

Belimumab: First targeted biological treatment for systemic lupus erythematosus

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder involving multiple organs and having diverse clinical manifestations. Among the rheumatic diseases, it has one of the highest mortality rates.^[1] Its prevalence around the world ranges from 20 to 70 per 100,000 person-years.^[2] Clinical features of SLE range from mild involvement of skin and joints to severe debilitating complications at later stages, such as infections and problems of renal, cardiovascular, and central nervous system, which are responsible for considerable morbidity and mortality. Being an autoimmune disease, SLE is characterized by the presence of antibodies against the self-antigens. The deposition of autoantibodies and immune complexes in the tissues leads to inflammatory damage of various organ systems of the body.^[3]

The existing treatment options to relieve symptoms and control the progression of the disease include nonsteroidal anti-inflammatory drugs (NSAIDs), and immunosuppressants, such as hydroxychloroquine, corticosteroids, methotrexate, azathioprine, cyclophosphamide, and mycophenolate mofetil.^[4] Till now, we had mainly relied on nonspecific immunosuppression for keeping the disease under control. Recently, a drug has been approved specifically for SLE

after a long gap (hydroxychloroquine being the last drug to be approved by the Food and Drug Administration [FDA] 56 years back in 1955). The drug, belimumab, which was approved on March 9, 2011, by FDA, is the first ever targeted biological for the treatment of SLE patients with active, autoantibody-positive disease, who are already on standard therapy.^[5] It has been developed by Human Genome Sciences Inc. in collaboration with GlaxoSmithKline.

Biologicals for treatment of systemic lupus erythematosus

The heterogenous and unpredictable nature of the disease, along with the difficulty and delay in assessing the drug response, have been the major hurdles for designing and conducting clinical trials in patients with SLE.^[6] With better understanding of pathogenesis of the disease in recent times, trials have been initiated with many biologicals as targeted therapy against B cells, T cells, costimulatory signaling pathways, cytokines, and complement system.^[7] Rituximab had generated a lot of hope for SLE patients, after having been used successfully for other autoimmune disorders, but results of the Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) trial, which tested its efficacy and safety in patients with moderately-to-severely active extrarenal SLE, were disappointing.^[8] Against this backdrop, the success of belimumab, the first approved drug among biologicals for the treatment of SLE, is very encouraging and will pave the way for developing more targeted agents for this disease.

Pharmacological basis of belimumab therapy

The definite cause of SLE is not clear and various factors, such as environment, genetics, and so on, have been implicated in its pathogenesis. But once initiated, by the yet improperly defined triggering factors, the disease progression clearly

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involves B cells and B lymphocyte stimulator (BLyS), the two very important components responsible for mediating normal humoral immunity and autoantibody production.^[9]

B lymphocyte stimulator (BLyS), also known as B cell-activating factor (BAFF), is the costimulator for B-cell survival and function.^[10,11] BLyS belongs to the tumor necrosis factor superfamily, and is expressed by a wide variety of cells, such as monocytes, macrophages, and dendritic cells. It is present in membrane bound and soluble form, the soluble form being biologically active.^[11] Three types of BLyS receptors are expressed on the B-cells: BLyS receptor 3 (BR3; also termed BAFFr), Transmembrane Activator and Calcium modulator and cyclophilin ligand (CAML) Interactor (TACI), and B-cell maturation antigen.^[12] The interaction of BLyS with BR3 is stronger compared to the other two receptors. BLyS–BR3 interaction promotes the survival of the autoantibody-producing B cells by preventing their selection and apoptosis.^[13]

Preclinical experiments with transgenic mice suggested that the overexpression of BLyS increased the survival and growth of activated autoreactive B cells and decreased the self-tolerance leading to lupus-like autoimmune manifestations.^[14] BLyS has been shown to play a key role in the pathogenesis of SLE. The levels of BLyS are raised in SLE patients and there is associated rise of anti-double-stranded DNA (dsDNA) antibody of the IgG, IgM, and IgA classes, suggesting the importance of BLyS in initiating the loss of tolerance toward self-antigens.^[15] The BLyS levels correlate positively with the anti-dsDNA antibody titers.^[16] Monitoring of BLyS levels was seen to help in predicting the SLE disease activity.^[17]

Thus in the past few years, BLyS had become an attractive target in the quest for a drug to treat SLE because development of a BLyS inhibitor had the potential to effectively control the B-cell dysfunction in the disease.

Mechanism of action

Belimumab is a fully human IgG1 λ recombinant monoclonal antibody directed against BLyS.^[18] Specific binding of belimumab with the soluble BLyS prevents the interaction of BLyS with its three receptors and indirectly decreases the B-cell survival and production of autoantibodies.^[19]

Clinical trials

Two multicenter phase III trials, BLISS-52 and BLISS-76, have been conducted to evaluate the efficacy and safety of belimumab in SLE patients.^[20,21] In both the double-blind placebo-controlled trials seropositive patients were randomized to one of three treatment groups: 10 mg/kg belimumab, 1 mg/kg belimumab, or placebo. Standard of care therapy was given to all enrolled patients in addition to the treatment of the respective group. Intravenous belimumab was administered

on days 0, 14, and 28, then every 28 days thereafter for the duration of the study. Patient response rate was to be assessed by Systemic Lupus Erythematosus Responder Index (SRI).^[20,21]

BLISS-52 trial

In this study, 865 seropositive patients were assessed for efficacy and safety of the drug. Improvement in the SRI at week 52 was considered the primary efficacy endpoint. SRI rates were observed to be significantly higher in the belimumab 1 and 10 mg/kg group than with placebo at the end of week 52 (51% and 58% vs. 44%). No significant difference was found between belimumab and placebo with respect to adverse effect.^[20]

BLISS-76 trial

In this study, 819 seropositive patients were observed for 76 weeks. The patient response rates, to be measured by SRI at week 52 and 76, were the primary and major secondary endpoints, respectively.^[21] No significant SRI improvement was seen with belimumab 1 mg/kg compared to placebo (40.6% vs. 33.8%). The improvement was significantly higher in 10 mg/kg belimumab group than placebo at week 52 (43.2% vs. 33.8%) but could not be sustained later and the difference at week 76 was not statistically significant.^[21]

In both the studies, belimumab met the primary efficacy endpoint and the rates of adverse events with belimumab were similar to placebo. However, the improvement, although significant, was not large in BLISS-76 and could not be sustained at the end of week 76. Future trials with belimumab and other biologicals are necessary to see whether altering the criteria for improvement in BLISS trials causes any meaningful difference in the results.^[7] SLE trials have struggled with the problem of an efficient design and a standard response assessment scale. However, for a disease with limited treatment options, the BLISS trials have paved the way for designing further effective trials. The less favorable results in BLISS-76 trial could also suggest decreased efficacy of belimumab in the patients with late established SLE, since the mean disease duration of enrolled patients was longer in BLISS-76 trial.^[7,21]

Pharmacokinetics and dosage

Belimumab is administered as intravenous infusion. Half-life of belimumab is 19–20 days and it follows linear pharmacokinetics.^[22] Volume of distribution is small (69–112 mL/kg) and clearance is slow (7 mL/day/kg). No significant pharmacokinetic change was seen with concomitant use of belimumab and NSAIDs, antimalarials, corticosteroids, methotrexate, azathioprine, or mycophenolate mofetil.^[22]

Single-use vials containing 120 and 400 mg of belimumab as lyophilized powder are available for injection. Intravenous infusion of reconstituted 10 mg/kg belimumab is administered over 1 h, with a gap of 2 weeks for the first 3 doses and then repeated every 4 weeks.^[22] It is currently not available in India.

Adverse effects

Belimumab has been found to be well tolerated in the initial clinical trials. Infections, arthralgia, headache, rash, diarrhea, and nausea have been reported with the use of the drug.^[20,21] Infusion reactions, such as urticaria and chest pain can occur.^[20,21] Hematologic reactions, such as neutropenia and thrombocytopenia, have also been reported in some patients.^[20,21] Adequate studies on adverse effects of belimumab in pregnancy, nursing mothers, children, and elderly persons have not been done as yet, so it should be used with caution in these groups of patients.

A few events have been of serious concern during the clinical trials. More deaths were reported with belimumab 1 and 10 mg/kg than with placebo (0.7% and 0.9% vs. 0.4%).^[22] Serious infections and suicides due to severe depression were also reported during the trials. Incidence of serious psychiatric events with belimumab was more than with placebo (0.8% vs. 0.4%).^[22] As with any other newly approved molecule, the long-term safety of the drug needs to be monitored, since the results of any trial cannot fully predict a drug's safety profile in the real clinical scenario.

The effects of co-administration of other biologics or cyclophosphamide have not been studied yet, so use of these agents should be avoided with belimumab. The drug cannot be used in SLE with renal or central nervous system involvement as the trials have not been conducted in such group of patients.^[22]

CONCLUSIONS

Although belimumab has shown a modest success in the subgroup of serologically active patients of SLE, its approval has ushered in an additional class of specifically targeted drugs for SLE. Many other trials for targeted therapies are currently underway and the hope to manage the disease with this new approach has soared high after the successful results of this first biologic. We can look forward to some exciting trial results in the near future, with a positive anticipation for the development of further successful targeted therapies, which will be useful for all or a larger subset of SLE patients.

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