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OPINION

Does Belimumab Reduce Disease Activity in Adults with Systemic Lupus Erythematosus?

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Abstract: In March 2011, the FDA approved belimumab (Benlysta) for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy. Belimumab is a fully human monoclonal antibody directed against BLyS (B lymphocyte stimulator). BLyS, a member of the TNF ligand super family, promotes the survival and maturation of B cells. For patients on standard of care therapy and without active severe renal or central nervous system lupus, belimumab has been shown to be effective and safe. Further information will be gathered in the open label extensions of the phase II and III trials and post-marketing experience.

Keywords: systemic lupus erythematosus, belimumab, benlysta, B lymphocyte stimulator

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Introduction

The FDA approval of belimumab in March 2011 was a historic event as this was not only the first drug approval in Systemic Lupus Erythematosus (SLE) in over 50 years, but it was the first drug approved for SLE through the performance of randomized controlled trials. Trials in SLE have been particularly challenging owing to the heterogeneous manifestations, variable degrees of severity, and lack of standardized trial endpoints. This success will no doubt herald in an era of drug development that will lead to yet additional approvals in the future.

Biology and mechanism of action

Belimumab, a fully human neutralizing IgG1 monoclonal antibody that binds soluble BLyS (B-lymphocyte stimulator), has been investigated in multiple preclinical, one phase I, one phase II (with an extension study), and two phase III studies (with extension studies). BLyS (also known as BAFF or B cell activating factor) is a 285 amino acid type II transmembrane protein that is a member of the tumor necrosis factor (TNF) ligand superfamily.[1] BLyS is produced by macrophages, monocytes, dendritic cells, fibroblasts, neutrophils and T cells. Existing in both soluble and membrane bound forms, only soluble BLyS is biologically active.[2] Proinflammatory cytokines such as interferon-gamma, IL-10 and G-CSF stimulate the production of BLyS.

The main receptor for BLyS is BLyS receptor 3 (BR3; BAFF-R), which is expressed on human B cells (immature, transitional, naïve, germinal center and memory). Upon binding to BLyS-R, BLyS stimulates B cell maturation, inhibits B cell apoptosis, activates IgM+ IgD+ B cell class switch recombination and co-stimulates cytokine production with T cells. BLyS also binds to two other receptors with lower affinity: transmembrane activator and calcium-modulator and cytophilin ligand interractor (TACI) and B cell maturation antigen (BCMA). TACI and BCMA are receptors for APRIL, which is another member of the TNF family.[1,3]

That BLyS is an essential factor for B cell development and B cells are central to autoimmune disease pathology served as the impetus for developing BLyS inhibitors for the treatment of SLE.[4–7] Preclinical investigation in animals and observational studies in humans further justified this strategic approach to human disease.

Transgenic mice that overproduce BLyS have increased numbers of mature and effector B cells, have enlarged B cell follicles, numerous germinal centers, reduced dendritic cell numbers, and increased plasma cells in the mesenteric lymph nodes and in the spleen. These mice had high levels of total immunoglobulins, rheumatoid factor, and circulating immune complexes; some of these mice had high levels of anti-dsDNA, IgG deposition in the kidneys, and proteinuria.[8] In lupus prone mice (NZB/NZW F_1 mice) administration of antibody to TACI (Transmembrane activator and calcium modulator ligand interractor) lead to a decrease in proteinuria and prolonged lifespan.[9] In a study of 68 SLE patients and 20 control subjects, 50% of SLE patients had persistently elevated serum BLyS and 100% of the control patients had normal BLyS levels. While serum BlyS levels did not correlate with future flares, they did decrease with escalation of corticosteroid treatment and increase with tapering of corticosteroid therapy.[10]

In cynomolgus monkeys, belimumab (at 5,15, or 50 mg/kg every other week for 13 or 26 weeks) as compared to vehicle control, decreased CD20+ and CD20+/CD21+ lymphocytes in the spleen, peripheral blood and lymph nodes.[11] Belimumab was well tolerated in this toxicologic study; there was not a study drug related increase in infection and no significant laboratory, electrocardiogram or ophthalmic abnormalities were observed.[11]

Data supporting the scientific rationale, biologic efficacy, and safety of BLyS inhibition were sufficient to move forward into human trials in SLE.

Clinical Trials

There were four trials in the development of belimumab for SLE: LBLS01, LBLS02, C1056 and C1057. Details of the trial design can be found in Tables 1 and 2. LBLS01 was a phase I study, which demonstrated the safety and established the future doses of belimumab to be studied. LBLS02, a phase II safety and efficacy trial, failed to reach its co-primary endpoints. However, post-hoc analyses demonstrated a large subset of patients who benefitted from receipt of belimumab. More importantly, phase II served as a very important foundation for the two phase III studies, BLISS-52 (C1056) and BLISS-76 (C1057). The success of BLISS-52 was unveiled in a press release in July 2009, and BLISS-76 results were released

Table 1. Description of clinical trials.[12,13,15,18–20]

Trial	Study description	Duration	% Female	Race	Location
LBLS01	Phase I—Safety	84–105 days	91%	50% Caucasian 47% Black 3% Asian 19% Hispanic	USA
LBLS02	Phase II Efficacy/Safety	52 weeks	93%	70% Caucasian 22% Black 18% Hispanic/Latino	98% USA 2% Canada
C1056-BLISS-76	Phase III Efficacy/Safety	76 weeks	93%	70% Caucasian 3% Asian 14% Black; 13%Alaskan/indian 1%multiracial 21% Hispanic	53% North America 25% Western Europe, 11% Eastern Europe; 11% Latin America
C1057 BLISS-52	Phase III Efficacy/Safety	52 weeks	95%	27% Caucasian; 38% Asian; 4% Black 32% Native American 1% Multiracial 49% Hispanic	50% Latin America 38% Asia; 13% Australia and Eastern Europe

4 months later.[12] Data generated from the two pivotal phase III trials led to FDA Advisory Committee approval in November 2010 and FDA approval in March 2011. Health Canada and European authorities approved belimumab in July 2011.

Pharmokinetic profile

The pharmokinetic profile of belimumab was assessed in LBLS01 (Table 1). The pharmacokinetic parameters for belimumab were linear across the dosing range and were similar for the single and double dose cohorts. Pharmacokinetic parameters were as follows: Mean distribution phase half-life: 1.0–2.2 days; Mean terminal elimination half-life: 8.5–14.1 days; Mean clearance after single infusion: 7 mL/kg/day. Given that the glomerular filtration rate is much higher than the mean clearance after a single infusion, one could assume that renal clearance is not a factor in the metabolism of belimumab. In the phase I study, two patients developed human anti-human antibodies (HAHA), and those patients had 2–3.5 fold lower serum concentrations of belimumab when compared to the remainder of their respective cohorts.[13]

SLE Responder Index (SRI): A Novel Endpoint

Assessment of response in SLE is complicated because of the heterogeneity of disease manifestations as well as confounding by background therapies. Instruments used in lupus clinical trials include the Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI or SS), Systemic Lupus Activity Measure (SLAM), SLEDAI-2K (SLEDAI 2000 update), British Isles Lupus Assessment Group (BILAG), Short Form 36 Physical Component Summary (SF-36), and Physicians Global Assessment (PGA).[14] To assess efficacy of belimumab, a novel composite response endpoint, known as the SLE Responder Index (SRI) was developed after completion of the phase II study. The primary endpoint in the phase III trials was the SRI, a dichotomous responder index, which defines subjects as either responders or non-responders. To be a responder, a subject must meet all of the following criteria: (1) greater than or equal to a 4-point reduction in SELENA-SLEDAI score compared to baseline; (2) no worsening (ie, increase less than 0.3 points [10%] from baseline) in physicians global assessment (PGA); (3) no new BILAG A organ domain scores or 2 new BILAG B organ domain scores at the time of assessment (ie, week 52) compared to baseline.[14]

Efficacy of Belimumab

In trial LBLS02, a statistically significant difference in the primary efficacy variables of percent change in

Table 2. Patient selection in clinical trials.[12,13,15,18–20]

Trial	Treatment groups	Entry criteria	Exclusion criteria
LBLS01	Placebo (13); B 1 mg/kg, B 4 mg/kg, B 10 mg/kg, B 20 mg/kg (29 in single dose and 28 in 2 doses—21 d apart)	18 or over SLE by ACR criteria Stable disease for 2 months prior to entry Measurable antibodies SOC including [prednisone ≤15 mg/day, antimalarials, NSAIDs, methotrexate, azathioprine, mycophenolate mofetil]	Active nephritis Active CNS lupus Hemodialysis Cyclophosphamide High dose prednisone (>60 mg) Renal transplant Hypogammaglobulinemia IgA deficiency Serious infection within 4 weeks Within 6 months: {lefunomide, cyclosporine, IVIg, plasmapheresis]
LBLS02	Placebo (113) B 1 mg/kg (114) B 4 mg/kg (111) B 10 mg/kg (111)	18 or over SLE by ACR criteria SELENA SLEDAI 4 or greater History of antibodies and meet ACR SOC including: Prednisone 5–40 mg/day; antimalarials; immunosuppressive agents	Active lupus nephritis, CNS lupus, pregnancy Within the 6 months of screening: [Prednisone > 100 mg, cyclosporine, IVIg, biologics, cyclosporine]
C1056-BLISS-76	Placebo (275) B 1 mg/kg (271) B 10 mg/kg (273)	18 or over, ACR SLE SLEDAI of 6 or greater; pos ANA (>/1:80)/dsDNA (≥30) at 2 independent time points, stable SLE tx for 30 days prior to d0. SOC included [prednisone 7.5–40 mg/day when used alone, antimalarials, NSAIDs, methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, sirolimus, calcineurin inhibitors, oral cyclophosphamide, 6-mercaptopurine, and thalidomide]	Excluded severe active SLE nephritis or CNS lupus
C1057 BLISS-52	Placebo (287) B 1 mg/kg (288) B 10 mg/kg (290)	Same as C1056	Same as C1056

SELENA-SLEDAI at week 24 and median time to first SLE flare over 52 weeks was not achieved. The percentage change from baseline of the SELENA-SLEDAI was −17.2 ± 5.1 in the placebo group and was −19.5 ± 2.7 in all patients treated with belimumab.[15] Over the first 52 weeks, the median time to first flare was 83 days in the placebo group, 68 days in the belimumab 1 mg/kg group, 61 days in the 4 mg/kg group and 70 days in the belimumab 10 mg/kg group, which was not statistically significant.[15]

Rather than declare the drug ineffective at the completion of phase II, several post-hoc analyses were

Table 3. Medications at baseline.[12,14]

	Daily prednisone use at baseline (%)	Prednisone >7.5 mg at baseline (%)	Antimalarial use (%)	Immunosuppressive use at baseline (not antimalarials) (%)
LBLS02	68	35.8	70	50
C1056	76	46	63	56
C1057	96	67	67	42

undertaken focusing on those study subjects with serologic activity at baseline. In LBLS02, only 321 of the 449 subjects were seropositive (ie, ANA ≥1:80 and/or anti-dsDNA ≥30 IU/mL) at screening and day zero. Of note, in the seropositive group, there were significantly more African-American subjects (27% vs. 16%: $P = 0.0199$) and more detectable BLyS levels (51% vs. 24%: $P < 0.0001$). An analysis comparing response rates in the combined treatment group to placebo yielded the following: mean reduction in SELENA-SLEDAI at week 52 (–28.8% vs. –14.2%; $P = 0.0435$), and PGA (–32.7% vs. –10.7%; $P = 0.0011$). No significant differences were found in biomarker responses between the serologically active patients and the serologically inactive patients. Biomarker responses included immunoglobulin levels, C3 and C4 levels.[15]

Multiple secondary efficacy endpoints were evaluated in trial LBLS02. The time to first flare (mild to moderate flare by SELENA-SLEDAI index) from weeks 24–52 was 108 days (interquartile range: IQR 56–203) in the placebo group and was 154 (IQR 63–210) in all patients treated with belimumab ($P = 0.0361$). At 52 weeks, the placebo group had a 14% decrease in mean PGA while the belimumab-treated patients had a 31% decrease ($P = 0.0019$). Compared to the placebo group, the belimumab-treated group had significant decreases in anti-dsDNA levels and significant changes in C3 and C4 levels.[15]

At week 52, 46.0% of treated subjects had achieved a positive SRI response in LBLS02. From the extension of LBLS01, at week 76, 55.3% of subjects (n = 296) had achieved a positive SRI response, and at week 160, 55.0% of subjects (n = 170) had achieved a positive SRI response.[16] A subanalysis of 321 subjects with positive serology (positive ANA and/or positive dsDNA) in the phase II trial demonstrated that at week 52, 46% of belimumab treated patients achieved SRI response and 29% of placebo treated patients achieved a SRI response ($P = 0.006$).[14]

Six year follow up of the subjects from the phase II trial and the continuation trial of the phase II trial resulted in 1554 patient years of exposure to belimumab. When looking at the seropositive patients, the SRI response rate was 55%–61% at year 6. Further the adverse event rates per 100 patient years did not increase during the 6 year followup.[17]

In the two phase III trials (C1056 and C1057), the primary endpoint was the SRI at week 52, and secondary endpoints included mean change in SF-36 physical component score at week 24, proportion of patients who could reduce average prednisone dose by at least 25% from baseline to less than 7.5 mg/kg/day during weeks 40–52, percentage of patient with four or more point reduction in SS at week 52, mean change/percent change in PGA at week 24, assessment of three components of SRI, rate and time of flare, steroid sparing effects and biomarker changes from baseline. C1057 also studied the SRI at week 76.[12,16,18,19]

BLISS-52

In C1056, the SRI response rate at week 52 was significantly higher in both belimumab groups as compared to the placebo group. In the placebo group, 44% of the subjects achieved an SRI response, 51% in the belimumab 1 mg/kg group ($P = 0.0129$), and 58% in the belimumab 10 mg/kg ($P = 0.0006$). Reduction of SS by ≥ 4 points was seen in 46% of the placebo subjects, 53% in the belimumab 1 mg/kg group ($P = 0.0189$) and 58% in the belimumab 10 mg/kg ($P = 0.0024$). No worsening on BILAG was seen in 73% of the placebo-treated subjects and 81% in the belimumab 10 mg/kg ($P = 0.0181$). There was not a significant difference in the lower dose belimumab group. No worsening of the PGA was seen in 69% of the placebo subjects, 79% in the belimumab 1 mg/kg group ($P = 0.0078$) and 80% in the belimumab 10 mg/kg ($P = 0.0048$). There was a statistically significant difference when compared to the placebo of the percentage of subjects with no new 1A or 2B on the BILAG in the belimumab 10 mg/kg group ($P = 0.0016$) but not in the lower dose group. Significantly more patients in the treated group had an improvement in PGA score at week 52 (low dose $P = 0.0147$ and high dose $P = 0.0002$).[19]

There was a significant decrease in steroid requirement in the higher dose belimumab group. For the higher dose group as compared to the placebo, more subjects had a decrease in prednisone dose by ≥50% at week 52 (0.0122). In the placebo group, as compared to the treated group, there was a higher percentage of patients requiring an increase in prednisone dose to more than 7.5 mg/day ($P = 0.0196$). As compared to placebo, significant difference in

health related quality of life (as measured by the SF-36 PCS score absolute change from baseline) was seen at 52 weeks in both treatment groups (1 mg/kg: $P = 0.0272$ and 10 mg/kg: $P = 0.0247$) but not at 24 weeks (1 mg/kg: $P = 0.8127$ and 10 mg/kg: $P = 0.8870$).[19]

There were significant differences in the following biomarkers in the treatment groups as compared to the placebo group: median change in C3 from baseline to week 52, median change in C4 from baseline to week 52, median change in anti-dsDNA form baseline to week 52 and change of anti-dsDNA from positive to negative by week 52.[19]

BLISS-76

In the BLISS-76 trial, the percent of patients achieving an SRI response at week 52 was significantly higher in only the 10 mg/kg treatment group. In the placebo group, 34% of the subjects achieved an SRI response, 41% in the belimumab 1 mg/kg group ($P = 0.1041$) and 43% in the belimumab 10 mg/kg group ($P = 0.017$). Reduction of SS by ≥ 4 points was seen in 36% of the placebo subjects, 43% in the belimumab 1 mg/kg group ($P = 0.09$), and 47% in the higher dose belimumab cohort ($P = 0.006$). No worsening in BILAG was seen in 65% of the placebo-treated subjects and 75% in the belimumab 1 mg/kg group ($P = 0.01$). There was not a significant difference in the higher dose belimumab group. This is different from the BLISS-52 trial where there was a significant difference in the higher dose group but not the lower dose group. No worsening of the PGA was seen in 63% of the placebo subjects, 73% in the belimumab 1 mg/kg group ($P = 0.01$), and 69% in the belimumab 10 mg/kg ($P = 0.13$). Significant decreases in CD20+ B cells at 24, 52 and 76 weeks were observed.[18,20]

The efficacy seen at week 52 was not seen at week 76. At week 76, 32% of placebo-treated subjects were SRI responders, 39% in the low dose group ($P = 0.11$) and 39% in the high dose group ($P = 0.13$). Analysis of the three subcomponents of the SRI at week 76 revealed the following: 33% of the placebo group achieved a 4-point reduction in SS, 42% of the low dose ($P = 0.049$) and 41% of the high dose ($P = 0.067$) achieved a 4-point reduction in SS. While 58% of the placebo group achieved no worsening in PGA, 66% of the low dose ($P = 0.059$) and 63% of the high dose ($P = 0.27$) achieved no worsening in PGA. While 59% of the placebo group achieved no new 1A/2B BILAG domain scores, 69% of the low dose ($P = 0.01$) and 63% of the high dose ($P = 0.3$) achieved 1A/2B BILAG domain scores.[12,18]

Subgroup analysis of patients in BLISS-52 and BLISS-76 by BILAG organ domain or SS organ systems was performed to determine the responsiveness of specific organ systems to belimumab. In this analysis baseline scores were compared with scores at 52 weeks. Given the low numbers of subjects with certain areas of involvement, the power of these analyses is limited. For SS domains, there was significant improvement in the immunologic domain in both dosing groups compared to the placebo in both BLISS-52 ($P = 0.044$ for low dose, $P < 0.001$ in high dose) and BLISS-76 ($P = 0.009$ for low dose, $P < 0.001$ in high dose). In BLISS-76, improvement in the mucocutaneous domain was seen in 49% of the placebo group, 58% in the low dose ($P = 0.04$) and 60% in the high dose ($P = 0.01$). This finding was not replicated in BLISS-52. Comparing BILAG organ domain involvement at baseline and week 52, there was significant improvement seen in BLISS-76, but not BLISS-52. At 52 weeks in BLISS-76, both treatment groups had significant improvement in the mucocutaneous, vasculitis and musculoskeletal domains.[12,18] A combined analysis if BLISS-52 and BLISS-76 showed that belimumab had a significant effect on SLE flare rate, disease activity and reduced prednisone use. In the combined analysis including 1684 subjects, the SRI response rate was 38% in the placebo groups which was significantly different from 46.2% in the low dose belimumab ($P = 0.006$) and 50.6% in the high dose belimumab group ($P < 0.0001$).[21]

Safety

Safety was evaluated in following trials: the phase II trial and open label extension (L02 and L99), and the two phase III trials and open label extensions (C1056, C1057, C1066 and C1074).[12]

The overall safety profile for belimumab is quite favorable.

In the phase I trial, subjects received either one or two doses (21 days apart) and were subsequently evaluated for 84–105 days. There were no study withdrawals nor were there significant differences

in infection rates or serious adverse events. Two patients developed human-anti-human antibodies, and there was one infusion reaction in the highest dose group.[12,13]

Analysis of 449 subjects in BLISS-52, and its 24 week extension lead to 770 subject years of exposure to belimumab and 117 subject years of exposure to placebo over a 3 year period. Comparing the placebo with the belimumab treated subjects, there were similar rates of adverse events, severe adverse events, serious adverse events, malignancies and infections (scale used was event per 100 subject years of exposure). Further the rates were stable over the 3 year period.[22]

In LBLS02, BLISS 52 and BLISS 76, the placebo and treatment groups were similar in: (1) the percentage of patients experiencing an adverse event; (2) the exposure-adjusted incidence rate of malignancy; (3) the exposure—adjusted incidence of serious infection was higher in the belimumab treated subjects (5.2– vs. –6.0 per 100 patient years); (4) the rate of serious adverse events (5) the number of patients who discontinued due to an adverse event (7% placebo, 6% treated). Interestingly, twice as many patients died in the belimumab group during the study period (0.8% of the belimumab-treated patients and 0.4% of the placebo-treated patients). The causes of death in the treated group included cardiovascular, suicide, SLE-related complications, and malignancy.[12]

When compared to a large cohort of SLE patients (n = 9547; 76,948 subject-years), the subjects exposed to belimumab (n = 1982; 3976 subject years) had a malignancy rate per 100 subject years that was statistically similar (SLE cohort: 0.53 [C.I 0.48, 0.59] and belimumab: 0.45 [C.I. 0.27, 0.72]). During the phase II and III studies, the malignancies seen in the study population included melanoma, basal cell carcinoma, squamous cell carcinoma, breast cancer, carcinoid of the stomach, ovarian cancer and stage 0 cervical cancer. Malignancies seen in all belimumab-treated subjects included breast cancer, colon cancer, malignant melanoma, cervical cancer, rectal cancer, ovarian cancer, lung cancer, B cell lymphoma, multiple myeloma, basal cell carcinoma, squamous cell carcinoma, hepatic cancer, thyroid cancer, and soft tissue neoplasm.[12]

As with most monoclonal antibody therapies, there is a potential for development of anti-drug antibodies. In the phase III trials, 2% of the placebo-treated, 13.1% of the belimumab 1 mg/kg and 0.9% of the belimumab 10 mg/kg subjects did not develop antibodies to belimumab. As for the 1.8% of the placebo patients who developed persistently positive and the 0.2% of placebo patients who developed transiently positive antibodies to belimumab, these findings may be attributable to errors in drug administration or group assignment.[12]

Conclusion

Belimumab is the first drug to be successful in lupus clinical trials. While the results of BLISS-52 and BLISS-76 were not identical, the results of these trials do support the conclusion that belimumab is an effective and safe medication. Potential reasons for differences between these trials include differences in the use of immunosuppressants and/or differences in racial and other demographic parameters.

The ideal patient for belimumab is a seropositive individual with clinical activity that has been recalcitrant to standard of care therapies. An analysis of the combined phase III datasets suggests that patients with activity in the musculoskeletal, mucocutaneous, immunologic or vascular domains are more likely to respond to belimumab. Since patients with severe nephritis and central nervous system lupus were not studied, caution should be exercised when considering treatment options for such patients.

Although there is an acceptable safety profile for this medication, belimumab should only be used in patients where the potential benefit outweighs the risk. In addition in a cost-conscious health care environment, the cost of belimumab (approximately $35,000 a year in the US)[23] needs to be a factor in appropriate patient selection. At this point in time, there is no evidence to support the use of belimumab as a monotherapy, a first line treatment option or in seronegative patients. .

Future data from post-marketing studies and the open-label extensions of BLISS-52 and BLISS-76 will guide further applications of belimumab.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and

contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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