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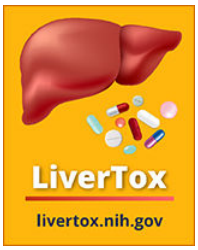

Reslizumab

Updated: March 14, 2017.

OVERVIEW

Introduction

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

Background

Reslizumab (res liz' ue mab) is a recombinant, humanized IgG4 monoclonal antibody to IL-5 which binds to the circulating cytokine and blocks its ability to cause maturation and proliferation of eosinophils. 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. Reslizumab lowers eosinophil counts in patients with hypereosinophilia as well as in normal, healthy controls. Therapy with reslizumab has been shown to reduce the requirement for inhaled corticosteroids and lower the frequency of exacerbations of eosinophilic asthma and other conditions associated with severe hypereosinophilia. Reslizumab was approved for use in the United States in 2016 for therapy of adult patients with severe eosinophilic asthma resistant to standard therapy with inhaled corticosteroids. Reslizumab is available in solution in single use vials of 100 mg in 10 mL (10 mg/mL) under the brand name Cinqair. The recommended dose is 3 mg/kg given intravenously over 20 to 30 minutes every 4 weeks. Side effects are not common, but can include injection site reactions, muscle pain, oropharyngeal pain, back pain, fatigue, nausea and creatine kinase (CK) elevations. Reslizumab can also cause severe hypersensitivity reactions including anaphylaxis, for which reason it should be administered in a health care setting and patients observed during and for a period of time after the infusion.

Hepatotoxicity

In large clinical trials, reslizumab was not associated with changes in serum aminotransferase levels during therapy, and rates of most adverse reactions were similar in patients who received placebo injections or standard care. There have been no published reports of clinically apparent acute liver injury attributed to reslizumab therapy. Thus, liver injury from reslizumab must be rare, if it occurs at all.

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

Mechanism of Injury

Reslizumab 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. Reslizumab lowers serum eosinophil counts, which seems to have no adverse effects on the liver and does not result in significant immunosuppression.

Drug Class: Antiasthmatic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Reslizumab – Cinqair®

DRUG CLASS

Antiasthmatic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Reslizumab	**241473-69-8**	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 14 March 2017

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 monoclonal 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; "the biological immuno-suppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists"; reslizumab is not specifically mentioned).

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).

Rothenberg ME, Klion AD, Roufosse FE, Kahn JE, Weller PF, Simon HU, Schwartz LB, et al.; Mepolizumab HES Study Group. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. N Engl J Med 2008; 358: 1215-28. PubMed PMID: 18344568.

(Among 84 patients with hypereosinophilic syndromes treated with mepolizumab or placebo intravenously every 4 weeks for 32 weeks, reduction in daily corticosteroid dose was more frequent with treatment and side effects were similar; while there were "no clinically relevant trends" in laboratory tests, one mepolizumab treated subject developed "hepatitis", but no details given).

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 6-85 [median=45] years, most responded to corticosteroids and resistant cases of therapy with monoclonal antibody to IL5).

Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, Wilkins HJ, et al.; Res-5-0010 Study Group. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med 2011; 184: 1125-32. PubMed PMID: 21852542.

(Among 106 patients with poorly controlled eosinophilic asthma treated with reslizumab or placebo injections every 4 weeks for 12 weeks, symptoms and pulmonary function improved more with reslizumab, adverse events rates were similar in the two groups, and there were "no clinically meaningful changes in laboratory values").

Spergel JM, Rothenberg ME, Collins MH, Furuta GT, Markowitz JE, Fuchs G 3rd, O'Gorman MA, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol 2012; 129: 456-63. PubMed PMID: 22206777.

(Among 226 children or adolescents with eosinophilic esophagitis treated with reslizumab [1, 2 or 3 mg/kg] or placebo every 4 weeks for 12 weeks, eosinophil counts in the esophagus decreased with reslizumab, but there were no differences in symptom scores or in adverse events between the two groups).

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).

Hilvering B, Xue L, Pavord ID. Evidence for the efficacy and safety of anti-interleukin-5 treatment in the management of refractory eosinophilic asthma. Ther Adv Respir Dis 2015; 9: 135-45. PubMed PMID: 25900924.

(Review of the efficacy and safety of monoclonal anti-IL5 therapy in asthma; mentions that side effect rates are similar to those with placebo and neutralizing antibodies have not been a problem; no mention of ALT elevations or hepatotoxicity).

Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, Murphy K, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015; 3: 355-66. PubMed PMID: 25736990.

(Among 953 adults with poorly controlled eosinophilic asthma treated with reslizumab [3 mg/kg] or placebo injections every 4 weeks for one year, there was a 50% reduction in episodes of acute asthma with reslizumab, but side effects were similar in the two groups; no mention of ALT elevations or hepatotoxicity, but mention of two cases of anaphylaxis after reslizumab infusions).

Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. Chest 2016; 150: 789-98 PubMed PMID: 27056586.

(Among 315 patients with poorly controlled eosinophilic asthma treated with reslizumab [0.3 or 3 mg/kg] or placebo every 4 weeks for 16 weeks, reslizumab was associated with an improvement in FEV1 and asthma symptoms and slight increase in rates of headache, nausea and vomiting, but there were no treatment related serious adverse events and no mention of ALT elevations or hepatotoxicity).

Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. Chest 2016; 150: 799-810. PubMed PMID: 27018175.

(Among 492 patients with poorly controlled asthma treated with reslizumab [3 mg/kg] or placebo every 4 weeks for 16 weeks, beneficial effects were limited to patients with baseline eosinophilia above 400 cells/μL, and chemistry results "did not reveal any meaningful treatment effect").

Mepolizumab (Nucala) for severe eosinophilic asthma. Med Lett Drugs Ther 2016; 58 (1486): 11-2. PubMed PMID: 26761344.

(Concise summary of the mechanism of action, clinical efficacy, safety and costs of mepolizumab shortly after its approval in the US for eosinophilic asthma; mentions side effects of headache, back pain, fatigue and infusion site reactions, but does not mention ALT elevations or hepatotoxicity).

Reslizumab (Cinqair) for severe eosinophilic asthma. Med Lett Drugs Ther 2016; 58 (1497): 81-2. PubMed PMID: 27305070.

(Concise summary of the mechanism of action, clinical efficacy, safety and costs of reslizumab shortly after its approval in the US; mentions side effects of oropharyngeal pain, CK elevations and myalgia and serious adverse events of anaphylaxis [0.3%] and malignancy, but does not mention ALT elevations or hepatotoxicity).

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).