Meant to B: B cells as a therapeutic target in systemic lupus erythematosus

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B cells have a prominent role in the pathogenesis of systemic lupus erythematosus (SLE). They are mediators of inflammation through the production of pathogenic antibodies that augment inflammation and cause direct tissue and cell damage. Multiple therapeutic agents targeting B cells have been successfully used in mouse models of SLE; however, these preclinical studies have led to approval of only one new agent to treat patients with SLE: belimumab, a monoclonal antibody targeting B cell–activating factor (BAFF). Integrating the experience acquired from previous clinical trials with the knowledge generated by new studies about mechanisms of B cell contributions to SLE in specific groups of patients is critical to the development of new treatment strategies that will help to improve outcomes in patients with SLE. In particular, a sharper focus on B cell differentiation to plasma cells is warranted.

Introduction

Systemic lupus erythematosus (SLE) is a potentially devastating autoimmune disease. It is a leading cause of death in young women in the United States, predominantly affecting those of Hispanic and African American ancestry (1). Although recent advances in diagnosis and treatment have led to substantial improvement in prognosis, the disease still has considerable morbidity and associated costs (2, 3). The currently available treatment options are not free of complications, and it is estimated that the percentage of deaths attributed to disease activity is similar to the percentage that can be attributed to infections secondary to immunosuppressive medications (4).

Unmet needs in patients with SLE include uncontrollable disease, recurrent flares, need for long-term immunosuppressive treatment, increased rates of infections, damage accrual that impairs quality of life, and diminished long-term survival. For these reasons, we need to develop new therapeutic strategies to treat SLE. These strategies must be based on knowledge about the mechanisms that drive inflammation and damage.

Despite the fact that some patients with SLE have low titers of autoantibodies, autoantibodies, especially of the IgG isotype, are considered the main effectors of SLE inflammation and damage. Anti–double-stranded DNA (anti-dsDNA) antibodies, in particular, are present in the kidneys of patients with lupus nephritis (LN) and in the skin. Transfer of anti-dsDNA antibodies from lupus-prone mice or SLE patients to healthy animals can cause nephritis (5–7) and induce the expression of inflammatory and profibrotic genes in renal cells (8, 9). Antibodies and immune complexes can induce local inflammation in the endothelium and interstitium, which in turn contributes to the inflammatory response (10). Evidence also supports CNS pathogenicity by a subset of anti-dsDNA antibodies that cross-reacts with the NMDA receptor (NMDAR) (11, 12). Other antibodies are also pathogenic: anti-phospholipid antibodies induce thrombosis (13, 14); anti–ribosomal P antibodies contribute to CNS manifestations (15); and anti-ribonucleoprotein (anti-RNP) antibodies induce neutrophil death by NETosis, which leads to production of type I interferon (IFN) by plasmacytoid dendritic cells (pDCs) (16). Supporting the relevance of this phenomenon, an association between IFN expression, anti-RNP antibodies, and kidney disease has been described (17). Importantly, it is not clear for all these antibodies whether affinity or fine specificity is critical for pathogenicity.

Antibodies are exclusively produced by plasma cells (PCs), which are terminally differentiated B cells. Thus, B cells are an obvious therapeutic target in SLE. However, B cells and antibodies also have critical functions in normal host defense against pathogens, and some autoantibodies, especially of the IgM isotype, have a protective role against the development of autoimmunity. IgM antibodies assist in the clearance of cellular debris. In the context of complement C1q and LAIR-1 activation, they inhibit inflammatory responses (18–21).

B cell function in health and SLE

B cells have functions in addition to being the precursors of PCs. B cells are important antigen-presenting cells (APCs) and are particularly instrumental in activating autoreactive T cells by presenting novel peptides of self-antigens (22–24). B cells function as APCs to drive the activation of autoreactive T cells in many autoimmune diseases, and this is presumed to be the basis for the benefit of B cell depletion therapy in multiple sclerosis and seronegative rheumatoid arthritis (25). Lupus-prone mice expressing a mutant transgene that allows the expression of surface immunoglobulin, but blocks the secretion of antibodies, develop nephritis (26); while this observation suggests that alternative functions of B cells in addition to secretion of autoantibodies are relevant in SLE pathogenesis, there is no clear evidence that B cells are important APCs in SLE.

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B cells make cytokines that can help support an immune response. For example, B cell–derived TNF is critical for the function of follicular dendritic cells in the germinal center (GC) response (27). A population of B cells with regulatory function (Bregs) has been also identified. The identification and presumably the function of these cells depend on their increased production of IL-10. Bregs can suppress inflammatory immune responses in mouse models of inflammatory arthritis, experimental allergic encephalitis, and lupus in an IL-10–dependent fashion (28, 29). The induction and suppressive activity of Bregs have been reported to be altered in SLE patients (30). However, IL-10 is considered to be pathogenic in SLE (31), and anti–IL-10 antibody has been used with success in a limited number of patients with SLE (32). Thus, the antiinflammatory role of IL-10–producing B cells and their relevance in SLE have yet to be defined.

B cell development

B cells are derived from a common lymphoid progenitor that also gives rise to T cells and NK cells. The main characteristic that differentiates B cells from other lymphoid cells is the expression in each cell of a unique immunoglobulin heavy and light chain, which allows recognition of antigen and is part of the B cell's signaling system. The diversity of the antibody repertoire derives from VDJ (or VJ) recombination and somatic hypermutation (33). All B cells initially express IgM with or without IgD; class switch recombination causes a change in the Ig isotype to IgG, IgA, or IgE, with each isotype having different functional characteristics.

The diversity of the B cell receptor (BCR) repertoire enables recognition of numerous pathogens but also generates a large number of immature B cells that recognize self-components, termed autoreactive B cells (34). As B cells mature, the percentage of autoreactive B cells is gradually reduced. This reduction is achieved by various tolerance mechanisms, including receptor editing, deletion, and anergy. Nonetheless, the mature B cell compartment still has a considerable percentage of autoreactive B cells (35, 36). The fact that IgG anti-dsDNA or anti-RNP antibodies are not detectable in the healthy population, while IgM autoantibodies are, highlights the importance of the peripheral tolerance checkpoints that prevent these autoreactive B cells from differentiating into IgG-producing PCs (37–40).

B cell subsets. There are different types of mature cells within the B cell lineage: B-1, marginal zone (MZ), and follicular cells. All types can differentiate into PCs, but they differ in many relevant characteristics, including their requirements for activation and differentiation and their role in the normal immune response in healthy subjects. B-1 cells are thought to represent a distinct lineage, and while they can produce autoantibodies, they are not thought to be a major contributor to SLE pathogenesis (41).

MZ and follicular B cells derive from immature B cells egressing from the bone marrow, termed transitional B cells (42). Transitional B cells are dependent for maturation on B cell–activating factor (BAFF) (43). Increased levels of BAFF allow autoreactive B cells to mature to immunocompetence. An expansion of transitional B cells has been reported in patients with SLE (44). This may relate to elevated levels of BAFF (45), which can be secondary either to disease activity or to therapy.

In mice, MZ B cells are localized within the MZ in the spleen, where they can serve as a first line of defense against antigens that arrive through the hematogenous route (46). They are highly responsive to TLR activation and costimulatory molecules, and rapidly differentiate into PCs (46–52) without a requirement for cognate T cell help. MZ B cells can also present antigen to T cells in the follicles and initiate T cell activation (53). In humans, IgM^+CD27^+ peripheral B cells are suggested to be a circulating population of MZ B cells (54, 55).

Follicular B cells have the most diverse repertoire among B cells and are the main contributor to the T cell–dependent responses, as well as to the GC response and memory B cell development.

B cell activation

After an encounter with antigen, follicular B cells migrate to the T-B border in lymph nodes or the spleen, where they interact with T cells (56, 57) that provide the costimulation and cytokines that contribute to B cell activation, proliferation, and differentiation. BCR engagement without costimulation induces B cell anergy. B cells receiving adequate signals become short-lived PCs in an extrafollicular response or enter into a GC response in which long-lived PCs (LLPCs) and memory cells are generated.

B cells in SLE have an increased response after BCR ligation (58, 59). This hyperresponsiveness can be intrinsic to the B cell (35), but also can be induced by the external milieu, as many molecules modify the threshold for BCR activation (60–62). Endosomal TLRs, TLR7 and TLR9, are activated by nucleic acids and enhance B cell activation. A higher expression of TLR9 in memory B cells and PCs has been observed in blood from patients with SLE and is associated with disease activity and the presence of anti-dsDNA antibodies (63–65).

Cytokines, such as IFNs, IL-21, and BAFF, can also contribute to B cell activation (66–68). Type I IFNs are considered central in SLE pathogenesis (69), and high levels of type I IFNs favor an extrafollicular over a GC response (41). BAFF and IL-21 stimulate B cell survival and proliferation and can induce IgM-to-IgG class switching (49, 70–72). Among cytokines, IL-21 is considered the strongest inducer of PC differentiation (73). IL-6 also induces PC differentiation (74); additionally, IL-6 induces IL-21 production by $CD4^+$ T cells (75). B cells are also subject to inhibitory signals: FcγRIIb, an inhibitory receptor that modulates B cell activation, is the only Fcγ receptor expressed on B cells. Although the mechanisms are not fully understood, impaired function of FcγRIIb is associated with SLE in mouse models and in humans (76).

Memory B cells initiate the secondary immune response, which arises faster than a primary response, and leads to higher titers of IgG antibodies with greater specificity and increased affinity for the antigen (77). Many anti-dsDNA antibodies possess features of secondary response antibodies (78–81). Delayed recovery of memory B cells in SLE patients who received B cell depletion therapy has been linked to better responses (82). Recently, a subpopulation of B cells called ABCs (83) has been described. This population is increased in patients with autoimmune disease. Its origin is related to B cell activation with TLR7, IL-21, and IFN-γ (84). ABCs are reported to be enriched in autoreactivity, and some evidence suggests they are precursors of PCs in patients with SLE. The presence of high numbers of ABCs in peripheral blood is associated with LN (85, 86).

The subpopulation of B cells that are the precursors of the autoreactive PCs in patients with SLE has not been clearly defined.

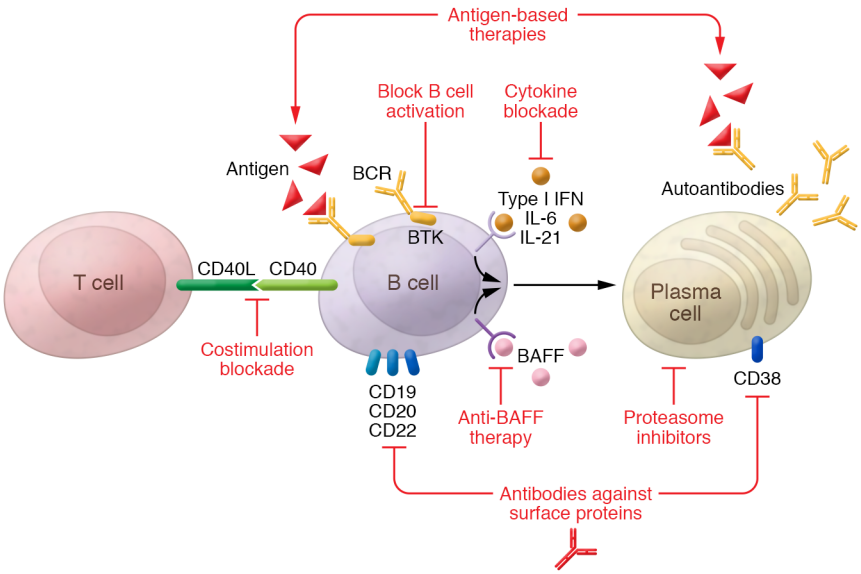

Figure 1. Different strategies to interfere with B cell proinflammatory function in patients with SLE. Strategies include B cell and plasma cell depletion (e.g., antibodies directed at surface proteins or proteasome inhibitors), selective depletion of autoreactive B cells (e.g., BAFF inhibition), antigen-based therapies that block pathogenic antibodies, and prevention of B cell activation (e.g., blockade of B-T cell costimulation or B cell–activating cytokines).

Using BCR sequencing to identify potential precursors of PCs, clones with similar BCRs to PCs were found in the naive, ABC, and memory compartments in patients with SLE (86, 87). There is also evidence suggesting that either the extrafollicular or the GC pathway is preferentially activated in patients with increased circulating plasmablasts (88).

Tolerance in SLE: selection versus activation defects

IgG autoantibodies in blood precede the clinical onset of SLE and are present in all patients at diagnosis. The origin and defects that lead to the production of autoantibodies have not been clearly established and may vary between patients (89). Some studies suggest an aberrant selection of B cells with defects in antigen-specific central tolerance or defective B cell anergy (38, 90–97), while other studies suggest that the major alteration in SLE is polyclonal activation and increased IgG PC differentiation (98, 99). This difference is not trivial, as the therapeutic strategies might be different in each case. Antigen-based therapies can be used in the case of selection defects; in contrast, in the case of abnormal polyclonal activation, the treatment might be focused on blocking the differentiation of B cells into PCs.

B cell–based therapeutics: approaches and experience with mouse models

Much of our understanding of SLE pathogenesis and treatment comes from mouse models. These models have been used to test therapeutic strategies prior to clinical trials. A full review of the available mouse models of SLE is beyond the scope of this article and can be found elsewhere (100, 101). The two strains that are more commonly used are NZB/NZWF1 (also known as NZB/W) and MRL/lpr. NZB/W mice develop splenomegaly and hypergammaglobulinemia with anti-nuclear antigen (ANA) and anti-dsDNA antibodies. Their clinical manifestations are immune complex glomerulonephritis and vasculitis (102). MRL/lpr mice have a complex genetic background but harbor a mutation in the FAS gene that reduces apoptosis in B and T cells and is considered a fundamental catalyst of disease. MRL/lpr mice develop prominent splenomegaly and lymphadenopathy and multiple autoantibodies (including anti-DNA, anti-SM, anti-Ro, and anti-La); their clinical manifestations are more diverse and include glomerulonephritis, arthritis, vasculitis, and skin rash (100).

There are multiple ways to interfere with B cell inflammatory function in SLE (Figure 1). These strategies can be classified as (a) B cell depletion, (b) anti-BAFF therapy, (c) therapy directed against PCs, (d) interference with B cell costimulation and activation, and (e) antigen-based therapies, each aimed to affect B cells with pathogenic specificities.

B cell depletion. A straightforward, but nonspecific, way to interfere with B cell function is by directly diminishing their number. There are multiple mechanisms to induce B cell depletion. Cyclophosphamide, which has been a mainstay of SLE therapy for decades, preferentially targets B cells.

Cytotoxic antibodies directed against markers present on the B cell surface are a more recently explored approach. As they mature, B cells express different programs of cell surface markers; thus, different subpopulations of B cells will be affected according to the molecule used as a target for B cell depletion. CD20 is expressed on the surface of most mature B cells, with the exception of PCs. The exact function of CD20 has not been clearly established. This receptor is the target of rituximab, a chimeric IgG1 monoclonal antibody. In lupus-prone mice that express a transgenic human CD20, rituximab was able to induce B cell depletion and ameliorate the manifestations of disease (103). Early administration of rituximab in young led to a long-term delay in disease onset. The mechanism of action included reduction in T cell activation (104). More recently, the use of chimeric antigen receptor T cells has been proposed as an alternative method to induce B cell depletion (105).

Selective depletion of autoreactive B cells by targeting of BAFF. BAFF is part of the TNF family. It is secreted by activated T cells, monocytes, macrophages, and dendritic cells and signals through three receptors: BAFF receptor (BAFF-R), transmembrane activator and calcium modulator interactor (TACI), and B cell maturation antigen (BCMA). The administration of exogenous BAFF increas-

es the levels of serum immunoglobulin (68), and BAFF-transgenic mice develop an SLE-like disease (106, 107). Deletion of the BAFF gene in lupus-prone mice prevents initiation of disease, and neutralization of BAFF improves lupus manifestations (108–112).

Excess BAFF rescues self-reactive early B cells from deletion (113). In murine studies, elevated levels of BAFF promote maturation of autoreactive B cells, and reduction of BAFF levels following B cell depletion reduces the number of autoreactive cells in the reconstituted B cell repertoire (114). The efficacy of anti-BAFF therapy is independent of an intensive reduction in total B cell numbers (115). As BAFF is most relevant for protecting autoreactive B cells, anti-BAFF therapy has a certain degree of specificity against this population.

Therapy directed against PCs. B cell depletion therapy with anti-CD20 antibodies spares LLPCs. It has been reported that the longevity of these cells is more than 10 years (116), highlighting their importance as long-term producers of antibodies or autoantibodies. Proteasome inhibitors cause accumulation of misfolded proteins within the endoplasmic reticulum, leading to apoptosis (117). Proteasome inhibitors affect predominantly the PC population, because of their extremely high rate of antibody synthesis. pDCs also have a high rate of protein synthesis and are also affected, causing a reduction in type I IFN levels. This may also be therapeutic, in part by diminishing B cell activation (118). In lupus-prone mice, proteasome inhibitors reduced the titers of autoantibodies and improved nephritis (118).

B cell activation and costimulation blockade. Because of the relevance of the B-T cell costimulation pathways to autoantibody production, they have been considered a potential target for many years. Studies conducted 25 years ago already showed a beneficial effect of CD40/CD40L blockade therapy in lupus-prone mice (119, 120), with both strategies characterized by reduced antibody titers and improved nephritis (121). However, clinical trials with anti-CD40L antibody in lupus patients were terminated because of thromboembolic events (122). This effect was not seen in mice (123), which precluded earlier detection of the phenomenon. Second-generation molecules for CD40/CD40L blockade with low prothrombotic effect have been developed (121).

IFN is a potent stimulator of B cells. An IFN signature has been described in patients with SLE; this signature correlates with disease activity in some studies (69). In most mouse models of SLE, including the NZB/W and MRL/lpr strains, overexpression of IFN-induced genes is observed but occurs with less magnitude than in humans, with the exception of the pristane-induced model of SLE (124). In some lupus-prone strains, treatment with anti–type I IFN receptor antibody (125) or deficiency of type I IFN receptor (126–128) increased survival and improved autoimmune manifestations, including levels of autoantibodies. Interestingly, in MRL/lpr mice, deletion of the type I IFN receptor increased autoantibody titers and worsened organ damage (129).

Use of an anti–IL-21 antibody reduced antibody titers and delayed glomerulonephritis progression in lupus-prone mice. This effect was associated with a reduction in GC B cells and plasmablasts (130). Anti–IL-6 and anti–IL-6 receptor antibodies caused reduction in anti-dsDNA titers and improvement in nephritis (131, 132). Administration of synthetic oligodeoxynucleotides with immunoregulatory sequences that specifically block TLR7 or TLR7/9 activation to lupus-prone mice improved nephritis and caused reduction in the titers of autoantibodies (133, 134). Bruton's tyrosine kinase (Btk) is an enzyme that modulates signaling downstream of the BCR and is required for BCR signaling. Btk inhibitors have shown improvement of nephritis and reduction of autoantibodies in multiple mouse models of lupus (135–138). Notably, Btk inhibitors are already approved for use in hematologic malignancies.

Antigen-based therapies. Use of antigen conjugates may, in theory, block pathogenic autoantibodies from interacting with their target. Also, in the absence of costimulation, recognition and binding of a cognate antigen by the membrane-bound antibody molecule on the surface of B cells might induce B cell tolerance.

There are examples in animal models of successful use of "tolerizing molecules." The administration to BXSB male lupus-prone mice of polyethylene glycol with tetrameric oligonucleotides, a molecule that mimics DNA, decreased the number of anti-dsDNA–producing cells and significantly increased survival (139). Administration of nucleosomal peptides to SNF1 mice delayed the onset of nephritis and improved survival (140); in the mechanistic analysis, an increment of regulatory T cells was shown, and a direct effect on B cells was not investigated. Finally, peptides that bind anti-DNA antibodies can prevent their pathogenicity in vivo (141, 142).

B cell–based treatment in patients with SLE

Information about relevant finished and ongoing clinical trials targeting B cells in patients with SLE is summarized in Tables 1 and 2.

B cell depletion. As mentioned, one of the earliest therapies for SLE, albeit not FDA approved, is cyclophosphamide, which targets B cells as well as other lymphoid cells. There is also evidence that mycophenolate mofetil causes a reduction of circulating plasmablasts (143), among other therapeutic mechanisms.

Rituximab was approved for rheumatoid arthritis in 2006 and since then has been used off label in patients with SLE. A benefit of rituximab was suggested in multiple nonrandomized observational studies (144, 145). Two randomized, double-blind, placebo-controlled clinical trials failed to show a beneficial effect of rituximab. In the LUNAR trial, 144 patients with LN were randomized to receive rituximab or placebo with concomitant mycophenolate and steroids. Treatment with rituximab did not improve clinical efficacy, even though statistically significant changes in serum complement and anti-dsDNA levels were found in comparison with placebo (146). In the EXPLORER trial, 257 patients with moderate to severe nonrenal SLE were randomized to receive rituximab or placebo. No differences were observed in the clinical response at week 24. There were increased complement levels and decreased anti-dsDNA levels in the rituximab arm (147). Despite the findings of the EXPLORER and LUNAR trials, current guidelines from the European League Against Rheumatism and the European Renal Association, and from the American College of Rheumatology, recommend the use of rituximab as a second- or third-line option in patients with LN (148, 149).

Clinical response in patients with SLE who received rituximab correlates with the degree (150, 151) and duration (152) of B cell depletion. Thus, there has been interest in higher-affinity and higher-activity anti-CD20 antibodies. Obinutuzumab, a type 2 glycoengineered anti-CD20 monoclonal antibody, has a more potent cytotoxic effect, probably because of more efficient engagement

Table 1. Relevant clinical trials targeting B cells in patients with SLE

Treatment (mechanism of action)	References	Type of study	Number of patients	Follow-up time	Main results
Rituximab (chimeric anti-CD20)	LUNAR trial (146)	Phase III	144	52 wk	Primary endpoint not met; significant changes in serum complement and anti-dsDNA levels were found in rituximab arm
Rituximab (chimeric anti-CD20)	EXPLORER trial (147)	Phase II/III	257	52 wk	Primary and secondary endpoints not met; increased complement levels and decreased anti-dsDNA levels in rituximab arm
Ofatumumab (fully human anti-CD20)	Masoud et al. (157)	Retrospective case series	16	24 wk	B cell depletion was achieved in 12 of 14 patients; 50% of patients with LN achieved renal remission
Obinutuzumab (humanized anti-CD20)	NOBILITY trial (154)	Phase II	125	104 wk	Sustained benefit of greater improvement in complete renal response, anti-dsDNA, C3, C4, and estimated glomerular filtration rate
Ocrelizumab (humanized anti-CD20)	BE-LONG trial (155)	Phase III	378	48 wk	Terminated early due to serious infection
Epratuzumab (humanized anti-CD22)	ALLEVIATE-1 and ALLEVIATE-2 trials (158)	Phase III	36 and 54	48 wk	Both studies terminated early due to an interruption of the drug supply
Epratuzumab (humanized anti-CD22)	EMBLEM trial (159)	Phase IIb	227	12 wk	Responder rate higher in epratuzumab arm
Epratuzumab (humanized anti-CD22)	EMBODY 1 and EMBODY 2 trials (160)	Phase III	793 and 791	48 wk	Primary endpoint not met
Obexelimab (bispecific antibody for CD19 and FcγRIIb)	Merrill et al. (190)	Phase II	104	~32 wk	Primary endpoint was not met, time to flare was significantly longer, and less recurrent disease was observed in the treatment group
Belimumab (anti-BAFF)	BLISS-52 (163) and BLISS-76 (164)	Phase III	867 and 819	52 wk	The trial met its endpoint and significantly higher SRI rates were noted in belimumab group
Belimumab (anti-BAFF)	BLISS-LN (167)	Phase III	448	104 wk	Improved primary efficacy renal response and complete renal response in belimumab arm
Belimumab (anti-BAFF)	EMBRACE trial (166)	Phase IV	503	52 wk	Primary endpoint (SRI-4 response) not met
Belimumab (anti-BAFF)	CALIBRATE trial (177)	Phase II	43	96 wk	Combination is safe, induced a more sustained B cell depletion
Atacicept (blocks BAFF and APRIL)	Ginzler et al. (168)	Phase II/III	6	52 wk	Terminated early due to serious infections
Atacicept (blocks BAFF and APRIL)	ADDRESS II (170)	Phase IIb	306	24 wk	Primary endpoint (SRI-4 response) not met
Atacicept (blocks BAFF and APRIL)	Isenberg et al. (169)	Phase II/III	461	48 wk	Primary endpoint not met; atacicept 150 mg arm discontinued due to 2 deaths
Blisibimod (inhibits soluble and membrane-bound BAFF)	PEARL-SC trial (171)	Phase IIb	547	24 wk	Primary endpoint (SRI-5 response) not met; blisibimod 200 mg superior over placebo
Blisibimod (inhibits soluble and membrane-bound BAFF)	CHABLIS-SC1 trial (172)	Phase III	442	52 wk	Primary endpoint (SRI-6 response) not met
Tabalumab (inhibits soluble and membrane-bound BAFF)	ILLUMINATE-1 trial (173)	Phase III	1164	52 wk	Primary endpoint (SRI-5 response) not met
	ILLUMINATE-2 trial (174)	Phase III	1124	52 wk	Primary endpoint (SRI-5 response) met with tabalumab 120 mg every 2 weeks superior over placebo
Telitacicept (TACI-Fc fusion protein)	Wu et al. (175)	Phase IIb	249	48 wk	All treatment groups met primary endpoint (SRI-4 response)
Rontalizumab (anti–IFN-α)	ROSE trial (198)	Phase II	238	24 wk	Primary endpoint (BILAG index 2004) not met
Anifrolumab (type I IFN inhibitor)	TULIP-1 trial (183)	Phase III	457	52 wk	Primary endpoint (SRI-4 response) not met
Anifrolumab (type I IFN inhibitor)	TULIP-2 trial (184)	Phase III	362	52 wk	BICLA response was 47.8% and 31.5% in anifrolumab and placebo groups, respectively
Sifalimumab (anti–IFN-α)	Khamashta et al. (199)	Phase II	431	52 wk	Treatment groups met primary endpoint (SRI-4 response)
PF-04236921 (anti–IL-6 antibody)	Wallace at al. (186)	Phase II	183	24 wk	Primary endpoint (SRI-4 response) not met
Sirukumab (anti–IL-6 antibody)	Rovin et al. (187)	Phase II	25	24 wk	Primary endpoint (reduction in proteinuria) not met

BICLA, Based Composite Lupus Assessment; SRI, SLE responder index.

of Fcγ receptors on NK cells and neutrophils (153). Obinutuzumab was evaluated in a placebo-controlled randomized trial including 125 patients with active class III or IV LN on background corticosteroids and mycophenolate. Patients who received obinutuzumab demonstrated a sustained benefit in renal response, anti-dsDNA titers, and C3 and C4 levels, with no unexpected safety concerns. The benefits were sustained at 104 weeks (154).

Other antibodies that target CD20 have been studied in SLE. Ocrelizumab failed to meet its primary outcome in a randomized trial of patients with LN, and raised safety concerns due to

Table 2. Relevant ongoing clinical trials targeting B cells in patients with SLE

Drug (mechanism of action)	Study title	Current status	Study phase	Estimated study completion date	Clinical trial number
Rituximab (chimeric anti-CD20)	Rituximab Objective Outcome Measures Trial in SLE (ROOTS)	Recruiting	Phase II	February 2020	NCT03054259
Rituximab (chimeric anti-CD20)	Efficacy of Individualized Rituximab in Maintaining Remission of Moderate and Severe Systemic Lupus Erythematosus	Recruiting	Phase IV	July 2023	NCT04127747
Obinutuzumab (humanized anti-CD20)	A Study to Evaluate the Efficacy and Safety of Obinutuzumab in Patients with ISN/RPS 2003 Class III or IV LN (REGENCY)	Recruiting	Phase III	January 2028	NCT04221477
Belimumab (anti-BAFF)	Study of Subcutaneous (SC) Belimumab in Pediatric Participants with Systemic Lupus Erythematosus (SLE)	Recruiting	Phase II	March 2023	NCT04179032
Belimumab (anti-BAFF)	Trial of Belimumab in Early Lupus	Recruiting	Phase IV	January 2023	NCT03543839
Rituximab and belimumab	A Randomized Trial to Investigate the Reset of Humoral Autoimmunity by Combining Belimumab with Rituximab in Severe Systemic Lupus Erythematosus Synergetic B-cell Immunomodulation in SLE – 2nd Study (SynBioSe-2)	Recruiting	Phase II	September 2025	NCT03747159
Rituximab and belimumab	A Study to Evaluate the Efficacy and Safety of Belimumab Administered in Combination with Rituximab to Adult Subjects with Systemic Lupus Erythematosus (SLE) (BLISS-BELIEVE)	Active	Phase III	July 2021	NCT03312907
Rituximab and belimumab	Belimumab after B cell depletion therapy as a new treatment for patients with systemic lupus erythematosus (BEAT-LUPUS)	Completed	Phase II	March 2021	ISRCTN47873003
KZR-616 (proteasome inhibitor)	A Study of KZR-616 in Patients with SLE With and Without LN (MISSION)	Recruiting	Phase I, phase II	June 2022	NCT03393013
Orelabrutinib (Btk inhibitor)	A Study of ICP-022 in Patients with Systemic Lupus Erythematosus (SLE)	Recruiting	Phase I, phase II	October 2021	NCT04305197
Ianalumab (VAY736) (anti-BAFF receptor mAb)	Study the Efficacy and Safety of VAY736 and CFZ533 in SLE Patients	Recruiting	Phase II	October 2024	NCT03656562
Anifrolumab (type I IFN inhibitor)	Long Term Safety of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus (TULIP SLE LTE)	Active	Phase III	December 2021	NCT02794285
Telitacicept (TACI-Fc fusion protein that inhibits BLyS and APRIL)	Study of Recombinant Human B Lymphocyte (RC18) Administered Subcutaneously to Subjects with Systemic Lupus Erythematosus (SLE)	Recruiting	Phase III	December 2021	NCT04082416

increased infection risk (155). Ofatumumab was reported to be effective in case series of patients with SLE (156, 157). Epratuzumab, an anti-CD22 antibody that engages an inhibitory receptor on B cells, showed some promising results in phase II studies that were not confirmed in a phase III clinical trial (158–160).

Anti-BAFF therapies. In patients with SLE, serum levels of BAFF are elevated, and these levels correlate with disease severity (161, 162). Belimumab is an IgG1 human monoclonal antibody directed against soluble BAFF. It interferes with the binding of BAFF with BCMA, TACI, and BAFF-R. The efficacy of belimumab in SLE has been tested in multiple trials, and it is now approved by the FDA for treatment of both adult and pediatric SLE.

The BLISS-52 and BLISS-76 trials randomized 867 and 819 patients, respectively, to receive belimumab or placebo with background treatment. Both trials met their clinical endpoints (163, 164). There were modest reductions in autoantibody titers and reduced flares at 76 weeks, perhaps related to lower antibody titers. Belimumab efficacy was confirmed in populations from China, Japan, and South Korea (165). The EMBRACE study, conducted to evaluate the efficacy of belimumab in African American patients with SLE, did not achieve its primary endpoint; however, significant improvement was found in patients who had high disease activity (166). A recent trial, BLISS-LN, randomized 448 patients with active LN to receive belimumab or placebo, plus standard therapy. Significantly more patients in the belimumab arm had renal response at week 104 than those who received placebo (167).

A trial of atacicept, which blocks BAFF and the related molecule APRIL (168–170), was terminated because of increased infections. Blisibimod, an inhibitor of soluble and membrane-bound BAFF (171, 172), tabalumab, a human molecular antibody that binds soluble and membrane-bound BAFF (173, 174), and telitacicept, a recombinant fusion protein constructed with the extracellular domain of the TACI receptor, thereby binding both BAFF and APRIL (175), have been tested in patients with SLE without success. Their failure despite the success of belimumab may reflect both the modest effect of belimumab and differences in trial design.

Combination therapy. Based on the observations that BAFF levels rise after induction of B cell depletion with rituximab (176), and that B cell reconstitution in a milieu of low BAFF leads to a reduction in the number of autoreactive B cells (114), a clinical trial testing the sequential administration of rituximab and belimumab was performed. The CALIBRATE study (177) included 43 patients with recurrent or refractory LN who were randomly assigned to be treated with rituximab, cyclophosphamide, and glucocorticoids or

the same treatment followed by belimumab. The trial demonstrated that the combination is safe, and induced a more sustained B cell depletion. Addition of belimumab diminished the maturation of transitional to naive B cells, and enhanced the negative selection of autoreactive B cells. The trial did not find any significant clinical benefit of adding belimumab to treatment; however, the study was not powered to ascertain clinical outcome.

Theoretically, the order in which the combination of rituximab and belimumab is administered might have differential effects. Belimumab reduces the number of B cells in lymphoid tissues (178), so initial administration of belimumab might cause mobilization of memory B cells into the circulation, where they would be more susceptible to rituximab-mediated cell death. This strategy of administering belimumab followed by rituximab is being examined in a clinical trial of nonrenal SLE, the BLISS-BELIEVE study. Rituximab and belimumab combinations are also currently being evaluated in the BEAT-LUPUS and SynBioSe-2 trials.

Therapy directed against PCs. Proteasome inhibitors have been tested in trials with small numbers of patients with SLE. Bortezomib has shown some clinical responses in patients with refractory SLE; however, a high percentage of patients developed severe adverse effects (179, 180), and for this reason, proteasome inhibitors are not part of the arsenal that is commonly used in patients with SLE. New-generation proteasome inhibitors that are relatively selective for immune cells also have significant toxicity.

Daratumumab is a human monoclonal antibody that targets CD38, a molecule expressed on PCs and plasmablasts (although not exclusive to these populations). Administration of daratumumab causes depletion of PCs and is approved for use in multiple myeloma. Successful use of daratumumab was reported in two patients with life-threatening manifestations of SLE (181). The clinical response was associated with depletion of LLPCs and reduction of type I IFN activity.

B cell activation and costimulation blockade. Multiple trials have been performed with anti-IFN therapy in patients with SLE. While this therapy might be expected to reduce PC differentiation (182), only small reductions in autoantibodies were seen (183, 184). In the TULIP-1 study, a phase III randomized trial of anifrolumab, a human monoclonal antibody against type I IFN receptor subunit 1, the primary clinical endpoint was not met (183). A second trial of anifrolumab, in which the primary clinical endpoint was selected based on the results from the first trial, showed efficacy; however, only a modest reduction in autoantibodies was observed (184). This phenomenon might reflect stable continued autoantibody production by LLPCs.

Tocilizumab, an anti–IL-6 antibody, caused reduction of PCs and memory cells in patients with SLE (185); however, two phase II clinical trials with anti–IL-6 antibodies failed to meet their primary outcomes (186, 187). A monoclonal antibody that interferes with IL-21 activity is being tested in a phase I/II study in patients with SLE (188). Initial trials in patients with SLE showed encouraging results for CD40/CD40L blockade, including reduced number of circulating PCs and anti-dsDNA antibodies (189). After the setback caused by the increased rate of thrombotic events with the first-generation antibodies targeting this pathway, second-generation molecules without thrombotic risk are currently being tested (121).

Iberdomide, a cereblon ligand, increases the ubiquitination and subsequent degradation of the transcription factors Ikaros and Aiolos in the proteasome. The genes encoding these transcription factors are risk alleles for SLE. Ikaros is necessary for the development of B cells and pDCs, and Aiolos is necessary for PC differentiation. Iberdomide affects both total B cell number and PC differentiation. Preliminary results showed a reduction in B cell number, with the higher dose inducing a significant clinical response compared with placebo (154). Whether there is also an effect on PC differentiation is not clear.

Dual-specificity antibodies. Obexelimab, a bispecific antibody that targets CD19 and simultaneously acts as an agonist of the inhibitory receptor FcγRIIb, was studied in a randomized phase II trial of 104 patients with SLE. In the obexelimab group, the time to flare was significantly longer and patients had less recurrent disease after treatment. The primary endpoint was not met, but a subgroup of patients with higher expression of genes associated with B cell and PC activation improved in comparison with placebo (190).

Antigen-based therapies. The experience with these molecules in patients with SLE has been limited. In a clinical trial, abetimus (LJP-394), a molecule that contains four strands of dsDNA bound to a carrier, caused reduction of the anti-dsDNA antibody levels but did not prolong the time to renal flares (191). It is not clear whether the reduction in titer reflected B cell tolerance or the generation and subsequent removal of immune complexes.

Perspectives and future directions

Selection of B cells as a target for therapy in SLE has a solid basis according to our knowledge of the disease. It is surprising, therefore, that BAFF inhibition is the only approved therapy that targets B cells and that this strategy has been successful with only one agent, belimumab. It is possible that trial design may have contributed to some trial failures. It is important to remember that success in a clinical trial requires achieving a predetermined effect size in a predetermined number of patients.

It has not been possible to show an association between changes in autoantibodies and clinical responses in clinical trials. This highlights the fact that we do not know the extent to which autoantibody titers need to be reduced to lead to diminished disease activity or whether a reduction to a threshold level is required. Other features of the antibodies besides titers are involved in immunogenicity, such as affinity and glycosylation state (192). The determination of these characteristics is labor intensive, and they have not been explored in clinical trials in SLE; however, they might represent a mechanism by which treatment alters antibody pathogenicity and should be considered in future trials.

While therapies targeting B cells have been disappointing in clinical trials, and those targeting PCs hazardous, none of the currently available therapeutic options have focused specifically on PC differentiation. We have demonstrated that abnormal PC differentiation might represent a critical checkpoint in patients with SLE. SLE patients have a similar frequency of ANA reactivity in all B cell compartments, including PCs, when compared with healthy subjects, suggesting no defect in antigen-specific tolerance. These patients have, however, more IgG PCs. Thus, they have more autoreactive IgG PCs and higher serum titers of IgG ANAs. This suggests an increased differentiation of IgG PCs (36).

Thus, targeting of pathways to reduce PC differentiation should be further explored. Some medications currently under study, such as iberdomide and Btk inhibitors, reduce PC differentiation. The hope would be that these treatments can dampen autoreactivity without causing global immunosuppression.

Furthermore, B cell activation can occur through an extrafollicular or GC pathway. Both pathways are considered to contribute to autoantibody production in patients with SLE (87, 193). Data from our laboratory suggest that SLE patients with increased circulating plasmablasts have different patterns of antigen-experienced autoreactive B cells and can be classified as having a predominant GC or a predominant extrafollicular response (88). The molecules that are differentially involved in each of these pathways are not clearly defined, but studies to identify them are currently ongoing. These molecules might represent a therapeutic tool for precision medicine.

Heterogeneity of SLE has been proposed as a major cause of failure in clinical trials. Microarray analysis and RNA sequencing (RNA-Seq) studies have allowed an interrogation of the transcriptome of immune cells in patients, and more recently, single-cell RNA-Seq has further increased the resolution of this analysis. Using these technologies, an IFN signature was described in SLE almost two decades ago (194, 195). A plasmablast signature that correlates with disease activity and a neutrophil signature that is associated with LN have also been described (196, 197) and are mutually exclusive (196). We have previously proposed that in some patients, myeloid cells are the drivers of SLE, while in others, SLE is driven by B cells. Indeed, a study of risk alleles in SLE showed that they are predominantly expressed in either myeloid cells or B cells. It may be that only those patients with a B cell–intrinsic pathway to SLE will benefit in the long term from a B cell–directed therapy. If so, clinical trials that do not select for patients with intrinsic B cell hyperresponsiveness may be underpowered for clinical efficacy. It would be a shame to discard potentially useful therapeutics because of trials that do not select for those patients with pathways of disease pathogenesis that are targeted by the therapeutic. A better understanding of SLE patient subsets is critical; in some, B cell–targeted therapies, especially those that block PC differentiation, may have long-term benefit.

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