasma cells are resistant to conventional and B-cell depleting strategies and play a critical role in the maintenance of autoimmunity in patients with refractory SLE [115]. Bortezomib, a proteasome inhibitor used in multiple myeloma, has successfully been used in patients with multiple refractory autoimmune diseases including ITP [116] and warm antibody hemolytic anemia [117]. In 12 patients with refractory SLE, it not only depleted plasma cells but also ameliorated clinical manifestations [118]. These encouraging results were not confirmed in a multicenter RCT including 14 patients: there were neither serological nor statistically significant clinical effects in the bortezomib group [119]. However, in patients with LN, it seemed to reduce proteinuria, improve renal function, and decrease autoantibodies, with mild adverse events [120].

10.3 Eculizumab

Eculizumab is a fully humanized IgG2/IgG4 monoclonal antibody directed at C5, preventing the formation of the terminal complement complex, used in atypical hemolytic uraemic syndrome (aHUS) and paroxysomal nocturnal hemoglobinuria (PNH) [121]. Eculizumab has been successfully used in patients with secondary TMA due to SLE and/or APS that are non-responsive to standard of care [122].

10.4 Irbedomide

Irbedomide is a cereblon modulator targeting transcription factors Ikaros, an essential regulator of common lymphoid progenitor (CLP) stem cells and Aiolos, necessary for memory B-cell and plasma cell formation [123]. In SLE patients, irbedomide seems to modulate B-cell activation and differentiation downstream of TLR7 [123]. In a phase 2 trial, 54% of the patients receiving irbedomide at the dose of 0.45 mg reached SRI-4 at week 24, compared with 35% in the placebo group (P = 0.01); this difference was not statistically significant in the other irbedomide dose regimens [124].

11. Concluding remarks

Despite recent advances in the management of the majority of autoimmune diseases and the emergence of novel biological therapies, therapeutic options in SLE are rather limited. For over 50 years, and before the approval of belimumab, corticosteroids, antimalarians and traditional immunosuppressants were the only therapeutic options. This is probably due to the heterogeneity and multi-organ involvement of the disease, problems in study designs including too strict endpoints (such as no BILAG B and complete renal response), racial differences in terms of prognosis and treatment response, and the difficulty in the achievement of statistically significant difference when novel biological therapies are tested on top of the already effective, standard of care. Moreover, severely affected patients including patients with lupus nephritis and NPSLE are frequently excluded from RCTs, leading to a lack of information for these patients. Targeted treatment guided by patient's clinical and biological phenotype with the use of biomarkers and omics may result in an optimal management of the disease and achievement of remission.

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