

The Outlook of Belimumab in the Treatment of Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by a myriad of immunological aberrations, of which B cell hyperactivity is the final pathway that contributes to increased autoantibody production [1,2]. Autoantibodies mediate tissue injury by the formation of immune complexes and subsequent complement activation, as well as through the direct mechanism of antibody-mediated cytotoxicity. A number of qualitative and quantitative defects of B cells have been identified in patients with SLE, ranging from abnormal calcium signaling and aberrant expression of co-stimulatory molecules on B cells to a change in the proportion of peripheral naïve B cells, transitional B cells, plasma cells and activated memory B cells [3-6]. In addition, B cells may mediate autoimmunity by antibody independent mechanisms such as presenting auto antigens to T cells that contribute to their activation and polarization, as well as cytokine and chemokine production that reduces regulatory T cell activity and enhances dendritic cells recruitment [7-9].

Belimumab in the Treatment of SLE

B-lymphocyte stimulator (BLyS), or B-cell-activation factor (BAFF), is a member of the tumor necrosis factor (TNF) ligand superfamily [10]. BLyS, mainly produced by monocytes, binds to any of the three receptors on B cells, namely TACI, BCMA and BAFF-R, which activates signals for B cell maturation, survival, proliferation and immunoglobulin class switching. Levels of BLyS and BLyS mRNA are elevated in SLE patients [11,12] and correlate with disease activity.

Belimumab (Lymphostat-B, Benlysta[®]) is a fully humanized monoclonal antibody that specifically binds to soluble trimeric BLyS and prevents BLyS interaction with its receptors. Belimumab inhibits human B cell proliferation in vitro [13], and leads to in vivo depletion of CD19+B cells, naïve B cells (CD20+/CD27-), activated B cells (CD20+/CD69+), plasmacytoid B cells (CD20+/CD138+) and plasma cells (CD20-/CD138+), while memory B cells (CD20+/CD27+) are not affected [14].

Clinical Trials of Belimumab in SLE

Two phase I/II studies were conducted for the efficacy and safety of belimumab in patients with SLE. The first phase I dose escalation study was published in 2008 and reported safety of a 3-month treatment course of belimumab in 57 SLE patients [15]. The second phase II study involved 449 North American patients (70% Caucasians) with active SLE (SELENA-SLEDAI score ≥ 4) [14]. Participants were randomly assigned to intravenous belimumab (1, 4, or 10 mg/kg) or placebo infusion, on top of background immunosuppressive therapies. At week 52, the reduction in SELENA-SLEDAI scores from baseline and the median time to first lupus flare was not statistically different between the belimumab and placebo-treated patients. However, in the subgroup (72%) of serologically active patients (ANA $\geq 1:80 \pm$ anti-dsDNA ≥ 30 IU/ml), belimumab treatment led to significantly better responses than placebo for the reduction in SELENA-SLEDAI score, physician's global assessment (PGA), and the physical component score of the SF-36. The frequency of adverse events and serious adverse events was not increased in belimumab-treated patients.

This study was extended in an open-label fashion [16]. After one year, placebo-treated patients were shifted to belimumab (10mg/kg) and belimumab-treated patients could remain on their current doses or have the dose increased to 10 mg/kg. A SLE Responder Index (SRI), which is a composite clinical outcome defined by an improvement in SELENA-SLEDAI scores by ≥ 4 , no BILAG worsening (new A or two B flares), and no worsening in PGA (increase by ≥ 0.3 compared to baseline), was worked out for the assessment of a clinically useful endpoint. In serologically active patients, SRI rate was 46% at week 52 (vs placebo 29%, $p < 0.05$) which increased to 55% by week 76, and was maintained through week 272. The frequency of new BILAG A or 2 B flares decreased from 30% at 6 month to 23% at 1 year (vs placebo 33% and 25%, respectively) and declined to 11% at 4.5-5-year interval. The incidence of adverse events remained constant after 5 years. It was suggested that belimumab added to standard therapy was well tolerated. Serologically active patients treated with belimumab showed sustained improvement in disease activity and a decline in BILAG and SRI flares over 5 years.

Two phase III global studies were subsequently conducted-the BLISS-52 and BLISS-76. The BLISS-52 is a 52-week double-blind randomized placebo-control study that included 865 patients from Asia, Eastern Europe and Latin America [17]. The BLISS-76 is a 76-week study of the same design that involved 819 patients from North America and Europe [18]. The inclusion criteria were sero-positive SLE patients (ANA $\geq 1:80 \pm$ anti-dsDNA ≥ 30 IU/ml) with a SELENA-SLEDAI score of ≥ 6 and receiving stable treatment regimens for at least a month. Participants were randomized to receive intravenous belimumab at 1 and 10 mg/kg or placebo on days 0, 14, 28 and then every 28 days on top of ongoing therapies.

In the BLISS-52 study [17], the SRI rates were 51% in the 1 mg/kg and 58% in the 10 mg/kg belimumab dose groups, which were significantly higher than that of the placebo group (44%). The difference in the rate of SRI between the treatment and placebo groups became apparent at week 16. In the BLISS-76 study, the SRI rate at week 52 was only significantly higher in the 10mg/kg belimumab group (43%) than the placebo group (34%) [18]. The significance was lost at week 76 (39% in belimumab vs 32% in placebo). In both studies, the cumulative risk of disease flares and time to first flare was in favor of 10mg/kg belimumab [17,18]. In the BLISS-52 trial, significantly more patients in the 10mg/kg belimumab group could have prednisone dose reduced

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by $\geq 50\%$ from week 24 to 52 compared to placebo. Other secondary outcomes in favor with belimumab were reduction in severe SLE flares, increase in complement levels, reduction/sero-conversion of anti-dsDNA, improvement in PGA and the physical component of the SF36 quality of life measure [17].

Sub-Analyses of the Belimumab Clinical Trials

By combining the data of the BLISS-52 and BLISS-76 studies, it was demonstrated that belimumab treatment led to a significant increase in complement levels, but a significant reduction in anti-dsDNA titer and immunoglobulin levels [19,20]. Belimumab 1mg/kg and 10mg/kg significantly reduced circulating naïve, activated and plasmacytoid B cells while belimumab 10mg/kg also significantly reduced plasma cells. However, memory B and T cells were not affected and antibody titers to pre-enrollment immunization were maintained. In addition, subgroup analyses of the two BLISS studies revealed that patients with more pronounced serological activity (low complements or elevated anti-dsDNA) at baseline had a greater difference in clinical response rate when treated with belimumab compared to placebo.

Overall, adverse events and serious adverse events were similar between the belimumab and placebo groups of patients in these trials. Opportunistic infections were reported in eight patients treated with long-term belimumab (10mg/kg). Malignancy and mortality was not increased in belimumab-treated patients. Depression was the commonest psychiatric event reported and was numerically more common with belimumab treatment than with placebo. There were two completed suicides in the belimumab-treated patients. Hypersensitivity and infusion reaction (mostly mild) occurred at a similar rate between the belimumab and placebo groups of patients (17% vs 15%), but serious infusion/hypersensitivity reaction was numerically more common in belimumab-treated patients (7 patients vs 1 patient in the placebo group).

The Outlook of Belimumab in the Treatment of SLE

Supported by the above evidence, belimumab is effective in reducing SLE activity on top of background immunosuppressive therapy and delaying the time to disease flares. The drug is well-tolerated up to 5 years. Serious infections and malignancy are not significantly increased. However, one should be cautious of the numerical increase in the rate of serious infusion reaction and depression in belimumab-treated patients.

Belimumab was approved by the US FDA in March 2011 for the treatment of autoantibody positive adult patients with active SLE who are receiving standard therapies. It is the first new medication approved for the treatment of SLE in over 50 years. Belimumab is approved at the dosage of 10mg/kg to be given intravenously at 2-week intervals for the first 3 doses, followed by 4-week intervals. Candidates for addition of belimumab treatment are those SLE patients with active musculoskeletal, mucocutaneous, hematological and serological disease despite ongoing therapies.

However, there are several uncertainties about the use of belimumab in SLE. First, the agent is not studied and hence not indicated in patients with serious active lupus nephritis and neuropsychiatric lupus. Belimumab is not recommended to be combined with cyclophosphamide or other biological agents. Second, the magnitude of clinical benefit is only modest and its cost-effectiveness in treating milder cases of SLE is unclear. Third, the effect of belimumab appears to be lost beyond 1 year (BLISS-76 study result). While the explanation for this observation remains speculative, the longer term efficacy of belimumab as

maintenance treatment to prevent lupus flares has to be established with extended observation. Moreover, the optimal duration of belimumab therapy is unknown. Based on the existing data, the clinical effect of belimumab is to be expected after at least 16 week's treatment. When a clinical response is achieved, belimumab can be continued for one year. The decision for further continuation of the agent beyond 1 year should be individualized. Lastly, it is still unclear whether there is a difference in the efficacy of belimumab in patients of different ethnic background, in particular renal disease in the Black race. Moreover, whether belimumab is beneficial as an add-on therapy for more severe lupus nephritis during the induction phase and how is it compared to existing agents such as mycophenolate mofetil and azathioprine as maintenance treatment remains an open question.

Conclusion

Belimumab is the first biological therapy that has proven clinical benefit in SLE. The success of belimumab reiterates that B cell modulation is a promising approach in the treatment of SLE. Persistent mild to moderate lupus activity despite standard medications is an indication for add-on therapy with belimumab. However, the cost-effectiveness, efficacy in more serious SLE manifestations, as well as the long-term safety of belimumab has to be evaluated further.

Declaration

I was one of the many investigators of the belimumab BLISS-52 study. However, I did not receive any personal honorarium as a result of participating in this trial. I was also a member of the one-off advisory board meeting organized by GSK in Hong Kong in March 2012. Other than these, I do not have any conflicts of interests to be declared.

References

1. Mok CC, Lau CS (2003) Pathogenesis of systemic lupus erythematosus. *J Clin Pathol* 56: 481-490.
2. Mok CC (2010) Update on emerging drug therapies for systemic lupus erythematosus. *Expert Opin Emerg Drugs* 15: 53-70.
3. Grammer AC, Lipsky PE (2003) B cell abnormalities in systemic lupus erythematosus. *Arthritis Res Ther* 5: 22-27.
4. Odendahl M, Jacobi A, Hansen A, Fiest E, Hiepe F, et al. (2000) Disturbed peripheral B lymphocyte homeostasis in systemic lupus erythematosus. *J Immunol* 165: 5970-5979.
5. Jacobi AM, Reiter K, Mackay M, Aranow C, Hiepe F, et al. (2008) Activated memory B cell subsets correlate with disease activity in systemic lupus erythematosus: delineation by expression of CD27, IgD, and CD95. *Arthritis Rheum* 58: 1762-1773.
6. Wei C, Anolik J, Cappione A, Zheng B, Pugh-Bernard A, et al. (2007) A new population of cells lacking expression of CD27 represents a notable component of the B cell memory compartment in systemic lupus erythematosus. *J Immunol* 178: 6624-6633.
7. Jacob N, Stohl W (2010) Autoantibody-dependent and autoantibody-independent roles for B cells in systemic lupus erythematosus: past, present, and future. *Autoimmunity* 43: 84-97.
8. Mamula MJ, Fatenejad S, Craft J (1994) B cells process and present lupus autoantigens that initiate autoimmune T cell responses. *J Immunol* 152: 1453-1461.
9. Pistoia V (1997) Production of cytokines by human B cells in health and disease. *Immunol Today* 18: 343-350.
10. Moore PA, Belvedere O, Orr A, Pieri K, LaFleur DW, et al. (1999) BLyS: member of the tumor necrosis factor family and B lymphocyte stimulator. *Science* 285: 260-263.
11. Petri M, Stohl W, Chatham W, Mc Cune WJ, Chevrier M, et al. (2008) Association of plasma B lymphocyte stimulator levels and disease activity in systemic lupus erythematosus. *Arthritis Rheum* 58: 2453-2459.
12. Collins CE, Gavin AL, Migone TS, Hilbert DM, Nemazee D, et al. (2006) B lymphocyte stimulator (BLyS) isoforms in systemic lupus erythematosus:

- disease activity correlates better with blood leukocyte BLyS mRNA levels than with plasma BLyS protein levels. *Arthritis Res Ther* 8: 6.
13. Baker KP, Edwards BM, Main SH, Choi GH, Wager RE, et al. (2003) Generation and characterization of LymphoStat-B, a human monoclonal antibody that antagonizes the bioactivities of B lymphocyte stimulator. *Arthritis Rheum* 48: 3253-3265.
 14. Wallace DJ, Stohl W, Furie RA, Lisse JR, McKay JD, et al. (2009) A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. *Arthritis Rheum* 61: 1168-1178.
 15. Furie R, Stohl W, Ginzler EM, Becker M, Mishra N, et al. (2008) Biologic activity and safety of belimumab, a neutralizing anti-B-lymphocyte stimulator (BLyS) monoclonal antibody: a phase I trial in patients with systemic lupus erythematosus. *Arthritis Res Ther* 10: 109.
 16. Merrill JT, Wallace DJ, Furie RA, et al. (2010) The LBSL02/99 Study Group. Five-year experience with Belimumab, a BLyS-specific inhibitor, in patients with systemic lupus erythematosus (SLE). *Arthritis Rheum* 62: 608.
 17. Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, et al. (2011) Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 377: 721-731.
 18. Van Vollenhoven RF, Zamani O, Wallace DJ, Tegzova, Merrill JT, et al. (2010) BLISS-76 Study group. Belimumab, a BLyS-specific inhibitor, reduced disease activity and severe flares in seropositive SLE patients: BLISS-76 study results through wk 76. *Arthritis Rheum* 62: 606.
 19. Hiepe F, Stohl W, Scheinberg, et al. (2011) BLISS-52 and BLISS-76 Study groups. The mechanism of action of belimumab, a BLyS-specific inhibitor, is consistent with biomarker and vaccine results from the phase 3 BLISS studies. Annual European Congress of Rheumatology.
 20. Vollenhoven R, Schneider M, Wallace DJ, et al. (2011) BLISS-52 and BLISS-76 Study groups. Efficacy of belimumab in patients with SLE: focus on patients with low complement and positive anti-dsDNA – results from BLISS-52/BLISS-76. Annual European Congress of Rheumatology.