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Review Article

The Future of B-cell Activating Factor Antagonists in the Treatment of Systemic Lupus Erythematosus

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To review B-cell activating factor (BAFF)-antagonist therapy in systemic lupus erythematosus (SLE), literature was searched using the search words and phrases, "BAFF", "B lymphocyte stimulator (BLyS)", "a proliferation-inducing ligand (APRIL)", "B-cell maturation antigen (BCMA)", "transmembrane activator and calcium-modulating and cyclophilin ligand interactor (TACI)", "BLyS receptor 3 (BR3)", "belimumab", "atacicept", "blisibimod", "tabalumab", and "lupus clinical trial". In addition, papers from the author's personal library were searched. BAFF-antagonist therapy in SLE has a checkered past, with four late-stage clinical trials meeting their primary endpoints and four failing to do so. Additional late-stage clinical trials are enrolling subjects to address some of the remaining unresolved questions, and novel approaches are proposed to improve results. The BAFF-centric pathway is a proven therapeutic target in SLE. As the only pathway in the past 50+ years to have yielded an United States Food and Drug Administration-approved drug for SLE, it occupies a unique place in the armamentarium of the practicing rheumatologist. The challenges facing clinicians and investigators are how to better tweak the BAFF-centric pathway and improve on the successes realized. **(J Rheum Dis 2017;24:65-73)**

Key Words. Systemic lupus erythematosus, BAFF, B lymphocyte

INTRODUCTION

The inclusion of the word, "future", in the title of this review is justifiable only if there is a "past". For B-cell activating factor (BAFF) antagonists, the past is a short one. In this review, I will highlight the salient properties of BAFF and its biologic associates, the importance of the BAFF pathway to systemic lupus erythematosus (SLE) pathogenesis, and the clinical successes and failures to date with different individual BAFF antagonists. With that as a backdrop, I will then speculate on the clinical "future" of BAFF antagonism in SLE.

MAIN SUBJECTS

BAFF, APRIL, and their receptors

BAFF (also known as B lymphocyte stimulator [BLyS]) is a 285-amino acid type-II transmembrane protein member of the tumor necrosis factor (TNF) ligand superfamily [1,2]. Cleavage of surface BAFF by a furin protease results in release of a soluble, biologically active 17-kDa molecule [1,3] which binds to three receptors, B-cell maturation antigen (BCMA), transmembrane activator and CAML interactor (TACI), and BLyS receptor 3 (BR3) (also known as B cell activating factor receptor [BAFFR]) on the surface of B cells [4-7].

BAFF serves as a vital survival and differentiation factor [8-11]. Mature B cells and circulating immunoglobulin (Ig) levels are profoundly reduced in mice bearing a disrupted *Baff* gene [12] or in mice genetically programmed to constitutively express high levels of a BAFF antagonist [13,14]. Conversely, B cell expansion and hypergammaglobulinemia develop in mice repeatedly injected with exogenous BAFF [2].

Closely related to BAFF is a proliferation-inducing ligand (APRIL), a 250-amino acid member of the TNF li-

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gand superfamily that shares substantial homology with BAFF and binds to two of the three BAFF receptors (BCMA and TACI) [15-20] but not to BR3 [6]. Unlike BAFF, APRIL also binds to heparan sulfate proteoglycans, such as syndecans, on B cells [21,22].

APRIL can co-stimulate B cells, induce Ig class switching, and promote plasmablast/plasma cell survival [16,18,23-26]. Nevertheless, APRIL-deficient mice remain phenotypically normal [27] or harbor selective deficiencies in circulating IgA levels and IgA responses to mucosal challenges [28]. Similarly, mice that constitutively over-express APRIL do not undergo B cell expansion or develop elevated circulating levels of IgG [29]. Intriguingly, BAFF and APRIL form heterotrimers [30,31], although the in vivo biological consequences of such heterotrimeric formation remain unexplored.

Roles for BAFF and APRIL in SLE

1) Murine studies

In mice, the link between BAFF and SLE is ironclad. Constitutive over-expression of BAFF in otherwise non-autoimmune-prone mice often leads to SLE-like features, including elevated circulating titers of multiple autoantibodies, renal immunopathology, and clinical disease [32-34]. Conversely, development of disease in SLE-prone mice is greatly attenuated by genetic disruption of the *Baff* gene [35] or by pharmacologic treatment with a BAFF antagonist [33,36-38].

Despite APRIL sharing many B cell-agonist activities with BAFF, the link between APRIL in SLE is tenuous. Constitutive over-expression of APRIL in non-autoimmune-prone mice fails to promote serologic or clinical autoimmune features [29]. Indeed, features of SLE are modestly exaggerated, rather than attenuated, in APRIL-deficient SLE-prone mice [39], and even the modest delay in development of proteinuria and death observed in some SLE-prone mice treated with an anti-APRIL mAb [40] may be related to reductions in circulating BAFF/APRIL heterotrimers and, hence, reductions in circulating BAFF activity rather than reductions in circulating APRIL activity.

2) Human studies

Whereas modern-day scientific tools and approaches permit investigators to genetically alter inbred strains of mice and experimentally manipulate them, use of such tools and approaches in humans is strictly unethical. It is not surprising, therefore, that the link between BAFF and SLE in humans is not as compelling as it is in mice. Nonetheless, the evidence, albeit circumstantial, is substantial. As many as 50% of SLE patients harbor elevated circulating BAFF levels at any given time point [41-43], and several longitudinal studies documented a significant correlation between circulating BAFF levels and clinical disease activity [44-47]. SLE patients who chronically harbor high circulating BAFF levels develop greater organ damage over time than do SLE patients who chronically harbor normal circulating BAFF levels [48]. Indeed, SLE patients with high circulating BAFF levels are at increased risk for development of moderate and severe SLE flares [49].

As with murine SLE, the link between APRIL and human SLE is flimsy. Genome-wide association studies, meta-analysis studies, candidate gene studies, and replication studies that have identified multiple SLE susceptibility genes have failed to document an association between the *APRIL* gene and SLE [50]. Whereas two small cross-sectional studies suggested a positive relationship between circulating APRIL levels and SLE disease activity [51,52], the findings were validated neither by independently testing a second SLE cohort nor by re-testing the original SLE patients at a later time point. In fact, two longitudinal studies pointed to a negative, rather than positive, association between circulating APRIL levels and SLE disease activity [53,54].

Experience with BAFF antagonists in SLE

To date, four anti-BAFF agents have undergone clinical evaluation in human SLE: belimumab, blisibimod, tabalumab, and atacicept. Of these, belimumab, blisibimod, and tabalumab have specificity for BAFF only, whereas atacicept has specificity for both BAFF and APRIL.

1) Belimumab

Belimumab is a fully human IgG1 λ mAb that binds and neutralizes soluble BAFF [55]. As assessed by the SLE response index (SRI) [56], both phase-III randomized, double-blind, placebo-controlled trials of belimumab in SLE demonstrated statistically significant increases in clinical responders among subjects treated with belimumab (10 mg/kg intravenously at weeks 0, 2, 4, and then every 4 weeks through week 52) plus standard-of-care (SOC) than among subjects treated with placebo plus SOC [57,58]. Pooled analyses of these two phase-III trials indicated that improvements in the mucocutaneous, immunological, musculoskeletal, vascular, and central nerv-

ous system domains were significantly more frequent among belimumab-treated subjects than among placebo-treated subjects [59].

Based, in part, on these two successful phase-III trials, the United States Food and Drug Administration (FDA) on March 9, 2011, approved belimumab for the treatment of SLE [60]. Since its approval by the FDA, "real-world" clinical experience with belimumab has largely been positive [61-63]. Also since approval of belimumab as an IV drug, a randomized, double-blind, placebo-controlled trial of belimumab (200 mg fixed dose SC weekly through week 52) plus SOC in SLE demonstrated a statistically significantly greater response rate among belimumab-treated subjects than among placebo-treated subjects [64]. It is anticipated that the FDA will soon approve the SC formulation, thereby giving SLE patients the option of receiving their medication away from an infusion center or a medical clinic.

2) Blisibimod

Blisibimod is a fusion protein between the Fc portion of IgG and a synthetic peptide selected for its ability to bind with high affinity to both soluble and membrane BAFF but not to APRIL [65]. Results from phase-Ia and phase-Ib studies in SLE documented a favorable safety profile for blisibimod [66]. However, a phase-IIb study in SLE of blisibimod at multiple dosing regimens failed to meet its primary endpoint with any dosing regimen [67].

3) Tabalumab

Tabalumab is an IgG4κ anti-BAFF mAb that binds to both soluble and membrane BAFF but does not bind to APRIL [68]. Clinical testing of tabalumab in SLE has been limited to two separate phase-III studies. The clinical endpoint was met in one of these trials [69] but not in the other [70]. The safety profile was favorable in each trial.

4) Atacicept

Atacicept is a fusion protein between the BAFF receptor, TACI, and the Fc portion of human IgG1. Since TACI binds both BAFF and APRIL, atacicept neutralizes both BAFF and APRIL. Consequent to its neutralization of both BAFF and APRIL, safety concerns with atacicept have emerged. A phase-II/III trial of atacicept in combination with mycophenolate in SLE nephritis patients was prematurely terminated after enrollment of only 6 subjects due to development of hypogammaglobulinemia and serious pneumonia in atacicept-treated subjects [71]. In a separate phase-II/III trial of atacicept in SLE, enrollment at the higher dose was discontinued prematurely due to two deaths, and neither the primary nor the main secondary endpoint was achieved in patients randomized to the lower (less toxic) dose [72].

Can the limited clinical efficacy of BAFF antagonists be overcome?

Despite the BAFF antagonist, belimumab, becoming the first drug approved in over 50 years by the FDA for SLE, many practitioners within the Rheumatology community remain ambivalent, at best, in their view toward BAFF antagonists. Of the eight late-stage clinical trials of BAFF antagonists in SLE reported to date in complete manuscript form, only four met their respective primary endpoints: each of the three phase-III trials of belimumab [57,58,64], and one of the two phase-III trials of tabalumab [69]. The phase-II belimumab trial, the phase-IIb blisibimod trial, the phase-II/III atacicept trial, and one of the two phase-III tabalumab trials all failed [67,70,72,73]. Even in the successful trials, the absolute percentage differences in clinical responses between BAFF-antagonist-treated and placebo-treated patients were only 10%～14%. Collectively, the limited ability of BAFF antagonists to adequately control human SLE disease activity points to a BAFF-independent component to human SLE. Stated differently, the maximum efficacy achievable through pharmacologic antagonism of BAFF may inherently be limited.

Even if, for argument's sake, we stipulate to this notion of an inherent limitation, the question becomes a quantitative one: have we reached this limitation? Although our BAFF-centric approaches to date have yielded absolute percentage differences in clinical responses of $\leq$15%, there, at present, is no reason to believe that this percentage could not be increased to 25% or 35% if our BAFF-centric approach were optimized. Surely the Rheumatology community would enthusiastically embrace a therapeutic approach that achieves such results while retaining a favorable safety profile.

Moving forward (Table 1)

1) Unresolved issues

(1) Responses in Black SLE patients

Although the three phase-III belimumab trials in SLE met their primary endpoints, sub-group analyses failed to document a positive effect for belimumab among Black SLE patients [64,74]. (Clinical responses among in-

Table 1. Late-stage randomized clinical trials of BAFF antagonists planned/ongoing in SLE

Agent	Route	Phase	N	Target population	Primary endpoint	Trial number
Belimumab	i.v.	III	464	Lupus nephritis patients	Renal response, week 104	NCT01639339
Belimumab	i.v.	III	709	SLE patients in Asia	SRI-4, week 52	NCT01345253
Belimumab	i.v.	IV	816	Black SLE patients	SRI-4, week 52	NCT01632241
Belimumab	i.v.	II	100	Pediatric SLE patients	SRI-4, week 52	NCT01649765
Belimumab	i.v.	II (open-label)	40	Lupus nephritis patients (RTX + CTX followed by belimumab vs. RTX + CTX followed by placebo)	Grade ≥3 infection by week 48	NCT02260934
Blisibimod	s.c.	III	442	Very active SLE patients (SELENA SLEDAI ≥10)	SRI-6, week 52	NCT01395745
Blisibimod	s.c.	III	350	Very active SLE patients (SELENA SLEDAI ≥10) with or without active nephritis	SRI-6, week 52	NCT02514967
Atacicept	s.c.	IIb	306	SLE patients	SRI-4, week 24	NCT01972568

BAFF: B-cell activating factor, SLE: systemic lupus erythematosus, RTX: rituximab, CTX: cyclophosphamide, SELENA SLEDAI: safety of estrogens in lupus erythematosus national assessment SLE disease activity index, SRI: SLE response index.

dividual racial/ethnic sub-groups were not reported in the successful ILLUMINATE-2 trial [69]). Whether these failures reflected underpowered sub-cohorts of Black SLE patients within the individual trials or whether Black SLE patients truly are less sensitive than other racial groups to the beneficial effects of BAFF-antagonist therapy is uncertain. A phase-IV trial of IV belimumab in Black SLE patients (NCT01632241) sufficiently powered to assess clinical efficacy is recruiting patients to address this issue.

(2) What about the very sick SLE patients?

As a rule, SLE subjects eligible for clinical trials are those whose overall health status is sufficiently robust so that anticipated adverse events related to the experimental drug do not unduly jeopardize life or vital organs. That is, the candidate subject must not only be sufficiently fit from a cardiopulmonary standpoint, but he/she must also not be on an immunosuppressive regimen that would increase the risk of infection to an "unacceptable" level. Accordingly, SLE patients with active nephritis or active CNS disease (who routinely require high-dose corticosteroid therapy plus mycophenolate or cyclophosphamide) have been excluded from the vast majority of the phase-II and phase-III trials of BAFF antagonists in SLE reported to date [57,58,67,69,70,72,73].

To address this deficiency, a phase-III trial of belimumab (along with standard-of-care therapy, including high-dose corticosteroids plus cyclophosphamide or mycophenolate) in SLE nephritis patients (NCT01639339) is currently recruiting subjects. (As discussed below, a phase-II trial of belimumab in SLE nephritis patients following treatment with rituximab plus cyclophosphamide is also currently recruiting subjects). The subjects in these trials will be at high risk for infection and will need to be monitored very closely.

(3) What about the children?

Although SLE is predominantly a disease of women in their child-bearing years, it is not solely a disease of women in their child-bearing years. SLE does develop in the pediatric population, and successful therapeutic approaches in adults do not necessarily translate to children. The clinical trials to date of BAFF antagonists in SLE have all focused on adults. To address the efficacy and safety of BAFF-antagonist therapy in pediatric SLE, a phase-II clinical trial (NCT01649765) is currently enrolling subjects.

2) If at first you don't succeed, try, try again

Just because a clinical trial with a given drug fails to achieve its primary endpoint does not mean that the drug is a "failure". The road traversed by belimumab to its ultimate approval by the FDA was neither straight nor smooth and had its "failures" along the way [60], so there remains hope that at least some of the other BAFF antagonists that have so far "failed" will also be able to cross the FDA-approval finish-line.

(1) Blisibimod

Although it failed to achieve its primary endpoint, post hoc analysis of the phase-II blisibimod trial pointed to a favorable clinical response among patients with high disease activity [67]. Based on this impression, one phase-III trial of blisibimod in patients with very active SLE (NCT01395745) has been completed. Results from this trial have not yet been reported in a peer-reviewed format,

but top-line results have been made public. Disappointingly, the clinical endpoint was not achieved in this trial. A second phase-III trial of blisibimod in patients with very active SLE (including patients with active nephritis; NCT02514967), is currently enrolling subjects.

(2) Atacicept

Not deterred by the serious complications associated with high-dose (150 mg) atacicept in a previous phase-II/III trial of atacicept in SLE [72], another phase-IIb trial of atacicept in SLE (NCT01972568) has been completed. Results from this trial have not yet been reported as a peer-reviewed manuscript, but an abstract was presented at the 2016 American College of Rheumatology annual meeting. Once again, the primary endpoint was not achieved. However, pre-specified sensitivity analyses pointed to atacicept promoting greater clinical responses among patients with high disease activity and/or serologically active disease. Serious infections were not over-represented among atacicept-treated subjects. Looking at the glass as half-full rather than half-empty, it is likely that phase-III trials with atacicept in SLE are in the offing.

(3) Tabalumab

Based on the failure of one phase-III trial of tabalumab in SLE to achieve its primary endpoint [70] and the "belimumab-like" limited success of tabalumab in the second phase-III trial in SLE [69], a corporate decision was made to withdraw tabalumab from further testing in SLE. Although it takes three strikes in baseball for the batter to be called "out", tabalumab was called "out" after only a strike and a half.

3) Targeting of BAFF as part of sequential therapy

Combination therapy is an approach used not just in Rheumatology but throughout Medicine. Combinations of DMARDs are used to achieve optimal disease control in patients with rheumatoid arthritis; combinations of anti-hypertensives are used to achieve optimal disease control in patients with refractory hypertension; and combination of anti-hyperglycemics are used to achieve optimal disease control in patients with brittle diabetes. By extension, there is no a priori reason that a BAFF antagonist could (should) not be used as part of combination therapy to achieve optimal disease control in patients with SLE.

Indeed, BAFF neutralization may contribute in an additive or synergistic manner as part of a sequential pharmacologic approach. In SLE patients treated with rituximab, circulating BAFF levels rise concurrent with depletion of the B cells [75]. As B cells recover, circulating BAFF levels decline. Circulating BAFF levels at the time of SLE clinical relapse are greater than those at times of disease remission and greater than those prior to rituximab treatment [76]. Since BAFF is critical to the survival of many autoreactive B cells [77,78], these observations point to the rebounding BAFF levels as important contributors to the emerging disease flare.

If correct, then neutralization of the "BAFF rebound" could clinically be highly efficacious. Accordingly, a phase-II trial of belimumab in SLE nephritis patients following treatment with rituximab plus cyclophosphamide (NCT02260934) is currently recruiting subjects. One can imagine that the subjects in this trial may be at high risk for infection, and development of grade ≥ 3 is the primary endpoint of this trial. It is hoped that the anticipated benefit through enhanced clinical efficacy will outweigh the morbidities associated with increased serious infections.

4) Targeting of BAFF receptors rather than of BAFF

To date, all reported BAFF-centric clinical trials to date have targeted BAFF±APRIL, whereas there have been no reports of targeting any of the BAFF receptors (BCMA, TACI, or BR3). This is rather surprising, since efforts in SLE at other biologic targets have been directed against both ligand and receptor, sometimes with highly divergent results.

Clinical trials directed against type-I interferon (IFN) collectively serve as an illustrative example. The primary endpoint was not achieved in the phase-II trial of the anti-IFNα mAb, rontalizumab [79], whereas the primary endpoint (assessed at week 52) was achieved in the phase-IIb trial of a different anti-IFNα mAb, sifalimumab. In this latter trial, the absolute percentage difference in clinical response between patients treated with the highest dose of sifalimumab and those treated with placebo was 14% [80], similar to the absolute percentage differences observed in the successful trial with belimumab or tabalumab. Of note, however, were results from the phase-IIb trial of the anti-IFNα receptor mAb, anifrolumab, in which the absolute percentage difference in clinical response between patients treated with the optimal dose of anifrolumab and those treated with placebo being 26% [81]. Although comparisons of response rates across different trials are notoriously unreliable and must be taken with a large grain of salt, the strikingly greater response rate in the trial that targeted the IFNα receptor rather than IFNα itself raises the plausibility of im-

proved results in BAFF-centric trials that target BAFF receptors rather than BAFF itself.

Based on studies in SLE-prone NZM 2328 (NZM) mice, more than one BAFF receptor may need to be targeted. NZM mice deficient in any single BAFF receptor develop clinical SLE with a time course indistinguishable from that of NZM wild-type mice [82]. That is, there is sufficient functional redundancy among the BAFF receptors to render any single BAFF receptor dispensable to the development of SLE in NZM mice. By extension, pharmacologic targeting of any single BAFF receptor might not be therapeutically beneficial in human SLE. Nevertheless, development of clinical disease is greatly attenuated in NZM mice deficient in specific pairs of BAFF receptors (BR3+BCMA or BR3+TACI) [83]. This raises the possibility that agents that target both BR3 and BCMA or both BR3 and TACI may be therapeutically efficacious. To date, no agents have been developed that specifically block the relevant pairs of BAFF receptors, so no clinical trials with such agents are currently planned.

CONCLUSION

The BAFF-centric pathway is a proven therapeutic target in SLE. As the only pathway in the past over 50 years to have yielded an FDA-approved drug for SLE, it occupies a unique place in the armamentarium of the practicing rheumatologist. The challenges facing clinicians and investigators are how to better tweak the BAFF-centric pathway and improve on the successes realized to date.

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CONFLICT OF INTEREST

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