Belimumab in Systemic Lupus Erythematosus

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Abstract
Belimumab is the only approved biological agent for the treatment of systemic lupus erythematosus (SLE). It is a fully humanized IgG1γ monoclonal antibody directed against soluble B lymphocyte stimulator (BLyS). It is indicated as an add-on therapy for the treatment of adult patients with active, autoantibody-positive SLE, who are receiving standard therapy. Belimumab is generally well-tolerated, common adverse effects include infections, infusion reactions, hypersensitivity, headache, nausea, and fatigue. Psychiatric events including suicidal tendency, progressive multifocal leukoencephalopathy and malignancies too have been reported. Apart from SLE, the drug is also being tried for other autoimmune disorders.

Key Words: Adverse effects, B lymphocyte stimulator, belimumab, systemic lupus erythematosus

Q1. What is belimumab?
Answer: Belimumab is a fully humanized IgG1γ monoclonal antibody directed against soluble B lymphocyte stimulator (BLyS). Currently, it is the only approved biological for the treatment of systemic lupus erythematosus (SLE).[1,2]

Q2. When was belimumab approved?
Answer: Belimumab was approved by the US Food and Drug Administration (FDA) on March 9, 2011, and it became the first targeted therapy for the treatment of SLE.[3] It was also approved by the European Medicines Agency in July 2011.[3] Before belimumab, the last drug to be approved by the FDA was hydroxychloroquine in 1955.[1]

Q3. Indication for belimumab?
Answer: Belimumab is indicated as an add-on therapy for the treatment of adult patients with active, autoantibody-positive, SLE, who are receiving standard therapy.[1,4] However, currently, it is not indicated for patients with severe active lupus nephritis or active central nervous system (CNS) lupus.[1,5]

Q4. Discuss the dosage and administration of belimumab?
Answer: In the approved regimen, belimumab is administered in a dose of 10 mg/kg intravenous (IV) on days 0, 14, and 28, and then every 28 days thereafter. The onset of action for B-cell suppression is 8 weeks, with improvement in clinical manifestations in 16 weeks.[6]

It is available as lyophilized powder in single-use vials containing 120 and 400 mg of belimumab. These vials are reconstituted with 1.5 and 4.8 ml of sterile water, respectively, so that the reconstituted solution contains 80 mg/ml of belimumab. It is then dissolved in 250 ml of normal saline for IV infusion to be administered over 1 h. For dissolution, dextrose solution is not compatible.[7]

Q5. What is the mechanism of action of belimumab?
Answer: Belimumab is a recombinant, fully human, monoclonal antibody directed against the cytokine BLyS, also known as B-cell activating factor (BAFF).[1] It belongs to the tumor necrosis factor (TNF) superfamily and plays a central role in B-cell survival and function.[6] Overexpression of BLyS promotes survival of B-cells (including autoreactive B-cells) whereas its inhibition results in autoreactive B-cell apoptosis. BLyS, thus, plays a key role in the pathogenesis of autoimmune diseases.

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diseases such as SLE. Elevated circulating BlyS levels are common in SLE patients, in comparison with healthy individuals, and higher levels correlate with increased disease activity and antidouble-stranded DNA (dsDNA) antibody titers.\(^1,\)\(^9\) Therefore, inhibiting the biological activity of BlyS is potentially helpful in the treatment of the disease. Belimumab is one such agent that acts by binding to soluble BlyS.

Q6. Discuss in detail about the B-cell activating factor (BAFF)/A proliferation-inducing ligand axis (APRIL)

Answer: BlyS or BAFF is a cytokine involved in B-cell maturation and survival. It belongs to the TNF superfamily and is produced by a wide variety of cell types, including neutrophils, dendritic cells, monocytes, and macrophages. It is present in two forms: Membrane-bound and soluble, the soluble form being biologically active. It acts by binding to three types of BlyS receptors expressed on the B-cells:\(^6\)

1. BlyS receptor 3 (BAFF receptor 3 [BR3] or BAFF-R)
2. Transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI)
3. B-cell maturation antigen (BCMA).

The interaction of BlyS with BR3 is stronger as compared to the other two. Binding of BlyS/BAFF to BR3/BAFF-R activates the nuclear factor-kappa B pathway and mitogen-activated protein kinase pathway, leading to the expression of genes essential for B-cell survival.\(^10\) These downstream signaling pathways eventually result in expression of antiapoptotic proteins that promotes survival of autoantibody-producing B-cells by preventing their apoptosis.\(^4\)

APRIL, which stands for “a proliferation-inducing ligand,” is another cytokine of TNF superfamily. It is regarded as “sister” cytokine of BlyS. BlyS and APRIL share two receptors, TACI and BCMA, while the third receptor, BR3, does not bind APRIL.\(^6\) Both of these cytokines are needed for B-cell maturation and survival; however, preimmune B lymphocytes rely on BlyS signaling for their survival whereas antigen-experienced B lymphocytes generally interact more avidly with APRIL.\(^6\)

The BAFF/APRIL axis, therefore, plays a pivotal role in the pathogenesis of various autoimmune diseases including SLE, rheumatoid arthritis (RA), Sjogren’s syndrome, and antineutrophil cytoplasmic antibody-associated vasculitis.\(^8,\)\(^10\)

Q7. Enumerate various inhibitors of the B-cell activating factor/a proliferation-inducing ligand axis

Answer: Inhibitors of the BAFF/APRIL axis include\(^6,\)\(^10,\)\(^11\)

- Belimumab – inhibits BAFF but not APRIL
- Tabalumab – inhibits BAFF but not APRIL
- Blisbimod – inhibits BAFF but not APRIL
- Atacicept – inhibits both BAFF and APRIL.

Q8. Apart from systemic lupus erythematosus, what are the diseases in which belimumab can be used therapeutically?

Answer: Belimumab is currently under clinical trials for several autoimmune disorders including RA, Sjogren syndrome, systemic sclerosis, idiopathic thrombocytopenic purpura, myasthenia gravis, vasculitis, and renal transplant.\(^10\)

Q9. What are the adverse effects of belimumab?

Answer: Data from the clinical trials and long-term follow-up studies indicate that belimumab is generally well-tolerated.\(^12-\)\(^14\) The rate of adverse events noted in various studies varies from 6% to 38%.\(^6\) The most common adverse effects include infections, infusion reactions, hypersensitivity, headache, nausea, and fatigue.\(^1,\)\(^5\) Other adverse effects include psychiatric events including insomnia, anxiety, depression, and suicidal ideation. The risk of developing a psychiatric disorder was 2-fold in patients with a history of psychiatric illness.\(^13\) Some patients also developed neutropenia, thrombocytopenia, and hypogammaglobulinemia.\(^9,\)\(^14\)

Among infections, upper respiratory tract infections predominate; however, severe infections including cellulitis and pneumonia (including fatal Cytomegalovirus pneumonia) have been noted.\(^12,\)\(^14\) Furthermore, two cases of progressive multifocal leukoencephalopathy have been reported.\(^15\) Overall, the rate of serious and/or severe infections peaked in the 1st year of treatment with belimumab and declined in later years.\(^12,\)\(^14\)

Risk of malignancy: The most common malignancies were nonmelanoma skin cancers-squamous cell carcinoma and basal cell carcinoma; however, solid organ as well as hematologic malignancies have also been reported.\(^5,\)\(^12,\)\(^14\)

A study\(^{12}\) reported that the malignancies (excluding nonmelanoma skin cancer) observed in patients on belimumab are consistent with those expected in an SLE population (which is largely composed of women), and the malignancy rate is similar to the background rate reported in patients with SLE.

Mortality: Ginzler et al.\(^{12}\) reported that there was no apparent increased risk of mortality associated with belimumab treatment over 7 years. The mortality rate of 0.4/100 patient-years observed in the long-term continuation study of belimumab is below the rate of 1.63 reported for SLE. Mortality in patients on belimumab was attributed to infections, suicide, cardiac disease, and malignancy.

Q10. Discuss the present role of belimumab in treatment of systemic lupus erythematosus

Answer: At present, belimumab is indicated as an add-on therapy in adults with active, antinuclear antibody or anti-dsDNA-positive SLE with a high degree of disease...
activity in the skin and/or musculoskeletal systems that remain moderately to severely active despite optimized standard immunosuppression.[2] However, patients with severe lupus nephritis or active CNS lupus are not the candidates for belimumab.[1,5]

The role of belimumab in SLE was evaluated in two, large, multicentric, randomized, placebo-controlled Phase III trials: BLISS-52 and BLISS-76. In both these trials, belimumab at doses of 1 and 10 mg/kg plus standard therapy was compared with placebo plus standard therapy in patients with autoantibody-positive active SLE.

Results from BLISS-52:[14] Belimumab was found to be well-tolerated, reduced SLE disease activity, prevented flares, improved serologic activity in patients with serologically active disease, and reduced corticosteroid use. Improvement in the SLE responder index (SRI) at week 52 was considered the primary efficacy end-point. 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. Furthermore, rates of adverse events were similar in all the three groups.

Results from BLISS-76:[9] This trial was similar to BLISS-52 in terms of methodology. SRIs at week 52 and 76 were the primary and major secondary end-points, respectively. The primary end-point, however, was met with the higher (10 mg/kg) dose of belimumab, and not with the lower dose (1 mg/kg). Significant reductions in anti-dsDNA antibody titers and increases in C3 and C4 concentrations were observed with both belimumab doses at week 8 and persisted through week 76. The incidence of adverse effects, laboratory abnormalities, and infections was similar in all the three groups.

At present, belimumab is not recommended for patients with severe active lupus nephritis and CNS manifestations since these patients had been excluded in the above trials.

Q11. Which aspects of belimumab and systemic lupus erythematosus need further exploration?

Answer: Following aspects of belimumab are yet to be explored:
• At present, belimumab is approved as an additional agent for patients who are already receiving standard care. Its efficacy as a monotherapy is still to be proved
• Role in lupus nephritis and CNS lupus: The safety and efficacy of belimumab have not been established in these patients. However, these groups of patients are more likely to need a novel therapy since renal involvement is the major cause of morbidity and mortality in SLE. Furthermore, risk of developing neuropsychiatric complications in patients with CNS lupus is also a concern
• Safety and efficacy in childhood SLE and pregnant patients
• Long-term safety of the drug is yet to be established. Serious adverse effects such as progressive multifocal leukoencephalopathy, depression, suicidal tendency, and malignancy are to be watched for
• Efficacy in other autoimmune diseases such as RA, Sjogren’s syndrome, and various forms of vasculitis

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Conflicts of interest
There are no conflicts of interest.

What is new?
• The Baff/ APRIL axis plays an important role in the pathogenesis of various autoimmune diseases including SLE; inhibitors of this axis are therefore useful in treatment of these disorders
• Results from BLISS-52 and BLISS-76 trials have shown belimumab to be efficacious in treating patients with SLE
• Serious adverse effects noted with belimumab such as progressive multifocal leukoencephalopathy, depression, suicidal tendency, and malignancy are to be watched for.

References
1. Dubey AK, Handu SS, Dubey S, Sharma P, Sharma KK, Ahmed QM. Belimumab: First targeted biological treatment for systemic lupus erythematosus. J Pharmacol Pharmacother 2011;2:317-9.
2. Vilas-Boas A, Morais SA, Isenberg DA. Belimumab in systemic lupus erythematosus. RMD Open 2015;1:e000011.
3. Specchia ML, de Waure C, Gualano MR, Doria A, Turchetti G, Pippo L, et al. Health technology assessment of belimumab: A new monoclonal antibody for the treatment of systemic lupus erythematosus. Biomed Res Int 2014;2014:704207.
4. Stohl W, Hilbert DM. The discovery and development of belimumab: The anti- BLyS-lupus connection. Nat Biotechnol 2012;30:69-77.
5. Hui-Yuen JS, Li XQ, Askanase AD. Belimumab in systemic lupus erythematosus: A perspective review. Ther Adv Musculoskelet Dis 2015;7:115-21.
6. Frieri M, Heuser W, Bliss J. Efficacy of novel monoclonal antibody belimumab in the treatment of lupus nephritis. J Pharmacol Pharmacother 2015;6:71-6.
7. Label Approved on 03/10/2011 (PDF) for BENLYSTA, BLA No. 125370. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125370s000lbl.pdf. [Last accessed on 2016 Apr 07].
8. Treml JF, Hao Y, Stadanlick JE, Cancro MP. The BlyS family: Toward a molecular understanding of B cell homeostasis. Cell Biochem Biophys 2009;53:1-16.
9. Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum 2011;63:3918-30.
10. Lenert A, Lenert P. Current and emerging treatment options for ANCA-associated vasculitis: Potential role of belimumab and other BAFF/APRIL targeting agents. Drug Des Devel Ther 2015;9:333-47.
11. Raychaudhuri SP, Raychaudhuri SK. Biologics: Target-specific treatment of systemic and cutaneous autoimmune diseases.
Indian J Dermatol 2009;54:100-9.
12. Ginzler EM, Wallace DJ, Merrill JT, Furie RA, Stohl W, Chatham WW, et al. Disease control and safety of belimumab plus standard therapy over 7 years in patients with systemic lupus erythematosus. J Rheumatol 2014;41:300-9.
13. Wallace DJ, Navarra S, Petri MA, Gallacher A, Thomas M, Furie R, et al. Safety profile of belimumab: Pooled data from placebo-controlled phase 2 and 3 studies in patients with systemic lupus erythematosus. Lupus 2013;22:144-54.
14. Merrill JT, Ginzler EM, Wallace DJ, McKay JD, Lisse JR, Aranow C, et al. Long-term safety profile of belimumab plus standard therapy in patients with systemic lupus erythematosus. Arthritis Rheum 2012;64:3364-73.
15. Fredericks CA, Kvam KA, Bear J, Crabtree GS, Josephson SA. A case of progressive multifocal leukoencephalopathy in a lupus patient treated with belimumab. Lupus 2014;23:711-3.
16. Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: A randomised, placebo-controlled, phase 3 trial. Lancet 2011;377:721-31.