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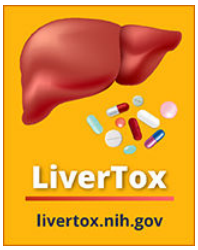

Belimumab

Updated: December 28, 2020.

OVERVIEW

Introduction

Belimumab is a human monoclonal antibody to the soluble B-lymphocyte stimulator (BLsY) which is used in the therapy of systemic lupus erythematous. Belimumab has been linked to an uncommon incidence of transient serum enzyme elevations during therapy, but has yet to be linked to instances of clinically apparent liver injury.

Background

Belimumab (be lim' ue mab) is a human monoclonal IgG1 antibody to the B-lymphocyte stimulator (BLyS, B cell activating factor), a growth factor required for B cell activation, survival, maturation into plasma cells and immunoglobulin production. Belimumab binds to soluble BLyS and blocks its binding to B cell receptors, which results in a depletion of activated B cells. This monoclonal antibody has been shown to be effective in reducing disease activity in patients with systemic lupus erythematosus, a disease marked by elevated levels of soluble BLyS, B cell dysregulation and production of pathogenic autoantibodies and immune complexes. Belimumab was approved for use in the United States in 2011 and current indications are for treatment of children (ages 5 years and above) and adult patients with active, autoantibody positive systemic lupus erythematosus (SLE) who are receiving standard therapy. It is also approved as therapy for lupus nephritis. Belimumab is available in two forms under the brand name Benlysta: as a lyophilized powder in 120 and 400 mg single dose vials for intravenous use in children or adults, or as a solution of 200 mg/mL a prefilled autoinjector or singe-dose syringe for subcutaneous use in adults only. For the intravenous formulation, the recommended dose is 10mg/kg every 2 weeks for 3 doses and then every 4 weeks. Premedication with an antihistamine is recommended. For the subcutaneous formulation, the dose is 200 mg once weekly. Adverse effects include infusion reactions, nausea, diarrhea, headache, insomnia, depression, pain in the extremities and low grade fever. Rare, but potentially serious side effects include anaphylactic reactions, serious infections, progressive multifocal leukoencephalopathy (PML), depression and suicide.

Hepatotoxicity

In publications on the large scale trials of belimumab, elevations in serum aminotransferase levels were uncommon (less than 1%) and no more frequent during belimumab therapy than in placebo treated controls. In the prelicensure studies there were no reports of clinically apparent liver injury attributed to belimumab and, since its approval and more wide scale use, there have been no case reports of liver injury with jaundice linked to belimumab therapy. Reactivation of hepatitis B can occur with use of immunosuppressive monoclonal antibodies such as infliximab and adalimumab, but instances have not been reported with belimumab. However, belimumab does result in a decrease in circulating B cells and immunoglobulin levels and thus might be a cause

of reactivation of HBV replication in a susceptible patient. Nevertheless, severe liver injury has not been reported with use of belimumab.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The cause of the rare serum enzyme elevations during belimumab therapy is not known. Monoclonal antibodies are generally metabolized to small peptides and amino acids by multiple tissues including the liver and are not intrinsically toxic to hepatocytes. Most clinically significant liver injury induced by monoclonal antibodies is due to induction of autoimmunity or reactivation of hepatitis B.

Outcome and Management

The serum aminotransferase elevations that have been reported during belimumab therapy were generally transient, mild and asymptomatic and did not require dose modification or delay in therapy. Elevations above 5 times the upper limit of normal should lead to more careful monitoring and suspension of further infusions, at least until levels return to normal or near normal levels. There is no evidence of cross sensitivity to hepatic reactions among the various monoclonal antibodies.

Drug Class: Monoclonal Antibodies; Immunosuppressive Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Belimumab – Benlysta®

DRUG CLASS

Immunosuppressive Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Belimumab	356547-88-1	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 28 December 2020

Abbreviations: PML, progressive multifocal leukoencephalopathy; SLE, systemic lupus erythematosus.

Zimmerman HJ. Drugs used to treat rheumatic and musculospastic disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 517-54.

(Expert review of hepatotoxicity published in 1999, well before the availability of most antibody therapies).

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 569-91.

(Review of hepatotoxicity of immunosuppressive agents does not mention belimumab).

Krensky AM, Azzi JR, Hafler DA. Immunosuppressants and toleragens. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 637-53.

(Textbook of pharmacology and therapeutics).

Furie R, Stohl W, Ginzler EM, Becker M, Mishra N, Chatham W, Merrill JT, et al; Belimumab Study Group. 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. 2008;10:R109. PubMed PMID: 18786258.

(Among 70 patients with systemic lupus erythematosus [SLE] given 1 to 2 infusions of 4 doses of belimumab or placebo, CD20+ B cells decreased, but indices of disease activity did not change; ALT elevations above 5 times ULN occurred in 1 of 57 belimumab vs none of 13 placebo recipients).

Wallace DJ, Stohl W, Furie RA, Lisse JR, McKay JD, Merrill JT, Petri MA, et al. A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. Arthritis Rheum. 2009;61:1168–78. PubMed PMID: 19714604.

(Among 449 patients with SLE treated with 3 doses of belimumab or placebo for 52 weeks, rates of adverse events were similar except for urticarial [4% vs 0%], no mention of ALT elevations or hepatotoxicity).

Jacobi AM, Huang W, Wang T, Freimuth W, Sanz I, Furie R, Mackay M, et al. Effect of long-term belimumab treatment on B cells in systemic lupus erythematosus: extension of a phase II, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum. 2010;62:201–10. PubMed PMID: 20039404.

(Analysis of 17 patients treated with belimumab long term showed decreases in B cells and IgM levels, but not in T cells, IgG or anti-dsDNA levels).

Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, Li EK, et al; BLISS-52 Study Group. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377(9767):721–31. PubMed PMID: 21296403.

(Among 865 patients with SLE treated with two doses of belimumab or placebo for 52 weeks, adverse events were similar in the 3 groups; 3 patients developed anaphylactoid reactions; no mention of ALT elevations or hepatotoxicity).

Sanz I, Yasothan U, Kirkpatrick P. Belimumab. Nat Rev Drug Discov. 2011;10:335–6. PubMed PMID: 21532557.

(Short review of the development, mechanism of action, efficacy, safety and market value of belimumab).

Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D, Sanchez-Guerrero J, et al; BLISS-76 Study Group. 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. PubMed PMID: 22127708.

(Among 819 patients with SLE treated with one of two doses of belimumab or placebo for 52 weeks, a higher proportion of those treated with 10 mg/kg met the response criteria at week 52 [43%] than those treated with 1 mg/kg [41%] or placebo [34%], while rates of most adverse events were similar and ALT elevations were not mentioned; infusions reactions and depression were more frequent with belimumab).

Belimumab (Benlysta) for systemic lupus erythematosus. Med Lett Drugs Ther. 2011;53(1366):45–6. PubMed PMID: 21659968.

(Concise summary of the mechanism of action, efficacy, safety and costs of belimumab for SLE mentions that belimumab can modestly reduce disease activity, and common side effects are infusion reactions, nausea, diarrhea and fever; no mention of ALT elevations or hepatotoxicity).

Gamble RG, Dellavalle RP. A randomized controlled trial of belimumab for the treatment of active systemic lupus erythematosus. Arch Dermatol. 2012;148:376–8. PubMed PMID: 22431778.

(Commentary on Navarra [2011]).

Merrill JT, Ginzler EM, Wallace DJ, McKay JD, Lisse JR, Aranow C, Wellborne FR, et al; LBSL02/99 Study Group. Long-term safety profile of belimumab plus standard therapy in patients with systemic lupus erythematosus. Arthritis Rheum. 2012;64:3364–73. PubMed PMID: 22674457.

(Analysis of 1165 patient years of exposure to belimumab during the first 4 years of treatment, states that infusion reactions occurred only during the first year of treatment and that liver test abnormalities [≥grade 3] occurred in <2% of patients and did not increase over time).

Manzi S, Sánchez-Guerrero J, Merrill JT, Furie R, Gladman D, Navarra SV, Ginzler EM, et al; BLISS-52 and BLISS-76 Study Groups. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis. 2012;71:1833–8. PubMed PMID: 22550315.

(Combined analysis of trials reported by Furie [2011] and Navarra [2011]).

Wallace DJ, Navarra S, Petri MA, Gallacher A, Thomas M, Furie R, Levy RA, et al. BLISS-52 and -76, and LBSL02 Study Groups. 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. PubMed PMID: 23213069.

(Pooled data on safety from 3 large trials of belimumab in patients with SLE found similar rates of serious infusion reactions, serious infections and malignancies in placebo vs belimumab treated subjects; no mention of ALT elevations or hepatotoxicity).

Hahn BH. Belimumab for systemic lupus erythematosus. N Engl J Med. 2013;368:1528–35. PubMed PMID: 23594005.

(Review of the clinical features and pathogenesis of SLE and the mechanism of action, efficacy and safety of belimumab in its treatment; in combined studies, responses occurred in 51% of belimumab vs 39% of placebo recipients; adverse events include infusion reactions, depression of serious infections; no mention of ALT elevations of hepatotoxicity).

Stohl W, Merrill JT, McKay JD, Lisse JR, Zhong ZJ, Freimuth WW, Genovese MC. Efficacy and safety of belimumab in patients with rheumatoid arthritis: a phase II, randomized, double-blind, placebo-controlled, dose-ranging Study. J Rheumatol. 2013;40:579–89. PubMed PMID: 23547209.

(Among 283 patients with active rheumatoid arthritis treated with one of 3 doses of belimumab or placebo for 24 weeks followed by an open label 24 week extension, responses were higher at 24 weeks with belimumab [29% vs 16%] and adverse events, that were more frequent with belimumab, included infusion reactions [13% vs 6%], but ALT elevations were not mentioned).

Askanase AD, Yazdany J, Molta CT. Post-marketing experiences with belimumab in the treatment of SLE patients. Rheum Dis Clin North Am. 2014;40:507–17. PubMed PMID: 25034159.

(Analysis of 3 postmarketing observational studies of belimumab focusing largely on efficacy; "No new safety signals were noted with regards to infections, malignancies, depression or deaths").

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. PubMed PMID: 24531080.

(40 year old woman with SLE developed neurological decline 10 months after starting belimumab infusions [while on mycophenolate mofetil and prednisone as well], with JC viral DNA detected in cerebral spinal fluid, a progressive downhill course and death within 6 months).

Sthoeger Z, Lorber M, Tal Y, Toubi E, Amital H, Kivity S, Langevitz P, et al. Anti-BLyS treatment of 36 Israeli systemic lupus erythematosus patients. Isr Med Assoc J. 2017;19:44–8. PubMed PMID: 28457114.

(Among 36 adults with SLE treated with belimumab for at least one year, it "was well tolerated without significant adverse events").

Ginzler EM, Wallace DJ, Merrill JT, Furie RA, Stohl W, Chatham WW, Weinstein A, et al; LBSL02/99 Study Group. Disease control and safety of belimumab plus standard therapy over 7 years in patients with systemic lupus erythematosus. J Rheumatol. 2014;41:300–9. PubMed PMID: 24187095.

(Among 449 patients with SLE treated with belimumab for up to 7 years, adverse events were reported as being stable and decreasing in frequency over time; no mention of ALT elevations, hepatotoxicity or deaths from liver disease).

Henegar CE, Eudy AM, Kharat V, Hill DD, Bennett D, Haight B. Progressive multifocal leukoencephalopathy in patients with systemic lupus erythematosus: a systematic literature review. Lupus. 2016;25:617–26. PubMed PMID: 26743322.

(Systematic review of the literature identified 35 cases of PML reported in patients with SLE, 3 of whom were on no immunosuppressive medications, but possibly implicated drugs included corticosteroids, cyclophosphamide, mycophenolate, azathioprine and rituximab [n=5], while only one had received belimumab).

Stohl W, Schwarting A, Okada M, Scheinberg M, Doria A, Hammer AE, Kleoudis C, et al. Efficacy and safety of subcutaneous belimumab in systemic lupus erythematosus: a fifty-two-week randomized, double-blind, placebo-controlled study. Arthritis Rheumatol. 2017;69:1016–27. PubMed PMID: 28118533.

(Among 836 patients with SLE treated with intravenous belimumab or placebo for 52 weeks, response rates were higher with belimumab while adverse events were similar; injection site reactions occurred in 6% vs 2%; no mention of ALT elevations or hepatotoxicity).

Furie RA, Wallace DJ, Aranow C, Fettiplace J, Wilson B, Mistry P, Roth DA, et al. Long-term safety and efficacy of belimumab in patients with systemic lupus erythematosus: a continuation of a seventy-six-week phase III parent study in the United States. Arthritis Rheumatol. 2018;70:868–77. PubMed PMID: 29409143.

(Among 268 patients with SLE enrolled in a long term extension trial of intravenous belimumab for up to 7 years, response rates continued to increase, and mean corticosteroid dosage decreased; while adverse events were mostly mild-to-moderate arthralgias, nausea, headache and infections, there were no deaths that were drug related and no mention of ALT elevations or hepatotoxicity; 10% of patients discontinued therapy because of adverse events).

van Vollenhoven RF, Navarra SV, Levy RA, Thomas M, Heath A, Lustine T, Adamkovic A, et al. Long-term safety and limited organ damage in patients with systemic lupus erythematosus treated with belimumab: a Phase III study extension. Rheumatology (Oxford). 2020;59:281–91. PubMed PMID: 31302695.

(Among 738 patients with SLE entered into an open-label extension trial after two 1-year randomized controlled trials of intravenous belimumab, adverse events decreased or remained stable over time and no deaths were attributed to drug toxicity; ALT elevations above 5 times ULN occurred in <1% of patients during the first 4 years and in none during the subsequent follow up period; no mention of hepatotoxicity, HBV reactivation or liver related severe adverse events).

Brunner HI, Abud-Mendoza C, Viola DO, Calvo Penades I, Levy D, Anton J, Calderon JE, et al; Paediatric Rheumatology International Trials Organisation (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG). Safety and efficacy of intravenous belimumab in children with systemic lupus erythematosus: results from a randomised, placebo-controlled trial. Ann Rheum Dis. 2020;79:1340–8. PubMed PMID: 32699034.

(Among 93 children with SLE treated with belimumab or placebo infusions every 4 weeks for 52 weeks, clinical responses were more frequent with belimumab [53% vs 44%] while adverse event rates were similar [79% vs 83%], although serious adverse event rates were less [17% vs 35%], and one patient on belimumab discontinued therapy because of aminotransferase elevations).

Furie R, Rovin BH, Houssiau F, Malvar A, Teng YKO, Contreras G, Amoura Z, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. N Engl J Med. 2020;383:1117–28. PubMed PMID: 32937045.

(Among 448 patients with lupus nephritis treated with intravenous belimumab of placebo for 2 years, a primary renal response was more frequent with belimumab [43% vs 32%], while overall and serious adverse event rates were similar between the two groups including herpes zoster [6% vs 4%], opportunistic infections [13% vs 15%], serious infections [4% vs 3%]; no mention of ALT elevations or hepatotoxicity).