Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Clinical evidence of the role of belimumab in the treatment of systemic lupus erythematosus

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Belimumab is a human monoclonal antibody that binds soluble B lymphocyte stimulator, thus preventing the binding to its receptors on B cells. B lymphocyte stimulator has proven to be a key factor in the selection and survival of these cells. Two Phase III trials have demonstrated that belimumab, in combination with standard therapy, was generally well tolerated and significantly reduced disease activity and flare rates in patients with active systemic lupus erythematosus (SLE), thus allowing its approval by the European and American regulatory agencies as the first biological therapy for SLE. The aim of this article is to review the evidence-based clinical effectiveness of belimumab in the treatment of SLE patients.

Keywords: B-lymphocyte stimulator • belimumab • biological therapy • systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is the most representative of the autoimmune diseases. One of its main pathogenic mechanisms is the production of autoantibodies leading to the generation of immune complexes that, finally, produce organ damage [1]. B cells play a central role in the pathogenesis of SLE through antibody-dependent and antibody-independent functions [2]. Therefore, B cell-targeted therapies may represent a valuable treatment of patients with SLE.

The primary rationale of these therapies would be the elimination of autoantibodies. One of the main strategies for B-cell targeting is represented by the inhibition of factors involved in the survival or differentiation of B cells. B lymphocyte stimulator (BLyS), also known as B cell–activating factor, has proven to be a key factor in the selection and survival of naive autoreactive B cells [3]. BLyS is a type II transmembrane protein of the TNF family that exists in both membrane-bound and soluble forms and is expressed by a wide variety of cell types such as monocytes, macrophages, and monocyte-derived dendritic cells. Its gene expression and secretion are regulated by inflammatory cytokines, in particular interferon-γ and, to a lesser extent, IL-10 and IL-2. BLyS can bind to three receptors: BLyS receptor 3 (BR3 or B cell-activating factor-R), transmembrane activator-1 and calcium modulator and cyclophilin ligand-interactor, and B-cell maturation antigen. Via BR3, BLyS antagonizes apoptosis of transitional immature B cells, thus allowing differentiation and entrance of cells into the mature, preimmune B-cell populations [4]. Therefore, if this biologic process is impaired, it could allow the survival of naive autoreactive B cells instead of their elimination by apoptosis.

Belimumab is a human monoclonal antibody (IgG1) that binds soluble BLyS and inhibits its binding to transmembrane activator-1 and calcium modulator and cyclophilin ligand-interactor, B-cell maturation antigen, and BR3. The *in vitro* and *in vivo* pharmacological properties of belimumab suggest that it binds soluble BLyS and inhibits stimulation of B-cell proliferation and antibody secretion induced by BLyS [5]. Conversely, belimumab does not affect IgG plasma cells; therefore, there is not much effect on autoantibodies. The aim of this review article is to analyze

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the evidence-based information about its clinical usefulness in the treatment of patients with SLE.

BLyS in SLE patients

Several authors have studied the role of BLyS in SLE patients [6–10]. Cheema *et al.* analyzed the relationship between serum levels of BLyS and serum levels of immunoglobulins and/or autoantibody titers in 185 patients with various systemic autoimmune diseases (95 with SLE and 67 with rheumatoid arthritis) [6]. Serum BLyS levels were elevated in 21% of patients and correlated significantly with serum IgG levels. In addition, they correlated positively with anti-dsDNA antibody titers in SLE patients and in those with rheumatoid artritis with rheumatoid factor titers.

Collins *et al.* studied 60 patients with SLE, 30 patients with rheumatoid arthritis and 30 healthy individuals. BLyS protein, full-length BLyS mRNA, and ΔBLyS mRNA levels were greater in SLE patients than in rheumatoid arthritis patients or normal control individuals [7]. Full-length BLyS and ΔBLyS mRNA levels correlated significantly with BLyS protein levels in the SLE cohort. Furthermore, BLyS mRNA levels were more closely associated with serum immunoglobulin levels and SLE Disease Activity Index (SLEDAI) scores than were BLyS protein levels. Moreover, changes in SLEDAI scores were more closely associated with changes in BLyS mRNA levels than with changes in BLyS protein levels among the 37 SLE patients from whom repeat blood samples were obtained.

Hong *et al.* studied 56 patients with pediatric SLE over a 6 month interval. In this cohort, plasma BLyS protein and blood leukocyte BLyS mRNA levels were each significantly elevated, and plasma BLyS protein levels, but not blood leukocyte BLyS mRNA levels, were correlated with disease activity [8]. The BLyS expression profiles remained stable at 6 months.

Stohl *et al.* analyzed 68 patients with SLE in a longitudinal study for a median of 369 days and disclosed that serum levels of BLyS correlated with disease activity [9]. In total, 50 and 61% of SLE patients presented with persistently or intermittently elevated serum BLyS and blood BLyS mRNA phenotypes, respectively. In addition, surface BLyS expression by SLE peripheral blood mononuclear cells was also often increased. Interestingly, treatment of patients who had elevated serum BLyS levels with intensive courses of high-dose corticosteroids resulted in marked reductions in serum BLyS levels, and tapering of the corticosteroid dosage often resulted in increases in serum BLyS levels. Of note, serum BLyS levels generally correlated with anti-dsDNA titers.

Petri *et al.* designed another longitudinal study with a larger number of patients followed-up during a longer period of time [10]. These investigators tried to correlate plasma BLyS levels, immunosuppressive therapy and other clinical parameters with disease activity in 245 patients with SLE evaluated prospectively over a 2-year period. Disease activity was evaluated with the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) version of SLEDAI. Plasma BLyS levels were associated with anti-dsDNA titers and SELENA-SLEDAI scores. This correlation was endorsed in multivariate analysis in that a greater increase in the SELENA-SLEDAI score from the previous visit was associated with higher BLyS levels at the previous visit and with a greater increase in the BLyS level from the previous visit.

Belimumab in animal models

Preclinical data demonstrated that belimumab inhibited BLyS-induced proliferation of B cells *in vitro* [11]. Later on, in studies on cynomolgus monkeys treated with belimumab, reductions as great as 75% were observed in the number of lymphoid tissue and peripheral blood $CD20^+$ B cells and $CD21^+$ plasmacytoid cells that recovered to normal levels within 3–5 months after belimumab discontinuation. In this study, intravenous doses of up to 50 mg/kg delivered every 2 weeks over 6 months were well tolerated by the monkeys [12].

Belimumab in SLE patients

The evidence of the clinical effectiveness and safety of belimumab in human SLE patients comes from four clinical studies [13–19].

Belimumab in a Phase I study

In a Phase I dose-escalation study performed in 70 patients with SLE, belimumab did not show related serious adverse events [13]. This study randomized patients with mild-to-moderate SLE to receive placebo (n = 13) or belimumab (n = 57) at four different doses (1, 4, 10 and 20 mg/kg) as a single infusion (n = 34) or two infusions (n = 36), 21 days apart. Patients were followed for 84–105 days to assess adverse events, peripheral blood B cell counts, serology and SLE disease activity. There were no differences in the incidences of adverse events and laboratory abnormalities between belimumab and placebo groups. Overall, adverse events were reported in 12 (92%) patients treated with placebo and 55 (97%) patients treated with belimumab. Of note, there was no increase in the incidence of infections in the belimumab groups (37% for all patients treated with active agent vs 62% for placebo). The most common adverse event in patients treated with belimumab were arthralgia (26%) followed by headache (21%), rash (21%), diarrhea (18%) and nausea (18%). The frequency of adverse events did not

change with increasing doses of belimumab. Six patients (one placebo and five belimumab) developed eight serious adverse events, none of which were considered related to the study agent.

Significant reductions in median percentages of $CD20^+$ B cells were observed in patients treated with a single dose of belimumab versus placebo (day 42: $p = 0.0042$ and day 84: $p = 0.0036$) and in patients treated with two doses of belimumab versus placebo (day 105: $p = 0.0305$). In the same sense, reduction of anti-dsDNA antibody titers was demonstrated. Specifically, a subset analysis of 31 belimumab-treated patients with anti-dsDNA antibody levels 10 IU/ml or greater at baseline revealed significant changes from 28 to 56 days after the last dose across all cohorts ($p < 0.05$).

However, SLE disease activity did not change after one or two doses of belimumab. Overall, there was a trend toward reduced scores of SELENA-SLEDAI in both belimumab and placebo groups but it should be noted that a Phase I study is not powered to detect clinical efficacy.

Belimumab in a Phase II study

A subsequent Phase II dose-ranging trial was performed in 449 SLE patients [14]. In this study, patients were randomized to receive 1, 4 or 10 mg/kg of belimumab or placebo on days 0, 14, 28, and then every 28 days for 52 weeks. Belimumab or placebo was added to standard therapy. Active disease was defined by a SELENA-SLEDAI score of ≥4 at screening. In addition, patients had to receive a stable regimen of treatment including prednisone, antimalarials and immunosuppressive agents for at least 60 days before the first dose. Patients with active lupus nephritis or CNS involvement were excluded.

Belimumab was well tolerated, but the study failed to meet its primary end points, the change in the SELENA-SLEDAI score from baseline to weeks 24 and 52 and the time to first mild/moderate or severe flare as defined by the SLE flare index (SFI) during 21 weeks. In this sense, the authors did not observe dose-dependent changes in the SELENA-SLEDAI score. The percentage of patients who experienced an SLE flare was similar in all groups (including placebo). However, in a subgroup analysis of patients with serologically active disease at baseline, defined by antinuclear antibody (ANA) titer >1:80 and/or anti-dsDNA >30 IU/ml (72% of the total group of randomized patients), belimumab did lead to a significantly better response over placebo at week 52. Specifically, when compared with placebo group, they had significantly reductions in SELENA-SLEDAI scores from baseline (-28.8% vs -14.2%; $p = 0.0435$), improvements in physician's global assessment (PGA) (-32.7 vs -10.7%; $p = 0.0011$) and in Short Form 36 Physical Component Summary (SF-36 PCS; 3.0-point increase vs 1.2-point increase; $p = 0.041$).

Regarding the biologic activity of belimumab, the authors found a significant reduction of naive (-70.8%), activated (-70.4%) and plasmacytoid B cells (-62.5%) at week 52. Conversely, the median value of memory B cells was increased by 88% by day 28 and gradually returned to baseline at week 52. Belimumab treatment led to a significant reduction in immunoglobulin levels (10% for IgG, 14% for IgA, 29% for IgM and 34% for IgE) at week 52. Reductions were detected at week 8 in all immunoglobulin types. The reduction of IgG anti-dsDNA antibody levels was more pronounced in the belimumab group (29.4 vs 8.6%; $p = 0.0017$). Complement levels rose in patients with baseline low levels of complement.

The rates of adverse events and serious adverse events were similar in the belimumab and placebo groups. Only urticaria was more frequent in patients treated with belimumab (4 vs 0%). The incidence of infections and severe infections was similar among two groups. The preservation of long-lived plasma cells and memory B cells could have contributed to this low rate of infections.

This Phase II trial was later continued as an open-label extension study of which 4 year safety and efficacy data for 237 patients have been reported [17]. In this study, at week 56, patients who had been treated with placebo were switched to belimumab 10 mg/kg and those patients treated with belimumab could remain on their current dose or receive 10 mg/kg. At week 80, all patients received belimumab 10 mg/kg in a continuation trial over 4 years.

The results of this study were analyzed with a new disease activity index: the SLE responder index (SRI) [18]. This index was developed according to the recommendations of the US FDA, the Outcome Measures in Rheumatology Clinical Trials (OMERACT) and the European League Against Rheumatism (EULAR) for the development of drugs for the treatment of SLE that covered the use of disease activity index, flares and organ-specific outcomes. Specifcally, SRI was defined by a ≥4-point reduction in SELENA-SLEDAI score, no new British Isles Lupus Assessment Group (BILAG) A or no more than 1 new BILAG B domain score, and no deterioration from baseline in the PGA assessment by ≥0.3 points.

The incidence rate of adverse events in the extension study decreased (194 per 100 patient/years to 173 per 100 patient/years) over 4 years. In the subset of serologically active SLE patients, at week 52, SRI rate was 46% in those treated with belimumab versus 29% in those treated with placebo ($p < 0.0006$). SRI rate increased to 55% by week 76 and was maintained

through week 208 (in original belimumab patients). Taking into account placebo and belimumab patients after 1 year, the frequency of new BILAG A or 2B flares declined to 5% at 4 years and the frequency of flares by SFI declined to 16% at 4 years. This continuation trial demonstrated that belimumab added to standard therapy was generally well tolerated over 4 years and, interestingly, serologically active SLE patients treated with belimumab showed sustained improvement in disease activity and decline in BILAG and SFI flares over time.

However, it should be noted that cohort studies such as this extension trial have some limitations: for instance, those patients who do badly are likely to be included among the dropouts and they would not be in the study at the end of this time, so data are biased towards those who stay in cohort, as these are likely to be the best responders. It is unclear whether patients are doing better over time or whether those doing better all along are the ones still staying in the study. The important finding, however, could be that those who do continue to be treated seem to do quite well.

■ Belimumab in two Phase III studies

Finally, belimumab has been evaluated in two large randomized, double-blind, placebo-controlled, multicenter Phase III trials, BLISS-52 [15] and BLISS-76 [16], that included 867 and 819 seropositive (ANA- and/or anti-dsDNA antibodies) patients, respectively. All patients had active disease defined as SELENA-SLEDAI score ≥6 and were on stable therapy for at least 30 days before the first dose. Patients with active lupus nephritis or CNS involvement were also excluded in these two trials. The design of the 2 trials was the same, but BLISS-52 was a 52 week study that enrolled patients from Central and Eastern Europe, Latin America and Asia-Pacific region, while BLISS-76 was a 76 week study that enrolled patients from North America and Western and Central Europe. Included patients were randomized to receive 1 mg/kg belimumab, 10 mg/kg belimumab, or placebo. Belimumab or placebo was administered intravenously on days 0, 14, 28, and then every 28 days thereafter for the 48 weeks (BLISS-52) and 72 weeks (BLISS-76), respectively. All patients received standard therapy (as prescribed by their physicians in charge according to their experience) in addition to the study medication. The primary efficacy end point of the two trials was the SRI at week 52 and other efficacy analyses included the SELENA-SLEDAI, BILAG and SFI scores.

Regarding results of the BLISS-52 study, SRI response rates were higher in the 1 mg/kg (51.4%; p = 0.013) and in the 10 mg/kg belimumab dose group (57.6%; p = 0.0006) than in those patients treated with placebo (43.6%) (Table 1). In addition, significant improvement was found in at least one of the belimumab treatment groups for the other measures of efficacy (SELENA-SLEDAI ≥4-point reduction, improvement or no >0.3 point worsening in PGA, reduction in prednisone use, and reduction in flare rates by SFI and new BILAG 1A or 2B and increase in time to first flare). Besides, the authors evaluated the impact of belimumab on physical functioning, fatigue and other health-related quality of life measures of SLE patients. In this sense,

Table 1. Main clinical results of the randomized, multicenter Phase III trial BLISS-52.

Parameter	Placebo (n = 287)	Belimumab 1 mg/kg (n = 288)	Belimumab 10 mg/kg (n = 290)	p-value†
Primary end point				
SRI at week 52	125 (44%)	148 (51%)	167 (58%)	0.0006
Secondary end points				
SS ≥4-point reduction	132 (46%)	153 (53%)	169 (58%)	0.0024
No PGA >0.3 point worsening	199 (69%)	227 (79%)	231 (80%)	0.0048
No new BILAG 1A or 2B scores	210 (73%)	226 (78%)	236 (81%)	0.0181
Adverse events				
Serious adverse events	36 (13%)	47 (16%)	41 (14%)	NS
Infections	183 (64%)	197 (68%)	194 (67%)	NS
Serious infections	17 (6%)	22 (8%)	13 (4%)	NS
Infusion reactions	49 (17%)	47 (16%)	48 (17%)	NS

†p-values refer to difference between placebo and belimumab 10 mg/day treatment groups. There was no statistical difference between the two arms of belimumab treatment.

BILAG: British Isles Lupus Assessment Group; PGA: Physician's global assessment; SRI: SLE responder INDEX; SS: SELENA-SLEDAI.

Data taken from [15].

Table 2. Main clinical results of the randomized, multicenter Phase III trial BLISS-76.

Parameter	Placebo (n = 275)	Belimumab 1 mg/kg (n = 271)	Belimumab 10 mg/kg (n = 273)	p-value[†]
Primary end point				
SRI at week 52	92 (33%)	110 (41%)	118 (43%)	<0.05
Secondary end points				
SS ≥4-point reduction	97 (35%)	116 (43%)	127 (46%)	<0.01
No PGA >0.3 point worsening	173 (63%)	197 (73%)	190 (70%)	NS
No new BILAG 1A or 2B scores	180 (65%)	203 (75%)	189 (69%)	NS
Adverse events				
Serious adverse events	54 (20%)	63 (23%)	61 (22%)	NS
Infections	190 (69%)	202 (74%)	202 (74%)	NS
Serious infections	16 (6%)	19 (7%)	20 (7%)	NS
Infusion reactions	27 (10%)	42 (15%)	37 (14%)	NS

[†]p-values refer to difference between placebo and belimumab 10 mg/day treatment groups. There was no statistical difference between the two arms of belimumab treatment.

BILAG: British Isles Lupus Assessment Group; PGA: Physician's global assessment; SRI: SLE responder index; SS: SELENA-SLEDAI.

Data taken from [16].

mean improvements from baseline in SF-36 physical functioning, bodily pain and Physical Summary Scores were significantly greater with belimumab (1 and 10 mg/kg) versus placebo at week 52. Patients in the 10 mg/kg belimumab treatment group demonstrated greater mean improvement in Functional Assessment of Chronic Illness Therapy (FACIT) fatigue versus placebo patients by week 8 (3.9 ± 0.5 points vs 1.8 ± 0.5; p = 0.0015), and further improved, with significant differences observed at week 36 (4.4 ± 0.6 vs 2.7 ± 0.6; p < 0.05) and week 52 (4.8 ± 0.6 vs 2.1 ± 0.6; p < 0.05) [19].

In BLISS-76, SRI response rates at week 52 were 34% on placebo, 41% on 1 mg/kg (p = 0.104) and 43% on 10 mg/kg belimumab (p = 0.021) (Table 2). However, there were no differences in SRI response rates between the three groups at week 76 (32.4% for patients on placebo vs 39.1% for those on belimumab 1 mg/kg [p = 0.11] and 38.5% for those on belimumab 10 mg/kg [p = 0.13]). Furthermore, multiple landmark SRI analysis also did not show statistically significant difference earlier in the trial. In addition, BLISS-76 showed no benefit for belimumab in North American patients and suggested the possibility of poorer performance of belimumab among patients of African ancestry.

Interestingly, belimumab improved response rates using higher thresholds for SELENA-SLEDAI improvement (SRI 5–7 defined as improvement of SELENA-SLEDAI score ≥5–7 points) at week 52 and 76, with even greater differentiation from placebo, reduced SELENA-SLEDAI scores at week 52 and week 76, and reduced risk of severe flare (26.5, 18.5 and 20.5% for placebo patients, belimumab 1 mg/kg, and belimumab 10 mg/kg, respectively; hazard ratio for belimumab 1 mg/kg 0.66, p = 0.023). In addition, patients treated with belimumab had significant reductions in immunoglobulins (IgG, IgM, IgA), IgG anti-dsDNA IgG, and significantly greater increases in C3 and C4 levels and a higher percentage of normalization of low C3 and C4 compared with placebo patients at week 52. Conversely, statistically significant PGA improvement and steroid dose reduction were not detected with belimumab treatment.

The incidence of all adverse events, including serious infections was comparable between belimumab treatment groups and placebo in both studies. Whereas no malignancies were reported in BLISS-52, six malignancies occurred in BLISS-76 (one on placebo, three on 1 mg/kg, two on 10 mg/kg).

Overall, in these two Phase III trials belimumab significantly reduced SLE disease activity and SLE flare rates in patients with active SLE. In addition, it was generally well tolerated in combination with standard therapy. It must be emphasized that both Phase III trials did meet their prespecified primary end points despite the less robust results of the BLISS-76.

Future perspective

In the light of the results of these trials, the FDA and the European Medicines Agency have approved this monoclonal antibody as the first biological therapy for SLE. However, three questions should be answered. First, it will be very important to identify which SLE patients will benefit from this treatment. An interesting

exploratory conclusion of Phase II trial was that belimumab was effective in serologically positive patients defined as ANA titer ≥1:80 or positive anti-dsDNA, as tested at baseline by a central laboratory [14] (not to be confused with a history of such or a generally consistent test from place to place). In this sense, BLyS levels above the limit of quantitation at baseline were detected in 54% of serologically active patients compared with only 24% of those seronegative. However, it should be taken into consideration that autoantibody testing is not always consistent from laboratory to laboratory, so that it could be that some people labelled seronegative by a test might be seropositive at a different laboratory; this might mean that using autoantibodies as a surrogate marker for BLyS levels may be fundamentally flawed. Taking into account these data, patients included in Phase III trials had ANA ≥1:80 and/or anti-dsDNA antibodies ≥30 IU/ml together with SELENA-SLEDAI score ≥6. Therefore, the patients who seem more likely to benefit from this drug are those with high SELENA-SLEDAI scores and more serological activity (high anti-dsDNA and low complement levels).

The second important question to be answered is the effect of belimumab in daily clinical practice. In the previous trials, the changes in disease activity measures, such as SRI, SELENA-SLEDAI, PGA and BILAG from baseline to 52 weeks between patients treated with placebo and those treated with belimumab has been less than 15%. We do not know, however, which be the clinical effect in 'real life' management of SLE patients.

Finally, the third important question is to know which will be the effect in the most severe cases of SLE, and hence the ones that are in need for new targeted therapies, such as those with lupus nephritis and CNS involvement, that were excluded from all these trials.

Therefore, future studies on the effect of belimumab are expected, including 'real life' registries (with more emphasis in some populations such as North Americans and those of African descent) as well as specific trials on patients with lupus nephritis or CNS involvement.

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Executive summary

- Belimumab is a human monoclonal antibody that binds soluble B lymphocyte stimulator (BLyS), also known as B cell-activating factor, thus preventing the binding to its receptors on B cells.
- BLyS antagonizes apoptosis of transitional immature B cells, thus allowing differentiation and entrance of cells into the mature, pre-immune B cell populations. Therefore, if this biologic process is impaired, it could allow the survival of naive autoreactive B cells instead of their elimination by apoptosis.
- Evidence from animal and human studies has demonstrated overexpression of BLyS in systemic lupus erythematosus (SLE).
- A Phase II trial demonstrated that belimumab, added to standard therapy for the disease, was well tolerated and improved many disease activity indexes such as Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index (SELENA-SLEDAI) score, Physician Global Assessment, and Short Form 36 Physical Component Summary (SF-36 PCS) in a subset of serologically active SLE patients.
- In two Phase III trials, belimumab significantly reduced SLE disease activity and SLE flare rates in patients with active SLE. In addition, it was generally well tolerated in combination with standard therapy.
- The US FDA and the European Medicines Agency have approved this monoclonal antibody as the first biological therapy for SLE.

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