Belimumab: the first US FDA approved biological therapy for systemic lupus erythematosus

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KEYWORDS: BAFF ■ B-cell depletion ■ biologics ■ immunomodulation ■ lupus ■ novel ■ targeted therapy ■ therapeutics ■ therapy

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Systemic lupus erythematosus (SLE) is a complex multisystemic autoimmune disease with considerable clinical and immunological heterogeneity. Although the exact pathogenetic mechanisms have yet to be elucidated, both genetic and environmental factors are thought to be involved [1]. SLE is characterized by a myriad of immunological aberrations, which can be either the cause or effect of the disease. These abnormalities include aberrant apoptosis and defective clearance of apoptotic materials such as nuclear autoantigens and nucleosomes, as well as immune complexes by macrophages and the complement system [2], increased maturation of myeloid dendritic cells that drive the development of the proinflammatory Th17 cells [3], and defective functions of the regulatory T cells (Tregs) leading to hyperactivity of the helper T cells and autoreactive B cells [4]. The end result is B-cell hyperactivity contributing to increased autoantibody production. 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.

B-cell abnormalities in SLE

The hallmark of B-cell abnormalities in SLE is a loss of B-cell tolerance, leading to the production of a large amount of autoantibodies that direct against chromatin and self-antigens [5]. These B-cell defects may originate from a genetic basis and manifest as diminished B-cell activation threshold and increased B-cell longevity promoting the survival of the autoreactive B cells. Toll-like receptors (TLR7 and TLR9) on the surface of B cells and dendritic cells may be activated by endogenous DNA and RNA that are contained in SLE immune complexes, leading to cellular activation and production of inflammatory cytokines and type I interferons [6]. A number of qualitative and quantitative defects of B cells have been identified in patients with SLE. These range from increased calcium signaling upon stimulation of the B-cell receptors, aberrant expression of costimulatory molecules on B cells [7], reduction in peripheral naive B cells, expansion of peripheral blood plasma cells, transitional B cells and activated B-cell memory subsets [8–10]. In addition to the production of autoantibodies, B cells in SLE may mediate autoimmunity by a number of antibody independent mechanisms such as autoantigen presentation to T cells that contribute to T-cell activation and polarization, as well as cytokine and chemokine production that reduces regulatory T-cell activity and enhances the recruitment of dendritic cells [11–13].

B-cell modulation therapy in SLE

As B cells play a central role in the pathogenesis of SLE, modulation of B-cell function is an attractive novel target of SLE therapy. Strategies of B-cell modulation include depletion, tolerization, inhibition of survival and activation, as well as blockade of the costimulatory interactions between B and T cells [14]. A number of clinical trials have been conducted in the past decade on the efficacy of B-cell modulation in SLE. These involve novel therapeutic agents such as rituximab (anti-CD20), ocrelizumab (anti-CD20), epratuzumab (anti-CD22), abetimus sodium (Riquent), belimumab (anti-BLyS), atacicept (TACI-Ig) and abatacept (CTLA4-Ig). To the disappointment of the lupus community, most of these trials ended up with unfavorable results. While flaws in study design, effective background immunosuppressive therapies used, limitations of outcome measures, and heterogeneity of clinical and immunological profile of

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SLE may contribute to the futility of some of these studies, selection of appropriate SLE subsets, and utilization of organ-specific outcome parameters or composite index of disease activity may allow for a better delineation of the efficacy of the novel targeted therapies in SLE.

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Belimumab: clinical efficacy & safety in SLE

B-lymphocyte stimulator (BLyS), or B-cell-activation factor (BAFF), belongs to the TNF ligand superfamily and is mainly produced by monocytes and macrophages. It is an essential factor for B-cell maturation, survival, proliferation and immunoglobulin class switching. BLyS binds to any of the three receptors on B cells, namely TACI, BCMA and BAFF-R. In murine studies, repeated administration of exogenous BLyS leads to B-cell expansion and increased immunoglobulin production even in the absence of antigenic stimulation [15]. In humans, levels of BLyS and BLyS mRNA are shown to be elevated in patients with SLE [16,17] and correlate with disease activity scores. BLyS level is biomarker for lupus activity and may predict lupus flares [16].

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 has been shown to inhibit human B-cell proliferation *in vitro* [18]. Administration of belimumab leads to the depletion of $CD19^+$ B cells, naive 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 [19].

Phase I/II studies of belimumab in SLE

A short-term Phase I dose escalation study has established safety of belimumab in patients with SLE [20]. This was followed by a Phase II study of 449 patients with active SLE, defined by a Safety of Estrogen in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of ≥4 [19]. Participants were randomly assigned to receive belimumab (1, 4 or 10 mg/kg) or placebo, 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 groups of patients. However, in the subgroup (72%) of serologically active patients (antinuclear antibody ≥1:80 ± anti-dsDNA ≥30 IU/ml), belimumab treatment resulted in significantly better responses than placebo for the reduction in SELENA-SLEDAI score, physicians' global assessment (PGA), and the physical component score of the SF-36. The frequency of adverse events and serious adverse events was not significantly higher in the belimumab-treated patients.

The same cohort of patients was followed in an open-label extension study [21]. After 1 year, placebo-treated patients were shifted to receive belimumab (10 mg/kg), and belimumab-treated patients could remain on their current dose or receive 10 mg/kg at the discretion of investigators. A SLE Responder Index (SRI) was worked out for the assessment of a clinically useful outcome in the treatment of SLE. The SRI is a composite clinical outcome defined by an improvement in SELENA-SLEDAI scores by ≥4, no British Isles Lupus Assessment Group (BILAG) worsening (new A or two B flares), and no worsening in PGA (increase by ≥0.3 compared with baseline). At 5 years, the incidence rates (per 100 patient-years of follow-up) of adverse events remained constant. 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 two 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. It was concluded that belimumab added to the standard of care therapy was generally 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.

A subanalysis of laboratory indices showed that a higher proportion of patients treated with belimumab had an increase in complement levels, decrease in anti-dsDNA titer by ≥50%, decrease in anti-Sm and anticardiolipin antibody titers, and reduction of immunoglobulin levels [21]. Clinical responders had a greater reduction in the proportion of activated and plasmacytoid B cells.

Phase III studies of belimumab in SLE

The favorable results of the Phase II study leads to two further Phase III global studies – the BLISS-52 and BLISS-76 studies. The BLISS-52

is a 52-week double-blind randomized placebo-control study that included 865 patients from Asia, Eastern Europe and Latin America [22]. The BLISS-72 is a 72-week study of the same design that involved 819 patients from North America and Europe [23]. The inclusion criteria were seropositive SLE patients (antinuclear antibody ≥1:80 ± anti-dsDNA ≥30 IU/ml) with a SELENA-SLEDAI score of ≥6 and receiving stable SLE 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 [22], 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 10 mg/kg belimumab group (43%) than the placebo group (34%) [23]. This significance was lost at week 76 (39% in the belimumab group vs 32% in the placebo group). In both studies, the cumulative risk of disease flares and time to first flare was in favor of the 10 mg/kg belimumab group [22,23]. In the BLISS-52 trial, significantly more patients in the 10 mg/kg belimumub group could have prednisone dose reduced by ≥50% from week 24 to 52, when compared with the placebo group. Other secondary outcomes in favor with belimumab treatment included reduction in severe SLE flares, increase in complement levels, reduction/seroconversion of anti-dsDNA, improvement in PGA and the physical component of the SF36 health-related quality of life measure [22].

Latest data were presented in the EULAR 2011 meeting in London, UK, regarding belimumab in SLE [24,25]. By combining the clinical data of BLISS-52 and BLISS-76, it was demonstrated that belimumab treatment led to a significant increase in complement levels, and a significant reduction in anti-dsDNA titer and immunoglobulin levels compared with placebo. Belimumab 1 mg/kg and 10 mg/kg significantly reduced circulating naive, activated and plasmacytoid B cells while belimumab 10 mg/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 those SLE 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 with placebo.

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Overall, adverse events and serious adverse events were similar between the belimumab and placebo groups of patients in these studies. Opportunistic infections were reported in eight patients treated with long-term belimumab (10 mg/kg). Rates of malignancy and mortality were also comparable between belimumab and placebo treated patients. Depression was the most common 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 more commonly reported in belimumab-treated patients (seven patients compared with one patient in the placebo group).

Role of belimumab in the treatment of SLE

Supported by randomized controlled trials, belimumab is confirmed to be effective in reducing SLE disease activity on top of background immunosuppressive therapy and delaying the time to lupus flares. The drug is well tolerated in SLE patients up to 5 years. Serious infections and malignancy are not increased with belimumab treatment. However, one should be aware of the numerical increase in the rate of serious infusion reactions and depression in belimumab-treated patients.

In March 2011, belimumab was approved by the US FDA 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 10 mg/kg to be given intravenously at 2-week intervals for the first three 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.

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However, there are several limitations and uncertainties of the use of belimumab in SLE. First, the agent has not yet been studied, and hence, is not indicated, in patients with serious active lupus nephritis and neuropsychiatric lupus. Belimumab is not recommended to be used in combination with cyclophosphamide or other biological agents. Second, the magnitude of clinical benefit is only modest and the cost–effectiveness of the medication in the treatment of SLE is still unclear. Third, the effect of belimumab appears to be lost on extension 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 observational studies. Last, the optimal duration of belimumab therapy remains an open question. However, based on the currently available information, belimumab should be used for at least 16 weeks to expect a clinical response. If a clinical response is observed, the agent can be continued for at least 1 year. Further continuation of the agent will depend on the case-by-case judgment of attending physicians.

Conclusion

The approval of belimumab for SLE has undoubtedly caused excitement to physicians managing SLE patients. The success of belimumab suggests that B-cell modulation remains a promising approach in the treatment paradigm of SLE. However, this is just a start. The variability of clinical response among SLE patients may reflect the clinical and immunological heterogeneity of the disease and the failure of the B-cell biological agents to eliminate the pathological memory B-cell clones. Much more effort is needed to improve the treatment response of patients with more serious SLE manifestations, which are the major determinants for mortality and morbidity in this disease. Long-term safety and cost–effectiveness studies of the novel biological agents in the treatment of SLE are of utmost importance. It is hoped that more effective but less toxic treatment regimens will soon be available so that SLE patients can live longer with better quality of life.

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