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Targeting BLyS in rheumatic disease: the sometimes-bumpy road from bench to bedside

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Abstract

Purpose of review—BLyS family ligands and receptors are key players in the selection and survival of most mature B lymphocytes. The fundamental role of BLyS in transitional B cell selection, coupled with the relative BLyS-independence of memory B cells and plasma cells, suggests that BLyS may be a useful therapeutic target in strategies directed against pre-immune B cell pools. Several agents that target BLyS are in clinical trials now, and we summarize recent results here, with a focus on systemic lupus erythematosus (SLE).

Recent findings—Belimumab, a human neutralizing anti-BLyS monoclonal antibody, has delivered moderate but positive results in two separate phase III clinical trials for systemic lupus erythematosus (SLE), and was recently recommended for approval by an FDA advisory panel. Additional agents targeting BLyS or other members of this cytokine receptor family are also being tested in clinical trials.

Summary—Together, these trials should yield novel therapies for a debilitating and often intractable illness; and offer insights that in turn should foster subsequent generations of personalized, targeted therapies for rheumatic diseases.

Keywords

BLyS; BAFF; B cell targeted therapy; lupus; SLE

Introduction

Over the last decade, steadily increasing evidence has implicated the BLyS (also known as BAFF) family of ligands and receptors in mediating the selection and survival of most mature B lymphocyte subsets (reviewed in [1]). A connection with rheumatic disease was made early, based on the development of frank humoral autoimmunity in BLyS transgenic mice and the elevated BLyS levels in SLE, RA, and Sjogren's syndrome. This connection was strengthened by animal studies clearly linking BLyS with B cell tolerance and homeostasis (reviewed in [2]). Based on these observations, a variety of approaches have been developed to target BLyS and other members of this cytokine and receptor family in the treatment of rheumatic diseases. BLyS-targeted therapies are presently in clinical trials (summarized in Table 1). Among these, two independent phase III clinical trials in SLE with the human neutralizing anti-BLyS monoclonal antibody, belimumab (registered as

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Benlysta®), achieved their primary endpoints. The FDA and European Medicines Agency are currently conducting reviews, and in November 2010 an FDA advisory panel voted in favor of approving Benlysta as a therapy for SLE in the U.S. The FDA itself may give its final approval as early as the first quarter of 2011. This would make belimumab the first new drug approved for SLE in decades. Reaching this milestone, however, has not been without several bumps along the road.

BLyS family biology suggests targets in treating autoimmune disorders

The BLyS family is a subset of the TNF superfamily, and consists of two cytokines (ligands), BLyS and APRIL; and three receptors, BR3 (BAFF-R), TACI, and BCMA. Soluble trimeric BLyS can interact with all three receptors, whereas APRIL only interacts with TACI and BCMA. While the biological actions of all family members have been investigated, interrogation of the BLyS/BR3 axis has advanced most rapidly, probably because of the profound effects on mature B cells following experimental manipulation of BLyS or BR3, as well as the inferred relevance to autoimmunity [3]. In aggregate, these studies have shown that BLyS/BR3 signaling regulates homeostasis of the pre-immune B cell pool by governing the stringency of selection at late tolerance checkpoints and controlling the lifespan of primary B cells.

After immature B cells exit the bone marrow, they pass through a transitional checkpoint before joining the mature recirculating primary B cell pool. Under normal circumstances, only about one-third of these transitional B cells survive to maturity, with those B cells expressing self-reactive or polyreactive specificities being lost [4,5]. Since mature primary B cells require BLyS for survival, only B cells that compete effectively for BLyS persist through transitional development. Accordingly, elevated BLyS levels allow B cells that are otherwise at a survival disadvantage to pass the transitional checkpoint and become established in the mature follicular and marginal zone B cell pools [6]. Conversely, reducing available BLyS may augment the stringency of transitional selection and reduce mature B cell lifespan, leading to reduced mature B cell numbers.

Based on the phenotypes of knockout mice, neither the APRIL ligand nor the TACI and BCMA receptors play major roles in building or maintaining the mature naïve B cell compartment [7–9]. Nevertheless, both BLyS and APRIL have important, if subtle, functions during B cell activation and in the differentiation or maintenance of antigen-experienced subsets. APRIL can modulate certain aspects of B cell activation [10], and BLyS signaling can interact with TLR pathways, initiating processes that engender class switching [10,11]. Both BLyS and BR3 are required for optimal germinal center (GC) formation and kinetics (reviewed in [12]), and both BLyS and APRIL signaling through TACI modulate isotype switching [12,13]. Whether the selection of activated B cell subsets, particularly GC B cells, is affected by BLyS availability remains less clear.

Neither memory nor long-lived plasma cells rely solely on BLyS for their differentiation or survival [14**,15**]. Indeed, long-lived plasma cells and memory B cells are relatively resistant to BLyS depletion compared to naive precursors; however, unswitched (IgM-bearing) memory cells may retain some BLyS dependence [14]. Two studies show that BLyS works with inflammatory cytokines to drive human memory B cells to differentiate into plasma cells [16,17]. Animal studies show that APRIL signaling through BCMA is sufficient to support long-lived plasma cells in bone marrow [7]; and, consistent with their exclusive expression of BCMA, long-lived plasma cells can utilize either BLyS or APRIL for maintenance [15].

Many observations in humans implicate BLyS or BLyS family members in SLE pathogenesis, thereby suggesting them as potential therapeutic targets. For example, serum

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BLyS, APRIL, and BLyS/APRIL heterotrimer levels are elevated in many SLE patients (for examples, see [10,18–21]), and TACI upregulation and BR3 downregulation on peripheral B cells have also been observed [22].

The pivotal role for BLyS in transitional B cell selection, the relative BLyS-independence of memory B cell populations, and the dysregulation of BLyS in SLE collectively suggest BLyS as a prime candidate in therapeutic strategies for disorders resulting from failed peripheral B cell tolerance, or for diseases whose pathology relies on continued input from the pre-immune B cell pools. [23]. In such cases, neutralizing BLyS would have the safety advantage of leaving B cell memory, long-lived plasma cells, and natural antibodies intact. Conversely, if (pathogenic) autoreactive B cells are a component of the memory compartment, then BLyS neutralization may not be efficacious.

Treatment with belimumab (a BLyS-neutralizing monoclonal antibody)

Despite the strong salutary effects of BLyS antagonists in murine SLE models [24,25], demonstrating similar efficacy in human SLE has proven difficult. The greatest experience to date with BLyS antagonists has accrued with belimumab, a fully human IgG1λ mAb that binds and neutralizes soluble BLyS [26]. Preclinical studies with belimumab in cynomolgus monkeys demonstrated no cage-side toxicities and reversible effects on B cell numbers in peripheral blood or secondary lymphoid tissues [27]. Moreover, no untoward effects were observed in either mothers or babies of cynomolgus monkeys given belimumab throughout pregnancy [28].

This relative safety has been reproduced in human subjects. Belimumab was shown to be safe in a randomized, double-blind, placebo-controlled phase-I trial in SLE, in which the prevalence of adverse events was no different between belimumab- and placebo-treated patients [29]. Of note, only modest reductions in peripheral blood B cells were observed among belimumab-treated patients. No clinical efficacy was demonstrated in this phase-I trial, but the small number of patients (n = 70) and very brief treatment schedules (single infusion or two infusions 3 weeks apart) and follow-up period (12 weeks after final infusion) precluded demonstration of clinical benefit.

Armed with the very favorable safety profile of belimumab in human subjects along with compelling studies in murine SLE that demonstrated *in vivo* therapeutic efficacy for BLyS antagonism [30,31], a 52-week, randomized, double-blind, placebo-controlled phase-II trial of belimumab in SLE (n = 449) was undertaken. Disappointingly, the trial failed to meet its co-primary endpoints (disease activity at 24 weeks and time to first flare during the 52 weeks) when considering the entire SLE cohort [32]. However, extensive post hoc analysis led to a novel composite index of clinical response (SLE responder index or SRI; [33]) and demonstrated significantly increased clinical response among belimumab-treated patients at 52 weeks (but not at 24 weeks) among the ~70% of patients who were “seropositive” (ANA titer ≥1:80 and/or positive for anti-dsDNA antibodies) at entry.

Given the failure of belimumab to meet either of the co-primary endpoints in the phase-II trial, the initiation of two separate large randomized, double-blind, placebo-controlled phase-III trials (BLISS-52, n = 865; and BLISS-76, n = 819) of belimumab in “seropositive” SLE was met with skepticism. Nonetheless, both of these phase-III trials met their primary endpoints (increased percentage of responders at 52 weeks). In each trial, patients were given standard-of-care (SOC) + placebo (control group) or SOC + belimumab at one of two doses (1 or 10 mg/kg at weeks 0, 2, 4, and every 4 weeks thereafter). In BLISS-52 (conducted largely in Asia, South America, and Eastern Europe), SRI response rates were 44% in the placebo group, 51% (p = 0.013) in the 1 mg/kg belimumab group, and reached 58% (p = 0.0006) in the 10 mg/kg belimumab group [34]. In BLISS-76 (conducted largely

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in the US, Canada, and Europe), SRI response rates were 34% in the placebo group, 41% ($p = 0.09$) in the 1 mg/kg belimumab group, and were 43% ($p = 0.017$) in the 10 mg/kg belimumab group [35]. Importantly, analysis of the combined 1864 SLE patients in both BLISS trials at 52 weeks pointed to reductions in disease activity and prevention of worsening across vital internal organ systems, including hematological and renal [36**].

More bumps in the road lay ahead, however. The response rates at 76 weeks among belimumab-treated patients were no longer significantly different from that of placebo-treated patients, although the trend to greater response persisted [35]. This raises questions regarding the "staying power" of belimumab (and, by implication, other BLyS antagonists). This may reflect a lack of power afforded by the study cohort, or alternatively, the duration of belimumab-driven clinical efficacy is truly finite. Although patients treated with belimumab over 5 years in open-label extension (1415 patient-years) have shown stable SRI response scores and declining rates of flares, these patients have had their concurrent medications adjusted as clinically warranted [37], so the actual contribution of belimumab to the long-term favorable outcome remains uncertain. Nonetheless, belimumab is highly likely to win FDA approval for the treatment of SLE.

Once belimumab is approved, the questions of which patients to treat and for how long will immediately arise. No definitive answers to these questions can be offered at present, but we can offer the following suggestions. First, since only seropositive, but not seronegative, patients experienced a significant clinical response in the phase-II trial [32], it may be prudent to limit belimumab therapy to seropositive patients. (The phase-III trials are not informative in this regard, since all patients enrolled were seropositive.) Second, since clinical benefit in the phase-II trial was observed among patients taking prednisone ≥7.5 mg (or its equivalent)/day but not among patients taking <7.5 mg/day [32], it may be prudent to limit belimumab to patients that require ≥7.5 mg/day for disease control. (Analyses from the phase-III trials are not yet available but should be highly informative.) Third, since the responder rate among belimumab-treated patients continued to rise throughout the 52-week double-blinded portion of the phase-II trial [33], it may be prudent to give patients at least a 12-month trial of belimumab. Given the loss of significant difference between belimumab-treated and placebo-treated patients at 76 weeks in the BLISS-76 trial [35], the utility of protracted treatment with belimumab remains an open question that, at present, might be best left to a case-by-case adjudication by the attending physician.

Treatment with atacicept (TACI-Ig fusion protein)

In addition to belimumab, several other BLyS antagonists are undergoing clinical evaluation in SLE. The one furthest advanced in clinical evaluation is atacicept, a fusion protein between one of the BLyS receptors (TACI) and the Fc portion of IgG. Atacicept, in contrast to belimumab, binds and neutralizes both BLyS and APRIL. Accordingly, its clinical effects could substantially differ from those of belimumab. Since the roles for APRIL in the development and maintenance of antigen-experienced B cell subsets and in SLE are speculative, predicting the outcome of neutralizing both BLyS and APRIL is difficult. Indeed, the broader impact on B lineage pools could potentially afford greater efficacy, but might also prove less effective or detrimental due to unintended adverse events.

Preclinical studies with atacicept in mice and cynomolgus monkeys documented reversible sub-total depletion of B cells and reduction in circulating Ig (especially IgM) levels, with the only apparent systemic toxicity being transient elevations in liver-derived transaminases (without any histological changes in the livers) [38]. In humans, favorable safety and tolerability were demonstrated in a randomized, double-blind, placebo-controlled phase-I trial of atacicept in SLE [39]. SLE patients (n = 49) received a single dose of atacicept (0.3, 1, 3, or 9 mg/kg) or placebo or four weekly doses of atacicept (1 or 3 mg/kg) or placebo.

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Dose-dependent reductions in peripheral blood B cells and in circulating Ig levels were noted, but, as the case with the phase-I trial of belimumab in SLE, clinical efficacy could not be demonstrated due to the limited treatment and limited follow-up period.

Of concern, an unacceptable safety profile (increased risk of severe infections) was observed in a subsequent trial involving patients with SLE nephritis who were concurrently taking mycophenolate mofetil and corticosteroids (ClinicalTrials.gov identifier NCT00573157). As a consequence, this trial was prematurely terminated. Despite this bump in the road with atacicept, a separate phase-II/III trial of atacicept in SLE has recently been initiated (ClinicalTrials.gov identifier NCT00624338). Whether atacicept ultimately achieves clinical success from efficacy and safety standpoints remains an open question.

Treatment with other BLyS antagonists

Limited clinical information is available with regard to a third BLyS antagonist being tested in clinical trials, A-623 (previously known as AMG 623), a fusion between the Fc portion of IgG and a peptide sequence selected for its ability to bind with high affinity to BLyS. In a double-blind, placebo-controlled phase-I trial, SLE patients received a single dose (n = 54) or 4 weekly doses (n = 63) of AMG 623 (0.3, 1, or 3 mg/kg subcutaneously or 6 mg/kg intravenously) or matching placebo [40]. A dose-independent decrease in naive and total peripheral blood B cells was accompanied by an actual increase in memory B cells. Clinical responses were not reported, so the relevance of the disparate changes among B cell subsets to clinical parameters remains unknown. Of note, a similar (transient) increase in circulating memory B cells has been observed in belimumab-treated patients [41], raising the possibility that individual B cell subpopulations may be differentially affected by all BLyS antagonists.

In any case, a phase-II trial of A-623 in SLE has been initiated. It had been suspended due to “structural failure identified in some product vials” (ClinicalTrials.gov identifier NCT01162681), but the problem has been overcome, and the trial has resumed recruiting subjects.

A fourth BLyS antagonist in clinical development for SLE is LY2127399, a monoclonal antibody that binds both soluble and membrane BLyS [42]. Two phase-III trials in SLE (ClinicalTrials.gov identifiers NCT01205438 and NCT01196091) have just begun recruiting patients. Since the role for membrane BLyS in SLE pathogenesis is far from certain, it remains to be determined whether neutralization of soluble + membrane BLyS (as with LY2127399) will have greater therapeutic efficacy than neutralization of soluble BLyS alone (as with belimumab).

3. Conclusion

B cells play both protective and pathogenic roles in human health and disease, and there is increasing evidence that they are functionally more heterogeneous than originally imagined [43**,44]. The pivotal roles played by BLyS and its receptors in B cell homeostasis, selection, and survival, as well as their more recently appreciated roles among antigen-experienced subsets, suggest many advantages as potential targets in the therapy of humoral autoimmunity. Despite the strong potential for diseases in which primary B cell pools are crucial to sustained pathogenesis, targeting BLyS may not be effective in disease states in which autoreactive clones have already populated memory and/or long-lived plasma cell pools. Indeed, it is tempting to speculate that variable efficacy of belimumab in SLE patients may reflect differences in B cell profiles, due to the etiology and/or stage of the disease; and that as experience with BLyS and related targets increases, it will eventually help us to distinguish these variables.

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Key points

- We outline the roles played by BLyS and other members of this cytokine/receptor family in the biology of B cells, to explain why BLyS is likely to be a key target in effective treatment of SLE.
- This article provides a detailed summary of clinical trial experience with belimumab, a BLyS-neutralizing antibody that is likely to win FDA approval in 2011 for treatment of lupus.
- In addition, we summarize progress with three additional BLyS antagonists in recent clinical trials.

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Table 1

Summary of SLE clinical trial results with BLyS-targeting agents[a]

Agent	Target(s)	Trial	Results	References
Belimumab	BLyS	Phase I(n = 70)	Demonstration of safety	29
		Phase II(n = 449)	Failure to meet co-primary endpoints	32
			Use of novel SRI shows efficacy among seropositive patients	32, 33
		Phase III/BLISS-52(n = 865)	Primary endpoint met	34
		Phase III/BLISS-76(n = 819)	Primary endpoint met	35
		Open-label extension(patient-years = 1415)	Well-tolerated with sustained clinical benefit for as long as 5 years	37
Atacicept	BLyS, APRIL	Phase I(n = 49)	Demonstration of safety	39
		Phase II/III(targeted n = 200)	Terminated due to increased risk of severe infections	ClinicalTrials.gov NCT00573157
		Phase II/III(estimated n = 510)	Recruiting	ClinicalTrials.gov NCT00624338
A-623	BLyS	Phase I(n = 54; n = 63) [b]	Demonstration of safety	40
		Phase II(estimated n = 600)	Recruiting	ClinicalTrials.gov NCT01162681
LY2127399	BLyS	Phase III(estimated n = 1140)	Recruiting	ClinicalTrials.gov NCT01196091
		Phase III(estimated n = 1140)	Recruiting	ClinicalTrials.gov NCT01205438

[a] Summary of current clinical trials using BLyS-targeting agents in SLE.

[b] single vs. four doses.