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Benralizumab

Updated: July 5, 2018.

OVERVIEW

Introduction

Benralizumab is a humanized monoclonal antibody to the interleukin-5 (IL-5) receptor alpha which leads to a decrease in production and maturation of eosinophils and is used therapeutically to reduce allergic symptoms in patients with eosinophilic asthma. Benralizumab has not been associated with serum enzyme elevations during therapy or to instances of clinically apparent drug induced liver injury.

Background

Benralizumab (ben" ra liz' ue mab) is a recombinant, humanized IgG1 monoclonal antibody to the IL-5 receptor alpha which blocks the cytokine from inducing maturation and proliferation of eosinophils [3,12]. IL-5 is a cytokine growth and stimulating factor which has a selective role in recruiting eosinophils from the bone marrow and promoting their differentiation, activation and survival [4,5]. Both circulating and sputum eosinophils are decreased by benralizumab therapy and these effects are reversed when it is discontinued. Benralizumab therapy has been shown to reduce the requirement for inhaled corticosteroids and lower the frequency of exacerbations of eosinophilic asthma [6-12]. Benralizumab was approved for use in the United States in 2017 for therapy of patients 12 years and above with severe eosinophilic asthma resistant to standard therapy with inhaled corticosteroids. Benralizumab is available in solution in single use syringes of 30 mg under the brand name Fasenra. The recommended dose is 30 mg given subcutaneously every 4 weeks for 3 doses, followed by every 8 weeks thereafter. Side effects are not common, but can include injection site reactions, headache and oropharyngeal pain. Severe adverse reactions attributed to benralizumab include hypersensitivity reactions such as urticaria, angioedema and anaphylaxis, but these are rare [3].

Hepatotoxicity

In large clinical trials, rates of serum aminotransferase and alkaline phosphatase elevations were similar in patients receiving benralizumab as in those on placebo [6-11]. Indeed, rates of most adverse reactions were similar in patients who received placebo injections or standard care. In prelicensure trials in more than 200 patients, there were no instances of clinically apparent liver injury with jaundice and since its approval and more wide scale use, there have been no published reports of hepatotoxicity attributed to benralizumab therapy. Thus, liver injury from benralizumab must be rare, if it occurs at all.

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

Mechanism of Liver Injury

Benralizumab is a humanized monoclonal antibody and is unlikely to be inherently hepatotoxic. Recombinant proteins are usually metabolized in the cells on which they act but are also metabolized in the liver, largely to small peptides and amino acids which may be reused to synthesize proteins and are unlikely to be toxic or immunogenic [1,2]. Benralizumab lowers serum eosinophil counts, which seems to have no adverse effects on the liver and does not result in significant immunosuppression [5].

Drug Class: Antiasthmatic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Benralizumab – Fasenra®

DRUG CLASS

Antiasthmatic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Benralizumab	1044511-01-4	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 05 July 2018

Abbreviations: COPD, chronic obstructive pulmonary disease; IL-5, interleukin-5.

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 before the availability of benralizumab; "the biological immuno-suppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists").

Barnes PJ. Pulmonary pharmacology. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1031-65.

(Textbook of pharmacology and therapeutics).

Available at: https://www.accessdata.fda.gov/scripts/cder/daf/

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy).

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Ogbogu PU, Bochner BS, Butterfield JH, Gleich GJ, Huss-Marp J, Kahn JE, Leiferman KM, et al. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. J Allergy Clin Immunol 2009; 124: 1319-25. e3. PubMed PMID: 19910029.

(Among 188 patients with hypereosinophilic syndrome seen at 11 referral centers in the US between 2001 and 2006, 55% were male, ages 6 to 85 [median=45] years, most patients responded to corticosteroids and resistant cases often responded to therapy with monoclonal antibody to IL5).

Gleich GJ, Klion AD, Lee JJ, Weller PF. The consequences of not having eosinophils. Allergy 2013; 68: 829-35. PubMed PMID: 23742015.

(Review data on patients treated with monoclonal antibody to IL5 for several years failed to show any identifiable, long term adverse effects of inhibition or decrease in eosinophil counts).

Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, Gossage DL, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med 2014; 2: 879-90. PubMed PMID: 25306557.

(Among 324 adults with uncontrolled eosinophilic asthma treated with benralizumab [2, 20 or 100 mg every 4-8 weeks] vs placebo, rates of exacerbation were reduced with the 100 mg dose of benralizumab compared to placebo, while adverse event rates were similar except for nasopharyngitis and injection site reactions; no mention of ALT elevations or hepatotoxicity).

Brightling CE, Bleecker ER, Panettieri RA Jr, Bafadhel M, She D, Ward CK, Xu X, et al. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. Lancet Respir Med 2014; 2: 891-901. PubMed PMID: 25208464.

(Among 101 patients with chronic obstructive lung disease and sputum eosinophilia treated with injections of benralizumab [100 mg every 4-8 weeks] or placebo for 48 weeks, rates of acute exacerbation were similar in the two groups as were rates of adverse events).

Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, Sproule S, et al.; SIROCCO study investigators. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β(2)-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016; 388(10056): 2115-27. PubMed PMID: 27609408.

(Among 1205 patients with severe uncontrolled asthma treated with benralizumab [30 mg every 4 or 8 weeks] or placebo for 48 weeks, rates of exacerbation were lower with benralizumab compared to placebo and the reduction was most clear in those with preexisting eosinophilia; overall and serious adverse event rates were similar in all groups; no mention of ALT elevations or hepatotoxicity).

FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, Ferguson GT, et al.; CALIMA study investigators. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2016; 388 (10056): 2128-41. PubMed PMID: 27609406.

(Among 1306 patients with severe, uncontrolled eosinophilic asthma treated with benralizumab [30 mg in two dose regimens] or placebo for 48 weeks, exacerbation rates were lower with benralizumab while adverse event rates were similar).

Nixon J, Newbold P, Mustelin T, Anderson GP, Kolbeck R. Monoclonal antibody therapy for the treatment of asthma and chronic obstructive pulmonary disease with eosinophilic inflammation. Pharmacol Ther 2017; 169: 57-77. PubMed PMID: 27773786.

(Review of the role of eosinophils in asthma and chronic obstructive lung disease and clinical efficacy of monoclonal antibodies to IL5 including reslizumab and mepolizumab).

Ferguson GT, FitzGerald JM, Bleecker ER, Laviolette M, Bernstein D, LaForce C, Mansfield L, et al.; BISE Study Investigators. Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 2017; 5: 568-76. PubMed PMID: 28545978.

(Among 211 patients with mild-to-moderate asthma treated with benralizumab [30 mg every 4 weeks] or placebo for 12 weeks, improvements in forced expiratory volume and symptoms were minimally better with benralizumab than placebo and adverse event rates were similar).

Benralizumab (Fasenra) for severe eosinophilic asthma. Med Lett Drugs Ther 2018; 60 (1541): 33-35. PubMed PMID: 29485975.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of benralizumab shortly after its approval as therapy of eosinophilic asthma in the US; mentions adverse event rates were similar with benralizumab as placebo and does not mention ALT elevations or hepatotoxicity).