

Belimumab for the treatment of systemic lupus erythematosus

Over the last several years, there has been marked interest regarding the role of B cells in the pathogenesis of systemic lupus erythematosus (SLE) as well as multiple other autoimmune diseases. Owing to the multitude of evidence showing B-cell dysfunction in SLE, targeting B cells has been investigated as a modality for treating the disease. There are a number of strategies that can be used for B-cell-directed therapy. In this article, we focus on the use of B-lymphocyte stimulator (BLyS) inhibition. BLyS has been found to be an important cytokine in B-cell development and activity and is strongly implicated in SLE pathogenesis. Belimumab (Benlysta[®], Human Genome Sciences Inc., MD, USA) is a drug that inhibits BLyS and is thus a prime candidate to treat disorders with B-cell dysfunction and SLE in particular. Belimumab has now gone through numerous clinical trials, including an extensive Phase II trial and two Phase III trials. The drug looks very promising and in this paper we review the relevant data, including the recent Phase II studies.

KEYWORDS: B cell ■ belimumab ■ Benlysta[®] ■ B-lymphocyte stimulator ■ lupus ■ systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is a chronic multisystem disease associated with significant morbidity and mortality. There is substantial evidence that B cells play a central role in the pathogenesis of this disease [1,2], both in mouse models and humans [3]. It has been accepted that B cells are indirectly responsible for tissue destruction via conventional autoantibody production, but antibody-independent activities are also considered important [4]. Autoantibodies induce disease manifestations by a number of mechanisms, including immune complex-mediated activation of Fc receptors and antibody- and complement-mediated cytotoxicity. Antibody-independent mechanisms where B cells are important include antigen presentation, T-cell activation, synthesis of inflammatory cytokines and dendritic cell modulation. Both functional and quantitative B-cell abnormalities have been found in SLE [5].

B cell-targeted therapies

In recent years, there has been significant interest in B cell-targeted therapies for the treatment of inflammatory and autoimmune diseases [3]. The anti-CD20 monoclonal antibody, rituximab, initially approved for lymphoma in 1997, was approved by the US FDA in 2006 for use in patients with rheumatoid arthritis (RA) refractory to TNF inhibitors. Open-label studies, as well as off-label use, have suggested rituximab to be effective in

SLE, vasculitis, idiopathic thrombocytopenic purpura and other autoimmune disorders [6]. Although Phase III trials of rituximab have failed to substantiate the efficacy in lupus, the observations have supported novel drug development strategies in autoimmune diseases, such as SLE which focus on B cells and their growth factors.

BLyS activity & pathogenesis

B-lymphocyte stimulator (BLyS; BAFF) was discovered by scientists at Human Genome Sciences, Inc. in 1999. BLyS is a cytokine essential for B-cell growth and survival. It binds to any of three receptors on B cells: TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor), B-cell maturation and BLyS receptor 3 (BAFF-R) [7]. BLyS is a member of the TNF ligand superfamily [8] and is expressed by various cells, including monocytes, macrophages, dendritic cells and activated neutrophils [2]. It is an important molecule in B-cell maturation, proliferation and immunoglobulin class switching. Animal models where BLyS is overexpressed result in the development of autoantibodies and immune complex disease of the kidney [9], which suggests the importance of BLyS in autoimmune disease. Repeated administration of exogenous BLyS to mice results in B-cell expansion and increased serum immunoglobulin levels despite the absence of antigenic immunization [8].

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Increased levels of BLYS have been found in SLE patients. Collins *et al.* noted earlier studies that failed to show a clear correlation of circulating BLYS protein levels and disease activity in lupus [10]. It was hypothesized that this might be due to inadequate correcting for BLYS utilization and excretion. They therefore looked at BLYS mRNA levels in lupus patients versus RA patients and normal controls. Only two of 30 normals and four of 60 RA patients had elevated full-length BLYS mRNA levels, whereas 20 of the 60 lupus patients had elevated levels. In addition, these elevated levels of mRNA correlated significantly with SLE Disease Activity Index (SLEDAI) scores despite the fact that the plasma BLYS levels did not correlate with SLEDAI in this group.

Petri *et al.* looked at the relationship between BLYS levels, Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) SLEDAI (SS) scores and anti-double-stranded (ds)DNA in 245 lupus patients [11]. They found an association of plasma BLYS levels with anti-dsDNA titers and SS scores. In addition, an increase in the SS score at a subsequent visit correlated with elevated BLYS levels at the previous visit. This was the first study to demonstrate that BLYS levels may be a marker of disease activity in lupus, and an increase in BLYS concentration might predict subsequent flares.

Anti-BLYS therapy

Targeting BLYS could be of potential therapeutic benefit to SLE patients based on the B-cell hyperactivity and elevated serum levels of BLYS that have been observed in these patients. Monoclonal antibodies to BLYS, soluble BAFF or TACI receptors, and Fc-peptide fusion proteins (peptibody) with binding affinity for BLYS are some of the strategies that have been utilized to inhibit BLYS and/or APRIL.

Belimumab (Lymphostat-B, Benlysta®; Human Genome Sciences, Inc., MD, USA) is a human monoclonal antibody that binds soluble BLYS and prevents binding to its receptors. Belimumab has been shown to inhibit proliferation of B cells *in vitro* [12]. In animal studies, there were significant reductions in CD20⁺ B cells and CD21⁺ plasma cells in the peripheral blood and lymphoid tissue. Cynomolgus monkeys were injected with belimumab at 5, 15 or 50 mg/kg versus vehicle every 7 days for four cycles, and then necropsied on day 29 or 57 after being treatment free for 28 days. There was a significant decrease in B-cell levels in both the spleen and lymph nodes in the treated group of animals versus controls. Similar results were noted in mice experiments.

Clinical application: Phase I study

The first human studies with belimumab were performed in patients with SLE. Furie *et al.* presented a Phase I, double-blind, randomized study that evaluated the effects of belimumab versus placebo on 70 patients with mild-to-moderate SLE [13]. There were four belimumab dose groups ranging from 1 to 20 mg/kg, and one placebo group. Patients received one or two doses of belimumab and were followed for 84–105 days after receiving the drug. There were significant reductions in peripheral B cells in the treatment groups as compared with placebo; however, SLE disease activity in this cohort of patients with low disease activity at baseline did not change significantly. It was found that the drug was well tolerated with a similar side-effect profile as placebo. There were no serious adverse events related to the study drug. One person had an infusion reaction, which was easily treated with antihistamine. The half-life of the monoclonal antibody was found to be 8.5–14 days. The study concluded that belimumab was well tolerated and bioactive, and these results were a foundation for a large Phase II study.

Clinical efficacy: Phase II study

A Phase II study was subsequently performed by the LBSL02/99 group, which enrolled 449 patients who met American College of Rheumatology (ACR) diagnostic criteria for SLE, had active SLE disease and have been on stable SLE treatment regimen. Lupus activity was defined by presence of SS score of at least 4. Some of the exclusions were patients treated with intravenous cyclophosphamide in the past 180 days, patients with severe kidney disease and those recently treated with B cell-targeted therapy. Primary outcome measures were evaluation of frequency and rate of adverse events at 12 and 24 weeks, as well as baseline change in B cell and B-cell subsets in treatment patients at these time points. There were initially three belimumab groups (1, 4 or 10 mg/kg every 4 weeks) and a placebo group enrolled in a 52-week trial. After 1 year, placebo patients were switched to belimumab 10 mg/kg and those on the drug had the option of remaining on their regimen or having a dose increase to 10 mg/kg. At week 76, there were 296 subjects who chose to remain in a 5-year extension study where all participants received 10 mg/kg every 4 weeks. Efficacy in this trial was assessed using several measures: SS, SLE flare Index (SFI), The British Isles Lupus Assessment Group (BILAG) and Physicians Global Assessment. The co-primary end points

(neither of which were met) were: percentage change in SS at week 24; and time to first flare over 52 weeks. These values were not significantly better in the groups treated with belimumab at 52 weeks. However, it was noted that a significant percentage of patients entered into the trial were seronegative (i.e., antinuclear antibody [ANA] and dsDNA negative) and *post hoc* analysis was then performed.

The first of these *post hoc* analyses focused on serologic status. Baseline serologic activity was defined as an ANA titer of at least 1/80 or anti-dsDNA antibodies of at least 30 IU/ml. Using this definition, 71.5% of the original cohort had baseline serologic activity. As dose-dependent effects were not observed, the three treatment groups were combined for analysis. A 29% reduction in SS score at week 52 in serologically active treated patients was observed ($p = 0.044$) [14]. In addition to the clinical improvement, data demonstrating the bioactivity of belimumab were reported. Reductions in CD19-positive B cells, naive B cells (CD20⁺/CD27⁺), activated B cells (CD20⁺/CD69⁺) and plasmacytoid cells (CD20⁺/CD138⁺) were observed, while memory B cells (CD20⁺/27⁺) increased transiently (see data later).

The SS is a score based on disease activity that has 24 lines with varying point assignments. The parameters include both clinical (e.g., rash, arthritis) and laboratory (e.g., dsDNA antibodies, platelet count) markers. The SS tracks complete elimination, but not partial resolution, of symptoms. BILAG has the ability to measure changes in disease activity over a given period of time for a particular organ system. A BILAG A or two BILAG B flares is considered a suitably significant increase in disease activity to require therapeutic intervention such as steroids or immunosuppression.

Furie *et al.* subsequently reported an analysis of a novel composite end point known as the SLE Responder Index (SRI) [15]. It consists of multiple measures: four-point or greater improvement in SS score; no BILAG worsening (new A or two B flares); and no worsening in Physicians Global Assessment (<0.3 point increase).

The rationale for this was that the FDA has recommended that results of clinical trials be analyzed to verify that improved SLE disease activity score translates into a clinical benefit for the patient. It is also important to show that disease activity improvement in one area does associate with worsening of other manifestations. The SRI was felt to be more sensitive than SS alone in detecting clinical improvement with no worsening.

When this combined index was applied to the Phase II dataset, it was noted that belimumab significantly improved the response rate at 52 weeks in serologically active patients ($p = 0.006$). Serologically active patients treated with belimumab had a response rate of 46% at week 52 using the combined novel end point, whereas only 29% of those who received placebo met the definition of response ($p < 0.01$) [16]. At 72 weeks, the response rate with belimumab had increased to 56%. In the 52-week analysis, although there was a benefit to belimumab patients, there was no significant dose response.

At the 2008 EULAR Congress, Furie *et al.* also reported on the long-term follow-up of seropositive subjects in this cohort [17]. Seropositive patients included 321 of the original cohort (72%). The SRI response rates were maintained at approximately 55% through 3 years of therapy (TABLE 1). Those who were seropositive and on treatment for the entire 160 weeks (170 patients) had a 65% SRI response rate. The flare rates were 74% for placebo and 62% for

Table 1. Results of a 3-year follow-up for Phase II patients taking belimumab on open-label extension.

Parameter response	Week 52			Week 76	Week 128	Week 160
	Placebo n = 86 (%)	Belimumab n = 235 (%)	p-value	Belimumab n = 235 (%)	Belimumab n = 235 (%)	Belimumab n = 235 (%)
ITT LOCF						
SRI	29.1	46.0	0.0058	55.3	54.0	55.0
SS improvement ≥ 4	39.5	49.4	0.1169	57.9	58.3	62.1
No new BILAG 1A/2B	81.4	91.5	0.0152	94.0	93.6	95.2
No PGA worsening	76.7	90.2	0.0027	92.8	91.1	92.1
Active subjects	Placebo n = 86 (%)	Belimumab n = 235 (%)		Belimumab n = 187 (%)	Belimumab n = 156 (%)	Belimumab n = 125 (%)
SS flares	74	62	NS	57	31	7
Severe SS flares	11	8	NS	4	4	0

BILAG: The British Isles Lupus Assessment Group; ITT: Intent-to-treat; LOCF: Last observation carried forward; NS: Not supplied; PGA: Physicians Global Assessment; SRI: Systemic lupus erythematosus Responder Index; SS: SLENA SLEDAI.

belimumab patients at 1 year. By week 128, this declined to 31% and finally to 7% at the 3-year mark. It should be noted that data collected after year 1 lack a comparator group and have less rigorous collection of clinical and laboratory data. However, these data do suggest that belimumab reduces disease activity and reduces flare rates, and these effects are highly durable.

Another analysis of this trial was carried out by Chatham *et al.* with regard to B-cell subtypes and autoantibodies [18]. B cells, autoantibodies, immunoglobulin isotypes and other parameters from patients in the trial were analyzed every 1–2 months. Results demonstrated a reduction in activated (CD20⁺/69⁺), plasmacytoid (CD20⁺/138⁺) and total CD20⁺ B cells of 70, 63 and 54%, respectively, at week 52 with treatment (TABLE 2). An increase in memory B cells (CD20⁺/CD27⁺) occurred 4 weeks after administration of the first dose of belimumab; however, this population of B cells normalized by week 52. Clinical responders had a greater reduction in activated B cells (36 vs 20%) and plasmacytoid cells (32 vs 12%). There was not a significant difference in naive or memory cells. Mean plasma cells (CD20⁺/CD138⁺) increased 60% over baseline in belimumab-treated subjects versus 9% in placebo. In terms of immunoglobulin levels, treated subjects had a reduction of IgG, IgA, IgE and IgM levels (10, 14, 34, 29%, respectively), and 128 patients had elevated immunoglobulin isotype levels at baseline (TABLE 3). Of these patients, 52 (41%) normalized versus 16% (seven out of 45) on placebo. Thus, the conclusion of this analysis was that belimumab modulates peripheral B-cell counts, immunoglobulin and autoantibody levels. The reductions of autoantibodies and proportion of circulating activated B cells associated with clinical effects and, therefore, supports the utility of this treatment.

Stohl *et al.* also investigated autoantibody levels in subjects from this Phase II study and extension, where similar results were reported [19]. In addition they considered complement levels and subjects with low complement levels (C3: n = 135; C4: n = 180) showed an increase with treatment. C4 rose by 33% at week 52 versus 14% for placebo, and C3 rose by 6%, whereas placebo was down 1%. The

increases continued in a linear fashion during the extension until week 128. Lastly, this analysis looked at dsDNA antibodies. Again, belimumab-treated subjects decreased more than placebo patients and were more likely to have a significant anti-dsDNA reduction (>50% or becoming negative). Belimumab treatment resulted in at least 50% reduction in dsDNA antibodies in 30% of patients, whereas just 17% of subjects treated with placebo experienced this level of reduction. At week 128, 47% of patients had at least 50% reduction in dsDNA antibody. Patients with higher baseline levels of autoantibodies and those with clinical responses to the drug tended to have more significant reductions. Patients with hypocomplementemia at baseline had progressive increases in complement over time (TABLE 4).

The clinical responders were more likely to have a significant reduction than nonresponders. Anti-Smith antibody (n = 85) reverted from positive to negative by week 52 in 26% of treated patients versus 5% of placebo and 36% of patients reverted by week 128 (TABLE 4). Ribonucleoprotein reverted in 9% of treated patients versus 2% of placebo at week 52 and 27% had reverted by week 128.

The conclusions of this analysis were that belimumab reduced autoantibodies and immunoglobulin isotypes, normalized IgG and increased complement. Again, these changes support the positive effects of this drug on biologic activity and autoimmunity in SLE.

The safety results from this trial were reported by Merrill *et al.* [20]. Overall, belimumab was well tolerated even when used in combination with other SLE standard-of-care treatments. Rates of adverse events and serious and severe adverse events were all similar between the placebo and the belimumab groups.

The conclusions from the analysis of this trial were that belimumab offers a sustained improvement in SLE activity over time and reduces SLE flare rates. It appears to be safe and overall well tolerated. These results were promising and resulted in the initiation of two Phase III trials, BLISS-52 and BLISS-76.

Clinical safety & efficacy: Phase III studies

BLISS-52 was of 52-week duration and included 865 patients from Asia, Eastern Europe and South America. BLISS-76 was of 76-week duration, and enrolled and randomized 826 patients from North America and Europe. Both studies were designed as double-blind, placebo-controlled, multicenter

Table 2. Effects of belimumab on B-cell subtypes.

B-cell type	Activated B cell (CD20 ⁺ /69 ⁺)	Plasmacytoid (CD20 ⁺ /138 ⁺)	Total CD20 ⁺ B cells
Reduction (%)	70	63	54

superiority trials and aimed to assess the safety and efficacy of belimumab in patients with seropositive SLE. Similar to Phase II trial patients, this study enrolled patients with clinical diagnosis of systemic lupus as defined by the ACR criteria. Patients on stable SLE treatment regimens with at least 1:80 ANA and at least 30 IU/ml anti-dsDNA were enrolled. Exclusion criteria included (but were not limited to) pregnant or nursing women, patients who received B cell-targeted therapy, those with severe renal disease or active CNS disease and patients who received intravenous cyclophosphamide within the past 180 days. BLISS-52 patients were divided into three groups: group 1 received standard of care plus placebo, group 2 received standard of care and belimumab 1 mg/kg; and group 3 received standard of care and belimumab 10 mg/kg. Patients were treated on day 0, followed by day 14, 28 and every 28 days until the end of the study period. The primary end point of both studies was patient response. The response was assessed using the SRI, which was described above. In the group receiving belimumab 1 mg/kg SRI response rate was 51.4%, and in the 10-mg/kg group, SRI response was seen in 57.6% of patients versus 43.6% placebo response (TABLE 5). Of the patients who received belimumab and more than 7.5 mg/day of prednisone, a higher percentage of patients were able to have the dose of prednisone tapered by at least 25% from baseline when compared with the placebo group. Only the difference between belimumab 1 mg/kg-treated patients reached statistical significance when compared with the placebo group [21].

In patients whose baseline prednisone dose was less than 7.5 mg/day, a fewer number of patients in the belimumab 10 mg/day-treated group had to have their dose of prednisone increased to at least 7.5 mg/day. A similar result applied to the belimumab 1 mg/day-treated group; however, the difference noted in this group was not statistically significant compared with placebo. The time to first flare in active disease was delayed in both belimumab-treated groups of patients. Overall, the number of patients with severe SLE flare was reduced in the belimumab 1- and 10-mg/kg group. The rates of severe adverse

Table 3. Effects of belimumab on levels of different antibodies.

Antibody	IgA	IgE	IgG	IgM
Placebo change (%)	+3	Unchanged	+3	+5
Treatment change (%)	-14	-34	-10	-29

events, deaths and infections were similar in all groups. Infusion reaction rates were somewhat higher in groups treated with belimumab.

In the BLISS-76 study, patients were divided into three different groups (as in BLISS-52): belimumab 1 mg/kg, belimumab 10 mg/kg or placebo. All three groups also received standard-of-care therapy. The data in this study were analyzed at 52 weeks and patients were followed to complete a 76-week trial period.

The SRI response rate was 40.6% in the group receiving belimumab 1 mg/kg, 43.2% in the group receiving 10 mg/kg, and 33.8% in the placebo group (TABLE 5). The improvement seen in the 1 mg/kg belimumab group did not reach statistical significance. The reduction in SS score of at least 4 points were 46.9% in the belimumab 10-mg group and 42.8%, in the 1-mg group. In the placebo group, just 35.6% of patients were noted to have such a change [101].

A total of 16.7% of the patients in the belimumab 10 mg/kg group were able to reduce prednisone dose by at least 25%, versus 19.2% of patients in the belimumab 1-mg/kg group and 12.7% in the placebo group. However, this difference in reduction was not statistically significant. The drug was well tolerated in treatment groups and discontinuation secondary to adverse events was analogous among all groups.

Recently, the 76-week results of the Phase III trial were released. At week 76, 38.5 versus 39.1% of patients receiving 10 mg/kg of belimumab and 1 mg/kg, respectively, showed response as measured by SRI. In the placebo group, 32.4% of patients showed a similar response. Belimumab failed to demonstrate statistical significance on secondary end points, such as reduction in SS, improvement in Physician Global Assessment and reduction in steroid dose [102].

In the above-summarized studies, the treatment of seropositive lupus with belimumab reduced SLE disease activity, use of prednisone

Table 4. Autoantibody and complement changes in patients from Phase II belimumab study and extension.

Group	Change in complements at week 52 (%)		Reduction in dsDNA level by at least 50% at week 52 (% of patients)	Change in anti-Sm and ribonucleoprotein at week 52 (%; positive → negative)	
	C3	C4		Anti-Sm (n = 86)	Antiribonucleoprotein (n = 205)
Belimumab	+6	+23	30	-26	-9
Placebo	-1	+14	17	-5	-2

Table 5. Efficacy results expressed as SLE Responder Index improvement and SLEDAI reduction in Phase III belimumab trials (BLISS 52 and BLISS 76).

End point measure	BLISS-52			BLISS-76		
	Placebo (%)	Belimumab 1 mg/kg (n = 288)	Belimumab 10 mg/kg (n = 290)	Placebo (%)	Belimumab 1 mg/kg	Belimumab 10 mg/kg
Systemic lupus erythematosus Responder Index at week 52	43.6	51.4% (p = 0.013)	57.6% (p = 0.0006)	33.8	40.6% (p = 0.10)	43.2% (p = 0.021)
Reduction SELENA SLEDAI by 4 points	46.0	53.1% (p = 0.019)	58.3% (p = 0.0024)	35.6	42.8% (p = 0.087)	46.9% (p = 0.0062)

and increased time until first flare. There was a dose-related response seen among the groups studied. The rate of infections was also similar among all the groups studied. No malignancies were reported in BLISS-52. There were a total of six malignancies in BLISS-76: two in the belimumab 10-mg/kg group, three in the belimumab 1-mg/kg group and one in the placebo group. Overall, the medication was well tolerated and discontinuation due to unwanted side effects was comparable amongst treatment and the placebo groups in either study.

In conclusion, targeting B cells in SLE has a promising future in the treatment of SLE. Belimumab, which is an antibody against BLYS has shown positive results in multiple clinical trials. It appears to improve serologic profiles, offer clinical improvements and prevent flares.

The side-effect profile is very reasonable when viewed with the clinical benefits. We are hopeful that belimumab and other B-cell therapies will become a successful addition to SLE treatment strategies.

Future perspective

It is my view that B-cell therapy will likely become an important part of the treatment paradigm in SLE over the next 3–5 years. I think the data are suitably strong to justify the approval of belimumab as a treatment for SLE. If it does receive approval, then I think there will be continued investigation of B-cell therapies using other pathways to alter B-cell hyperactivity. This is contingent on the continued good overall side-effect profile of belimumab and B-cell inhibitors in general.

Executive summary

Systemic lupus erythematosus

- Multisystem disease with many organs involved.
- Significant morbidity and mortality.
- Limited selection of disease-specific therapy.

B-cell-targeted therapy

- Autoantibodies play a significant role in pathogenesis.
- B cells have been shown to contribute to the disease process in multiple areas.
- Targeting B cells is an attractive strategy for controlling autoimmune disease and systemic lupus erythematosus (SLE).

B-lymphocyte stimulator

- Cytokine that is essential for B-cell growth and survival.
- Increased levels are seen in SLE animal models and patients.
- Targeting this is likely to produce a therapeutic benefit in SLE by regulating B-cell activity.

Belimumab (Benlysta®)

- Monoclonal antibody that binds to B-lymphocyte stimulator preventing its activity.
- Monthly intravenous administration.
- *In vitro* evidence shows inhibition of B-cell proliferation.
- Animal studies confirm that belimumab reduces B-cell and plasma-cell levels.
- Human studies are now finished through Phase III.
- Belimumab is generally well tolerated without signals of major adverse events at this point.
- Efficacy results are statistically significant though the benefits are not dramatic.

Future perspective

- Belimumab is planned to be presented to the US FDA for approval in the near future for SLE.
- It would be the first biologic medication approved for use in SLE.
- If approved it would likely be administered to many lupus patients, especially those with significant internal organ disease, and those resistant to traditional therapy.

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