

Belimumab : B-Lymphocyte Stimulator Inhibitor For-Systemic Lupus Erythematosus

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ABSTRACT

Belimumab is a monoclonal antibody that inhibits B-lymphocyte stimulator (BLyS) that has been FDA approved for the treatment of systemic lupus erythematosus (SLE). It is the first new drug for the treatment of SLE approved in more than 50 years. Currently available treatment for SLE often involves symptomatic relief. Because belimumab modifies the proliferation of B cells, it has shown efficacy in reducing disease activity and flares in serologically active patients when combined with standard therapy versus placebo. In clinical trials, belimumab was administered by 2-hour continuous intravenous (IV) infusion every 2 weeks for the first month, then monthly thereafter. Current data indicate that belimumab does not increase the risk of infection, but additional long-term studies are needed.

Introduction -

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by exacerbations and remissions.¹ Patients most commonly experience a mixture of skin, musculoskeletal, hematologic, and serologic symptoms.¹ Women are more commonly affected than men and the disease is primarily diagnosed in patients aged 15 to 45 years.¹ Currently available therapies for SLE are usually given in response to symptoms within specific organ systems and include nonsteroidal anti-inflammatory drugs (NSAIDs), hydroxychloroquine, systematic corticosteroids, or methotrexate.² T cells, B cells, and cytokines all have a role in SLE.³ The involvement of B cells in the clinical presentation of SLE suggests that they are a potential target for drug therapy.

Belimumab (Benlysta, Human Genome Sciences and GlaxoSmithKline) is a B-lymphocyte stimulator (BLyS) inhibitor approved by FDA on March 9, 2011, for the treatment of SLE, the first new drug for the treatment of SLE approved in more than 50 years.

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BENLYSTA (belimumab) is a human IgG1-lambda monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab has a molecular weight of approximately 147 kDa. Belimumab is produced by recombinant DNA technology in a mammalian cell expression system.

Chemistry and Pharmacology -

Proinflammatory cytokines (such as tumor necrosis factor-alpha, interleukin-6, and interleukin-10) and autoantibodies contribute to many of the symptoms of SLE.³ Autoantibodies are released by proliferating B cells, which have been stimulated by autoreactive T cells and the freely circulated BLyS, which is a cytokine in the tumor necrosis factor family.¹ The overexpression of BLyS in patients with SLE is thought to contribute to the excessive B cell proliferation.³

Belimumab is a recombinant, fully human IgG monoclonal antibody that specifically recognizes and binds to soluble BLyS to inhibit its activity.⁵ By preventing BLyS from binding to B cell surfaces, the proliferation of B cells is halted and the B cells undergo apoptosis.⁵ This process then stops the production of autoantibodies, thereby decreasing the disease activity of SLE and the resulting symptoms.⁵

Pharmacokinetics -

Belimumab exhibits linear pharmacokinetics upon IV administration over a dose range of 1 to 20

mg/kg.⁶ The peak plasma concentration is approximately 20 mg/mL per 1 mg/kg dose of belimumab.⁶ Clearance is approximately 7 mL/day per kg and the volume of distribution ranges from 69 to 112 mL/kg.⁶ The elimination half-life ranges from 8.5 to 14.1 days, and is not affected by renal function.⁷ The metabolism of belimumab is unknown. Belimumab pharmacokinetics have not been affected by the co-administration of immunosuppressants, hydroxychloroquine, or prednisone.

Adverse Events -

In the phase 2 dose-ranging trial, rates of adverse events were similar between groups.⁸ Urticaria was statistically more frequent in belimumab-treated patients versus placebo-treated patients (4% vs 0%).⁸ Infection rates were not significantly different between belimumab and placebo groups (75.6% vs 72.6%, respectively).⁸

In the phase 3 trials, rates of overall adverse events, infections, or discontinuations due to adverse events were not statistically different between groups. In BLISS-52, there were more cases of diarrhea in the belimumab groups (9.7% for 1 mg/kg, 10.3% for 10 mg/kg, 7.0% for placebo). In BLISS-76, 7 cases of malignancy were reported; 4, 2, and 1 in the belimumab 1 mg/kg, belimumab 10 mg/kg, and placebo groups, respectively. Details about the types of malignancy have not yet been reported. No cases of malignancy were reported in BLISS-52. In both phase 3 trials, a total of 12 deaths were reported; 4, 5, and 3 deaths in the belimumab 1 mg/kg, belimumab 10 mg/kg, and placebo groups, respectively. Nine of the deaths were in the BLISS-52 trial; 2, 4, and 3 deaths in the belimumab 1 mg/kg, belimumab 10 mg/kg, and placebo groups respectively. 10 Causes were only reported for a portion of the deaths in BLISS-52; three of the deaths in the belimumab groups were due to infections and one patient in the placebo group died of cardiac arrest following sepsis. Causes of death from BLISS-76 have not been reported.

Drug Interactions -

Currently, there is limited data available regarding potential drug interactions with belimumab. A phase 1 trial evaluated the use of belimumab concomitantly with other standard SLE therapies such as prednisone, antimalarials, NSAIDs, methotrexate, azathioprine, and mycophenolate mofetil and no changes in pharmacokinetic parameters were observed.⁶ However, an increased risk of infection when administered with other immunosuppressants cannot be ruled out.

Dosing and Administration -

Clinical trials have evaluated belimumab administered via IV continuous infusion over 2 hours.^{6,8} Patients were given doses at days 0, 14, and 28, and then every 28 days thereafter. Phase 3 trials evaluated 1 mg/kg and 10 mg/kg. The approved dose is 10 mg/kg at 2-week intervals for the first 3 weeks and at 4-week intervals. It is administered as an IV infusion only, over 1 hour. Patients should be monitored for anaphylaxis reaction. Belimumab is not renally eliminated, so it is unlikely that dosing adjustments are needed for patients with renal insufficiency.⁶ The necessity for dosage adjustment in patients with hepatic insufficiency is unknown at this time.

Indications and Usage -

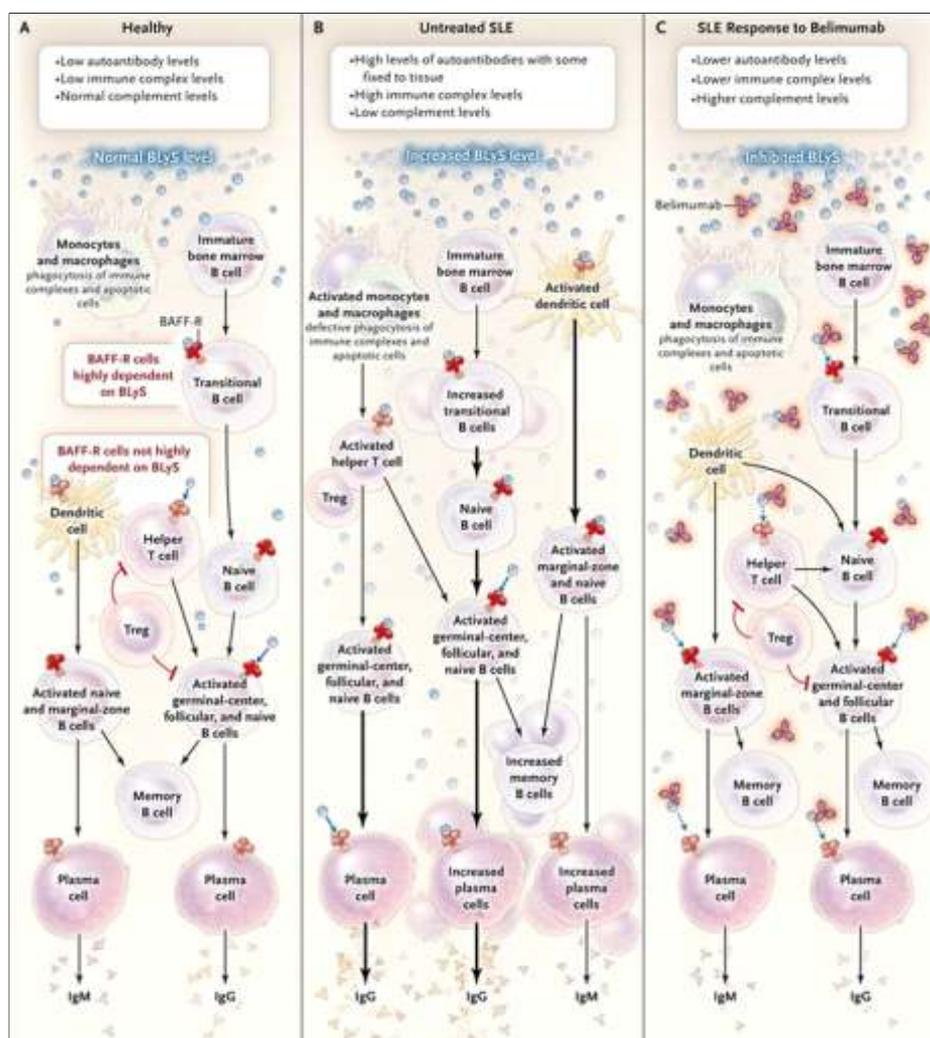
BENLYSTA[®] (belimumab) is indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.

Limitations of Use -

The efficacy of BENLYSTA has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. BENLYSTA has not been studied in combination with other biologics or intravenous cyclophosphamide.

Source of support : Nil

Conflict of interest : None declared



Mechanism of Action Belimumab

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