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REVIEW

Spotlight on blisibimod and its potential in the treatment of systemic lupus erythematosus: evidence to date

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Abstract: B cells in general and BAFF (B cell activating factor of the tumor necrosis factor [TNF] family) in particular have been primary targets of recent clinical trials in systemic lupus erythematosus (SLE). In 2011, belimumab, a monoclonal antibody against BAFF, became the first biologic agent approved for the treatment of SLE. Follow-up studies have shown excellent long-term safety and tolerability of belimumab. In this review, we critically analyze blisibimod, a novel BAFF-neutralizing agent. In contrast to belimumab that only blocks soluble BAFF trimer but not soluble 60-mer or membrane BAFF, blisibimod blocks with high affinity all three forms of BAFF. Furthermore, blisibimod has a unique structure built on four high-affinity BAFF-binding peptides fused to the IgG1-Fc carrier. It was tested in phase I and II trials in SLE where it showed safety and tolerability. While it failed to reach the primary endpoint in a recent phase II trial, post hoc analysis demonstrated its efficacy in SLE patients with higher disease activity. Based on these results, blisibimod is currently undergoing phase III trials targeting this responder subpopulation of SLE patients. The advantage of blisibimod, compared to its competitors, lies in its higher avidity for BAFF, but a possible drawback may come from its immunogenic potential and the anticipated loss of efficacy over time.

Keywords: BAFF, APRIL, lupus, B cells, blisibimod

Introduction

The primary role of B cells in initiating systemic autoimmune diseases has long been suspected. Production of autoantibodies, formation of circulating immune complexes with subsequent Fc-receptor engagement, and activation of the complement system have been considered to play a primary role in tissue inflammation in systemic lupus erythematosus (SLE).

It has been well established that B cells are excellent antigen-presenting cells for antigens that can bind to their surface Ig receptors.[1] Direct evidence for the role of B cells apart from autoantibody production was first demonstrated in mice carrying the *lpr/lpr* mutation which develop a lupus-like disease.[2] When MRL-*lpr/lpr* mice were crossed to J_H knockouts, mice lacking B cells were generated. While their littermates with B cells developed nephritis and vasculitis and made autoantibodies, mice lacking B cells showed no evidence of renal disease or vasculitis. A similar effect was also observed in another lupus strain, NZM 2328, where absence of B cells completely protected mice from development of lupus.[3] Subsequently, elegant experiments have shown that the requirement for B cells goes beyond their role as precursors of antibody-secreting cells and likely reflects their ability to serve as (auto)antigen-presenting cells.[4]

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This autoantibody-independent role of B cells has been demonstrated in experiments where a mutant transgene encoding surface Ig was introduced into MRL-*lpr/lpr* mice. While these mice failed to secrete serum antibodies, they still had functional B cells expressing surface Ig receptors. In contrast to mice that completely lack B cells, mice carrying a mutant gene for surface Ig developed mononuclear cellular infiltrates in their kidneys, the characteristic of lupus nephritis in this strain, and had increased mortality compared to controls. These mice exhibited increased number of activated and memory $CD4^+$ splenic T cells. Thus, this study showed that B cells themselves, independent of autoantibody secretion, likely play a primary pathogenic role in lupus.[4–6]

B cell processing of autoantigen can contribute to epitope spreading, a phenomenon in which initial reactivity to one epitope is followed by subsequent reactivity to additional epitopes expressed on the same or related autoantigens, a phenomenon commonly observed in lupus.[7] B cells may additionally be a source of proinflammatory (ie, interleukin-6 [IL-6], tumor necrosis factor alpha [TNF-α]) and/or regulatory cytokines (ie, IL-10),[8] and abnormalities in this cytokine-producing function have been observed in lupus mice.[9] Remarkably, B cells that lack one of the innate Toll-like receptors, TLR9, may lose this regulatory function.[10] Based on these observations, the Shlomchik lab was the first to suggest that B cell depletion, instead of bare mechanical removal of autoantibodies by plasma exchange, should be considered as a primary target for treating lupus.

However, the essential requirement for B cells early in the course of the disease does not rule out an important contribution from T cells, which serve downstream in the disease process as primary effector cells. For example, in autoimmune MRL-*lpr/lpr* mice, thymectomy or treatment with monoclonal T-cell-specific antibody could ameliorate lymphadenopathy and delay autoimmune-mediated inflammation.[11,12]

B cell hyperactivity has been recognized as an important characteristic of human SLE and animal models of lupus.[13,14] It is associated with polyclonal hypergammaglobulinemia and production of numerous autoantibodies, particularly those recognizing components of the nuclear chromatin (ie, histones and dsDNA) and certain extractable nuclear antigens (ie, Smith antigen and U1-RNP). These antibodies (against Smith and dsDNA) are highly specific for lupus.[15,16] Circulating levels of BAFF (B cell activating factor of the TNF family), a key B cell survival and activation factor, are elevated in SLE patients and in animal models of lupus.[17–21] It is hypothesized that BAFF can be at least partially responsible for this activated B cell phenotype in lupus.

In this review, we discuss new discoveries relevant to BAFF's role in the pathogenesis of SLE. We also discuss available therapeutics that specifically target human BAFF focusing on blisibimod, a novel high-potency tetravalent BAFF inhibitor. While other B cell-targeted approaches in SLE, such as B cell depletion with the anti-CD20 antibody rituximab, were largely unsuccessful,[22–24] BAFF neutralization with a monoclonal anti-BAFF antibody belimumab[25] met primary endpoints in two large phase III clinical trials leading to its approval in 2011 by the US Food and Drug Administration (FDA) for the treatment of adult patients with SLE.[26,27]

BAFF and its receptors

BAFF also known as Blys (B lymphocyte stimulator), TALL-1,[28] and THANK,[29] were discovered in 1999.[30,31] BAFF plays an essential role in B cell biology. Initial experiments suggested that BAFF may act as an important B cell growth factor by costimulating B cell proliferation induced by cross-linking of the B cell receptor for antigen. However, BAFF by itself fails to stimulate proliferation of resting B cells.[30] It soon became clear that BAFF works by providing a critical B cell survival signal (rather than a proliferation signal). Consequently, mice deficient in BAFF have a marked reduction in B cell numbers, along with low serum Ig concentration.[32] In contrast, excess production of BAFF causes an SLE-like disease in transgenic mice[33,34] and likely plays a role in human SLE and other systemic autoimmune diseases.[19–21,35]

BAFF is produced by a variety of cell types including macrophages/monocytes, dendritic cells, and neutrophils.[36] While initial reports failed to detect BAFF expression in freshly isolated or activated T- and B cells,[31] these cells can also make BAFF upon certain conditions.[37]

Similar to other members of the TNF family, BAFF can exist as a type II cell membrane-bound protein (285 amino acids) and as a soluble form. The furin protease cleaves the surface BAFF and releases the soluble form of this cytokine.[30,38] Soluble BAFF can adopt at least two different configurations: a typical homotrimer (3-mer) or a capsid-like structure that has 20 repeats of the 3-mer (60-mer).[39] All three forms of BAFF are biologically active and can contribute to cell signaling[39] (Figure 1). BAFF can also form heterotrimers with another B cell survival molecule APRIL (a proliferation-inducing ligand, CD256). However, it is not well understood under which conditions these heterotrimers are formed. Interestingly, the phenotype of mice that only express the membrane form of BAFF but lack the

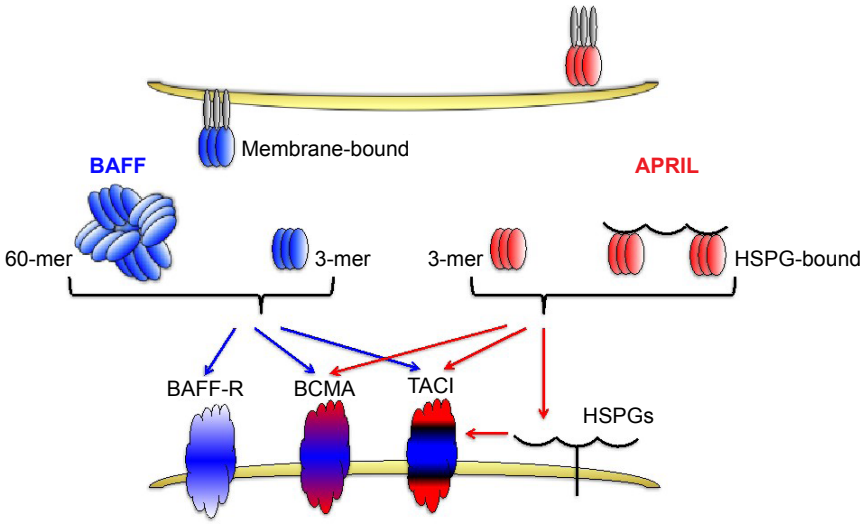

Figure 1 Interaction between BAFF and APRIL and their receptors.
Abbreviations: APRIL, a proliferation-inducing ligand; BAFF, B cell activating factor of the TNF family; BCMA, B-cell maturation antigen; HSPGs, heparin-sulfate proteoglycans; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor.

ability to make soluble BAFF is very similar to BAFF-deficient mice suggesting that membrane BAFF under normal conditions exerts a very limited role in B cell biology.[40]

BAFF binds to three receptors: transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI, CD267), B-cell maturation antigen (BCMA, CD269), and BAFF receptor (BAFF-R, also known as BR3, CD268).[38,41] BAFF-R solely interacts with BAFF, whereas another TNF-family member, APRIL, can bind and signal through the other two BAFF receptors, TACI and BCMA, but not through BAFF-R.[38] APRIL also binds to heparin-sulfate proteoglycans (HSPGs), with 3 mers and multimers bound to HSPGs, also contributing to signaling. BAFF-R-deficient mice have a phenotype similar to BAFF-deficient mice,[42,43] while this is not the case with mice lacking either BCMA or TACI receptors.[32,44]

A very nice review by Mackay and Browning[45] describes in much more detail the structure–function relationship between the existing ligands (BAFF and APRIL) and their respective receptors on B cells. Interestingly, the crystal structure of BAFF has revealed important differences between the BAFF and other members of the TNF family by revealing the existence of an extended loop in the BAFF, nonexistent in other TNF members, that may be involved in both receptor binding and viral-like assembly.

BAFF-R expression in B cells

Biotinylated and FLAG-tagged Blys/BAFF were initially used to search for BAFF-R receptor expression in different cell types. B cell tropism for BAFF was shown in peripheral $CD20^+$ B cells, and in a variety of B cell tumor lines (ie, Raji, Namalwa, RPMI-8226), but not in bone marrow plasma cells, nor in T cells (resting or activated), monocytes, natural killer cells, granulocytes, or myeloid-derived cell lines.[31] Furthermore, human BAFF/Blys acted across the species as it could bind and induce proliferation of murine B cells. BAFF-R recruits TNF receptor-associated factor 3 (TRAF3), which then leads to downstream signaling cascade resulting in activation of *c-jun* terminal kinase and nuclear factor kappaB (NF-κB) pathways.[46]

Rationale for targeting BAFF in SLE

In mice, autoreactive B cells, compared to non-autoreactive B cells, appear to be more dependent on BAFF for their survival.[17,33,47] Evidence presented in the following paragraphs suggests that an environment rich in BAFF may allow survival and expansion of autoreactive B cells, ultimately leading to systemic autoimmune disease.

Animal studies

Administration of soluble recombinant BAFF to healthy BALB/c mice disrupted the spleen architecture and caused elevation of serum Ig concentration (particularly IgM and IgA).[31]

Transgenic mice overexpressing BAFF produced a variety of autoantibodies including rheumatoid factors and antibodies against dsDNA and had an expanded population of mature B cells. Interestingly, the marginal zone B cell subset and plasma cells, but not follicular B cells, were expanded in spleens of these transgenic mice. Intense germinal center formation was also observed. Peripheral blood B cells from

these mice showed an increase in Major Histocompatibility Complex class II expression along with high expression of a survival (antiapoptotic) factor Bcl-2. Furthermore, these mice developed a clinical phenotype closely resembling SLE/Sjogren's syndrome with hypergammaglobulinemia, proteinuria, and immune-complex-mediated glomerulonephritis. Additionally, peripheral blood T cells in these transgenic mice displayed an activated effector T-cell phenotype, and their number was expanded by at least twofold in the spleen and mesenteric lymph nodes.[34]

Treatment of NZB/NZW-F1 mice with a specific BAFF antagonist was able to slow down the disease progression in this strain of lupus mice and had a positive effect on overall survival.[48,49]

In NZM model of animal lupus, BAFF-deficient mice had a milder phenotype, and BAFF deficiency could prevent acceleration of clinical kidney disease in response to treatment with type I IFN.[3,50]

Treatment of NZBW-F1 mice and NZM 2410 mice with either BAFFR-Ig (which only neutralizes BAFF) or TACI-Ig (which neutralizes both BAFF and APRIL) showed that TACI-Ig was more immunosuppressive, causing a drop in serum IgM and IgG levels and Ig-secreting plasma cells in the spleen and bone marrow.[49] However, both agents had a similar effect on clinical disease. When double-deficient (BAFF/APRIL) mice were compared to single-deficient BAFF mice, a similar effect on renal immunopathology was observed, despite pronounced differences in bone marrow plasma cells and serum autoantibodies.[51] Taken together, these results suggest that APRIL may have a minor role in lupus pathogenesis.

Concurring with animal studies, treatment of human SLE patients (with or without lupus nephritis) with atacicept (TACI-Ig) was associated with safety issues related to ~30% reduction in serum IgG levels within 4 weeks of treatment. So, while atacicept may be an efficient agent for SLE, its potential toxicity may outweigh any gains in efficacy.[52,53]

Interestingly, NZM 2328 mice deficient in BAFF-R still develop full blown lupus despite having reduced numbers of B cells.[54] This suggests that blockade of the BAFF-R alone may be therapeutically insufficient to control human SLE. At present, there are no clear plans of developing or using antibodies against BAFF-R, BCMA, or TACI for the treatment of lupus. However, a construct of two BAFF-R linked to the Fc domain of human IgG1 has been developed. This agent, named briobacept, binds BAFF (human, mouse, cynomolgus monkey) but not APRIL, and has been evaluated in phase I studies in rheumatoid arthritis (RA), but no plans for further development have been made.[55]

Human SLE

BAFF expression is increased in patients with SLE, and a clear correlation between BAFF levels and disease activity in SLE has been observed in some studies.[19–21] Biologically active heterotrimers composed of BAFF and APRIL are elevated in peripheral blood of SLE patients.[56,57] Interestingly, the membrane form of BAFF is abnormally expressed in B cells from patients with active SLE.[37] In contrast to BAFF, the association between APRIL and SLE demonstrated an inverse relationship, suggesting a possible protective role for APRIL.[58,59] Interestingly, BAFF levels are higher in African-American SLE patients as compared to European-American SLE patients,[60] and a greater degree of B cell activation has been observed in African-American SLE patients as well.[61]

Treatment of SLE patients with the anti-BAFF antibody belimumab met its primary endpoint in two phase III clinical trials in 2011.[26,27] Based on these studies, the FDA approved belimumab for the treatment of adult patients with SLE. It is worth mentioning that patients with active lupus nephritis or central nervous system (CNS) disease were excluded from these studies. While a study testing the efficacy of belimumab in lupus nephritis (BLISS-LN, NCT01639339) is ongoing, no similar trial in active CNS disease has been planned.

Interferons and BAFF

Type I and II IFN can regulate BAFF synthesis and thus play an important role in lupus pathogenesis. IFN-α can upregulate BAFF expression in mouse macrophages, human dendritic cells, and monocytes. Evidence of an IFN-signature in human SLE is found in about 50% of SLE patients and correlates with disease activity.[62–66] Administration of type I IFN can lead to development of SLE-like syndromes in some patients.[67,68] Therefore, type I IFN is a potential target for treatment of SLE, and several neutralizing agents are currently in the pipeline, with anifrolumab (anti-type I IFN receptor antibody) showing very promising effects in a recent phase II clinical trial in SLE.[69]

IFN-γ could induce a similar upregulation of BAFF in various cell types.[70,71] For example, BAFF/Blys expression on human monocytes, both at the mRNA and protein level, was upregulated by IFN-γ up to fourfold.[31] Not surprisingly, monocytes from SLE patients produced substantially more BAFF compared to healthy controls when stimulated with the same ligand.[72]

In SLE patients treated with a neutralizing anti-IFN-α antibody, BAFF mRNA expression was downregulated.[73] Moreover, a relatively good correlation existed between BAFF and type I IFN levels in patients with SLE.[60]

Genetic deletion of the type I IFN receptor (Ifnar I) could prevent lupus development in NZB and NZM 2328 mice.[74,75] Vice versa, the administration of type I IFN, or its upregulation, accelerated lupus nephritis, leading to death in several strains of lupus-prone mice. However, this was not the case with MRL-*lpr/lpr* mice as Ifnar-deficient MRL mice developed more severe disease compared to controls.[75–78]

Therefore, type I IFN and BAFF remain a legible target for treatment in SLE.[79,80]

B cell therapies in SLE

B cells are an important target for treatment of SLE patients. At first glimpse, it may look quite illogical why very similar treatment approaches aimed at targeting B cells result in quite different clinical outcomes in SLE. For example, rituximab, a CD20-directed B-cell-depleting antibody failed to show efficacy in two recent phase III clinical trials in SLE and lupus nephritis (NCT00137969 and NCT00282347), while belimumab, an anti-BAFF agent, became the first FDA approved drug for SLE in 50 years.[26,27,81–83] A potential explanation for this controversy comes from the observation that circulating BAFF levels actually rise in rituximab-treated patients which may subsequently favor the selection and survival of autoreactive B cells and plasmablasts in an environment with very few remaining B cells. Furthermore, elevated BAFF levels could engage T follicular cells, promoting their interaction with autoreactive B cells.[84–88]

Current portfolio of BAFF (and APRIL) inhibitors

The portfolio of BAFF inhibitors includes belimumab (anti-BAFF antibody), blisibimod (anti-BAFF peptibody), tabalumab (anti-BAFF antibody), briobacept (BAFF receptor, inhibits only BAFF), atacicept (TACI receptor, inhibits both BAFF and APRIL), and anti-BAFF-R. In contrast, GSK2857916, an antibody drug conjugate, antagonizes only the BCMA receptor and is currently undergoing phase I study in multiple myeloma (NCT02064387) with no immediate plans for clinical studies in SLE.

Briobacept, consisting of an extracellular domain of BAFF-R fused to human IgG-Fc, has been evaluated in a phase I study in patients with RA. A report in the form of an abstract has been published in 2008, but since then further advancement to phase II or III clinical studies has been abandoned.[55]

Another BAFF-neutralizing agent, tabalumab, achieved its primary endpoint in a recent phase III study ILLUMINATE-2 (NCT01205438).[89] However, important secondary endpoints such as time to severe flare, corticosteroid-sparing effect, and fatigue were not met. Therefore, the drug developer, Eli Lilly Co in 2014 decided to stop further clinical development of tabalumab in SLE.

Another interesting agent in development is atacicept, which neutralizes both BAFF and APRIL. While atacicept may still offer hopes for SLE, higher risk of serious infections and unsafe drop in serum IgG were observed in recent phase II/III trials.[52,90]

Several recent review articles have summarized clinical trials with the above agents, and thus will not be further discussed in this review.[91–94]

Development of A-623/AMG623/blisibimod as a novel high potency and selective BAFF-neutralizing agent

Dr Hsu et al[95] at Amgen's Department of Inflammation were looking for a new BAFF-neutralizing agent that would bind and neutralize both membrane-bound and soluble BAFF with high affinity. Their goal was to screen a 12-mer constrained phage library over Fc-BAFF protein immobilized on protein-A-coated magnetic beads. The next step involved fusing BAFF-binding peptides in tandem copies in-frame to the N-terminal part of the human IgG1-Fc region. The resulting construct (named peptibody) was then expressed in *Escherichia coli*. Purified peptibodies have a unique tetravalent structure, but since they are produced in *E. coli*, they lack the posttranslational glycosylation. A concern remains that BAFF-binding peptides in blisibimod may potentially become immunogenic in humans, causing the induction of neutralizing antibodies that will subsequently diminish blisibimod's potency for BAFF.

In vitro B cell proliferation and affinity studies with A-623/AMG623/blisibimod

These novel peptibodies were first studied in an anti-IgM plus BAFF-mediated B cell proliferation assay. AMG623 showed high affinity for BAFF and inhibited BAFF (and anti-IgM)-mediated B cell proliferation at low nanomolar range (IC-50 at 6 ng/mL).

AMG623 was also tested for its ability to inhibit binding of human BAFF, murine BAFF, or murine APRIL to Biacore chips containing immobilized soluble receptors. AMG623 blocked binding equally well of both human and murine BAFF to BAFF-R, TACI, and BCMA, but had no effect on APRIL binding to its receptors TACI and BCMA.[95]

Animal models

Contrasting with belimumab, which lacks cross reactivity with murine BAFF,[96,97] AMG623 could block murine BAFF activity in vitro. It was subsequently studied in healthy animals and in animal models of SLE and RA. Studies in healthy BALB/c mice showed the ability of AMG623 to reduce the number of B cells in peripheral blood and in spleens. Further animal testing showed the ability of AMG623, when injected intraperitoneally for 5 months, to delay the onset of proteinuria and prolong survival in lupus-prone NZB/NZW-F1 mice. However, this beneficial effect in lupus-prone mice was short-lived and disappeared 3 months after the last injection, suggesting that the defect in immune tolerance leading to disease induction in this model of lupus was not restored and that continuous BAFF inhibition is required.

Similar to animal models of lupus, AMG623 was also effective in collagen-induced arthritis, a mouse model of RA.[95]

Clinical trials with blisibimod

Early-phase trials

Stohl et al[98] conducted early-phase clinical trials with blisibimod in SLE to characterize safety and tolerability. Adult patients with mild stable or inactive SLE (mean SLEDAI ~3) on standard treatment (including prednisone ≤10 mg daily) were enrolled in two early-phase trials with blisibimod. The primary endpoints of both trials were safety and tolerability; additional secondary endpoints were pharmacokinetic and pharmacodynamic parameters, and exploratory endpoints such as changes in peripheral B cell counts and expression of B cell surface markers.

In the phase Ia ascending single-dose study (NCT02443506), patients were sequentially enrolled into one of seven dose cohorts and randomized 3:1 to single dose of blisibimod, administered either subcutaneous (SC) or intravenous (IV), or placebo. A total of 56 participants were randomized, and 54 received the assigned treatment. Participants were followed up to 42 days postdose, and participants in the highest dose cohort (6.0 mg/kg IV) completed a 4-week extension after end-of-study visit. Comparable proportion of participants in the blisibimod (70%) and control (79%) arms experienced ≥1 adverse effect (AE). A total of two serious AEs (SAE) were reported, with one each in the blisibimod and control arms, related to the study drug.

In the phase Ib ascending multidose study (NCT02411136), patients were sequentially enrolled into one of four dose cohorts and randomized 4:1 to receive 4 weekly doses of blisibimod (SC or IV) or placebo. A total of 64 participants were randomized, while 63 received the assigned treatment; 4 participants (2 in each group) withdrew due to an AE. Similar proportion of participants in each group reported ≥1 AE (96% blisibimod vs 92% placebo); nine SAEs were reported in eight participants (5 in blisibimod, 3 in placebo). In the blisibimod arm, SAEs were lupus flare (polyarthritis), depression, chest pain with fever, and syncope; one participant experienced QTc prolongation possibly related to the study drug.

The overall results of these two early-phase clinical trials confirmed that blisibimod had favorable safety and tolerability compared with placebo, providing support for further study in phase II trials. However, a large proportion of participants tested positive for neutralizing antibodies, which could be of some concern. Additional exploratory analyses demonstrated blisibimod's effect on decreasing peripheral B cell counts and changing B cell populations, with relative decrease in naïve B cells and increase in memory B cell compartments via BAFF-mediated differential B cell effects.

PEARL-SC (NCT01162681)

After promising phase I studies, PEARL-SC,[99] a randomized, double-blind, placebo-controlled, phase II study was conducted to assess efficacy and safety of SC blisibimod in patients with active SLE (baseline SELENA-SLEDAI ≥6). The primary outcome was the proportion of responders in the blisibimod pooled group compared with the placebo pooled group meeting the composite endpoint SLE responder index (SRI-5) at 24 weeks. This multicenter international study enrolled 547 participants, randomized in parallel to receive blisibimod SC (either 100 mg once weekly, 200 mg once weekly, or 200 mg every 4 weeks) or placebo. The major exclusions were SLE patients with severe lupus nephritis, CNS lupus, and vasculitis.

Patient baseline characteristics were similar between groups, except for immunosuppressive use, which was higher in the placebo group (52.3%) compared with the control group (38.2%). In both groups, participants were predominantly female (94%), Hispanic (71%), and with active SLE (mean SELENA-SLEDAI ~10) with ≥3 organ domains involved (61%–65%). The most common SLE disease manifestations were mucocutaneous (91%), immunological (77%), and musculoskeletal (75%); renal manifestations were observed in 14%. Treatment with corticosteroids (~90%) and antimalarials (~70%) was common in both groups.

The primary efficacy endpoint for the study, the proportion of SRI-5 responders for blisibimod compared with

placebo pooled groups, was not met. The proportion of SRI-5 responders in the highest blisibimod group (200 mg once weekly) was greater than pooled and regimen-matched placebo groups; however, this was not statistically significant. Similar trends were observed for modified SRI responses with blisibimod, ie, SRI-7 and SRI-8, compared with regimen-matched placebo. Additional subgroup analyses revealed favorable treatment response with blisibimod compared with placebo for severe SLE, defined as high baseline disease activity (SELENA-SLEDAI ≥10) and on corticosteroids. A higher difference in the responder rates (ΔSRI) between blisibimod and placebo was observed with increasing SRI responses, ie, from SRI-5 to SRI-8.

Compared to placebo, trends favoring blisibimod were seen for cumulative probability of severe flare and time to first severe flare, especially for the highest dose (200 mg once weekly). Among participants on prednisone >7.5 mg/d at baseline, more participants on the highest dose blisibimod (200 mg once weekly) were able to taper prednisone dose ≤7.5 mg/d compared with placebo (11.9% vs 9.5%). Subgroup analysis in participants with baseline proteinuria (urine protein to creatinine ratio of 1–6 g/g) achieved a greater mean reduction with blisibimod. Similar trends were seen for disease activity markers of SLE, with significant reduction of B cells and ds-DNA and increase in C3 and C4.

Further, Petri et al[100] reported on the effects of blisibimod on patient-reported fatigue and disease activity in PEARL-SC. Improvements in fatigue measured by the FACIT-Fatigue score were seen in both groups, but were more profound with higher dose blisibimod (100 mg and 200 mg once weekly), exceeding the minimal clinically important difference in SLE ($P<0.05$). SRI-5 responders had significantly higher mean changes in fatigue compared with nonresponders. Improvements in fatigue, however, correlated poorly with disease activity. In terms of safety, a comparable proportion of participants in the blisibimod and placebo groups reported any AE (82.5% vs 85%), while fewer blisibimod-treated participants reported SAEs (11.1% vs 15.8%); overall, no differences were observed for severe infections, death, or malignancy. The presence of antidrug antibodies was not reported, given the high rates of assay positivity in blisibimod-naïve patients, which according to the authors needs further refinement. Thus, the possibility of immunogenicity to blisibimod with repeated exposure remains a concern for sustained clinical efficacy.

Despite not meeting its primary outcome, the PEARL-SC study redemonstrated safety and tolerability of blisibimod, and provided a hint of efficacy (especially for the highest blisibimod dose of 200 mg once weekly) in SLE patients with severe disease meeting a higher responder threshold (SRI-8). This subpopulation of SLE would benefit from further targeted study in phase III trials. On completion of PEARL-SC, 382 participants were enrolled in the open-label blisibimod extension study, PEARL-OLE, with preliminary reports demonstrating favorable long-term safety of blisibimod.[101,102]

Early-phase clinical trials of blisibimod in SLE are summarized in Table 1.

Table 1 Early-phase clinical trials with blisibimod in SLE

Clinical trial	Phase	Status	SLE population	Exclusion	Primary outcome/results	Reference
PEARL-SC NCT01162681	II	Completed 4-2012	Age ≥18 years SELENA-SLEDAI ≥6 On stable GC dose +ANA and/or +ds-DNA	Active CNS Active LN Vasculitis	Proportion of patients achieving SRI-5 at 24 weeks	Furie et al[99]
PEARL-OLE NCT01305746	II	Completed 10-2013	Same as PEARL-SC	Same as PEARL-SC	Long-term safety	Furie et al[101]
NCT02443506	Ia	Completed 6-2007	Age 18–65 years "Mild" SLE[a] Stable or inactive SLE On Pred ≤10 mg/d +ANA	Active CNS Active LN Vasculitis	Safety and tolerability	Stohl et al[98]
NCT02411136	Ib	Completed 10-2007	Age 18–65 years "Mild" SLE[a] Stable or inactive SLE On Pred ≤10 mg/d +ANA	Active CNS Active LN Vasculitis	Safety and tolerability	Stohl et al[98]

Note: [a]Assessed by investigator (no objective measure reported).

Abbreviations: SLE, systemic lupus erythematosus; OLE, open label extension; SELENA-SLEDAI, SLE disease activity index with SELENA modification; SRI, SLE responder index; GC, glucocorticoid; ANA, antinuclear antibody; ds-DNA, double stranded DNA; +, positive; CNS, central nervous system; LN, lupus nephritis.

Table 2 Late-phase clinical trials with blisibimod in SLE

Clinical trial	Phase	Status	SLE population	Exclusion criteria	Primary outcome/results	Reference
CHABLIS-SC1 NCT01395745	III	Completed 9-2016	Age ≥18 years SELENA-SLEDAI ≥10 On stable GC dose +ANA and/or +ds-DNA	Active CNS Active LN Vasculitis Cytopenia	Proportion of patients achieving SRI at 52 weeks	Scheinberg et al[102]
CHABLIS-SC2 NCT02074020	III	Withdrawn prior to enrollment	Age ≥18 years SELENA-SLEDAI ≥10 ±Stable LN On stable GC dose +ANA and/or +ds-DNA	Active CNS Vasculitis Cytopenia	Proportion of patients achieving SRI-8 at 52 weeks	NA
CHABLIS 7.5 NCT02514967	III	Recruiting 6-2016	Age ≥18 years SELENA-SLEDAI ≥10 ±Stable LN On stable GC dose +ds-DNA and low C3 or C4	Active CNS	Proportion of patients achieving SRI-6 at 52 weeks	NA

Abbreviations: SLE, systemic lupus erythematosus; SELENA-SLEDAI, SLE disease activity index with SELENA modification; SRI, SLE responder index; GC, glucocorticoid; ANA, antinuclear antibody; ds-DNA, double stranded DNA; +, positive; CNS, central nervous system; LN, lupus nephritis; SRI, SLE responder index; NA, not available; C3, complement component 3; C4, complement component 4.

Late-phase trials

CHABLIS-SC1 (NCT01395745)

CHABLIS-SC1,[102] a phase III randomized, double-blind, placebo-controlled trial, builds on prior successful early phase trials with blisibimod in SLE with the aim of targeting the responder populations identified in the PEARL-SC trial.[102] This study enrolled 442 participants with active SLE (SELENA-SLEDAI ≥10) on systemic corticosteroids, randomized to blisibimod (200 mg SC once weekly) or placebo in addition to standard of care treatment. The primary endpoint was defined as SRI-6 at 52 weeks; additional secondary endpoints included time to first severe SLE flare, change in the number of tender and swollen joints, change in mucocutaneous disease activity, proportion of participants achieving prednisone ≤7.5 mg/d, and effect on biomarkers and safety. Due to the difficulty in evaluating new drug effect on background lupus treatment and high responder rates in placebo groups, this trial employed a strict requirement for early tapering of systemic corticosteroids after week 8 with the goal of achieving prednisone ≤7.5 mg/d.[102] The study was completed in September 2016; however, no study results have been reported yet.

CHABLIS 7.5 (NCT02514967)

CHABLIS 7.5 is a phase III randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of blisibimod in SLE participants with or without lupus nephritis. The study aims to enroll 350 patients with active SLE defined as SELENA-SLEDAI ≥10 despite systemic corticosteroids, who are positive for ds-DNA and have low complements. Participants will be randomized to blisibimod (200 mg SC once weekly) or placebo. The primary outcome is SRI-6 at 52 weeks, while secondary outcomes will be similar to those measured in CHABLIS-SC1. This trial is actively enrolling participants since June 2016 with the goal of completion in December 2018.

Late-phase clinical trials of blisibimod are summarized in Table 2.

Conclusion

The identification of BAFF's key role as a B cell survival, activation, and differentiation cytokine involved in SLE pathogenesis has led to the development of novel anti-BAFF agents with promising clinical results in SLE. The novel biologic agent blisibimod is building on the success of belimumab by targeting both soluble and membrane-bound BAFF. Early-phase clinical trials of blisibimod have proven its safety and tolerability and have provided a hint of efficacy, specifically in a subpopulation of SLE patients with higher disease activity. Blisibimod's immunogenicity, which leads to the emergence of neutralizing antibodies reported in clinical trials, likely driven by its phage manufacturing process, remains a clinical concern. Despite this clinical hurdle, anti-BAFF therapy remains a promising new therapeutic option for the management of patients with SLE, and the results of late phase clinical trials are eagerly awaited.

This review has focused on the state of the art knowledge about the new anti-BAFF agent, named blisibimod, and its potential advantage over other BAFF-neutralizing agents for the treatment of lupus. However, numerous other pharmaceuticals, including small-molecular signaling pathway inhibitors (eg, Bruton tyrosine kinase inhibitors or

proteasome inhibitors) are in various stages of preclinical and clinical development. It remains to be determined whether antibody-based neutralization of B cells may have any potential clinical advantages over these small-molecular inhibitors. Hopefully, we will not need to wait another 50 years for the next drug to be approved for the treatment of lupus.

Disclosure

The authors report no conflicts of interest in this work.

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