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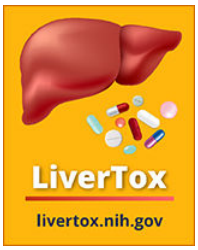

Anthrax Antitoxins

Updated: March 27, 2017.

OVERVIEW

Introduction

High titers of antibody to infectious bacteria and viruses can be used to both prevent and treat infectious diseases. In particular, antitoxins have been shown to be beneficial in several forms of severe acute infections such as diphtheria, rabies and anthrax. The recent use of active anthrax spores as a bioweapon, particularly in acts of terror, has renewed research efforts to develop potent, rapidly active means of prevention and treatment of anthrax after purposeful or accidental exposure. Several monoclonal antibodies to anthrax antigens have been developed as part of research efforts in bioterrorism, of which two are commercially available: raxibacumab (2012) and obiltoxaximab (2016). These two agents were approved for use based upon the so called "Animal Rule", which allows FDA approval based upon efficacy as shown in animal models of severe infectious diseases and upon safety data developed in healthy volunteers. Both monoclonal antibodies have had limited use in humans, but neither has been associated with serum enzyme elevations or with instances of clinically apparent liver injury during the limited preclinical safety evaluation in healthy volunteers. Updated information on prevention and treatment of anthrax is available from the Centers for Disease Control and Prevention on their website: https://www.cdc.gov/anthrax/index.html.

OVERVIEW

Introduction

Obiltoxaximab is a chimeric monoclonal antibody to the protective antigen of B. anthracis that is used to prevent and treat inhalation anthrax. Obiltoxaximab has had limited use in humans, but has not been associated with serum enzyme elevations during therapy or with instances of clinically apparent liver injury.

Background

Obiltoxaximab (oh" bil tox ax i mab) is a human-mouse chimeric monoclonal antibody to the Bacillus anthrax protective antigen that is the major immunogenic antigen produced by the bacterial infection. The binding of obiltoxaximab to the anthrax protective antigen blocks the binding of the bacterial toxin to host cells. In several animal models of inhalation anthrax, obiltoxaximab ameliorated the course of the disease and, if given before the onset of signs and symptoms, prevented clinically apparent disease. Obiltoxaximab was approved for use in the United States in 2016 for the prevention and treatment of inhalation anthrax. The approval was based upon the efficacy of obiltoxaximab in animal models of anthrax and on data on safety and pharmacokinetics in healthy human volunteers. Human anthrax is exceedingly rare, but has occurred in the United States as a result of acts of terrorism. Obiltoxaximab is available in single use vials of 600 mg in 6 mL (100 mg/mL) under the brand name

Anthim. The recommended dose is 16 mg/kg by slow (90 minute) intravenous infusion in adults and children above 40 kg in weight. Side effects were assessed in studies done in several hundred healthy adult volunteers. While described as "generally well tolerated" adverse events included headache, itching, rash, urticaria and local infusion and hypersensitivity reactions including anaphylaxis. Premedication with diphenhydramine (an antihistamine) is recommended.

Hepatotoxicity

In human volunteer studies, obiltoxaximab was associated with local infusion and general hypersensitivity reactions, but clinical laboratory results were said to be unchanged over time. There have been no reports of hepatotoxicity associated with administration of obiltoxaximab.

Likelihood score: E (unlikely cause of liver injury, but it has had very limited use in humans).

Mechanism of Injury

Obiltoxaximab is a monoclonal antibody and is unlikely to be inherently hepatotoxic. Recombinant proteins are often 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.

Drug Class: Antiinfective Agents, Antitoxins; Monoclonal Antibodies

OVERVIEW

Introduction

Raxibacumab is a human monoclonal antibody to the protective antigen of B. anthracis that is used to prevent and treat inhalation anthrax. Raxibacumab has had limited use in humans, but has not been associated with serum enzyme elevations during therapy or with instances of clinically apparent liver injury.

Background

Raxibacumab (rax" ee bak' ue mab) is a human monoclonal IgG1 antibody to the Bacillus anthrax protective antigen, a major component of the lethal toxin of anthrax. The binding of raxibacumab to the anthrax protective antigen blocks the binding of the bacterial toxin to host cells. In several animal models of inhalation anthrax, raxibacumab ameliorated the course of the disease and, if given before the onset of signs and symptoms, prevented clinically apparent disease. Raxibacumab was approved for use in the United States in 2012 for the prevention and treatment (combined with appropriate antibiotics) of inhalation anthrax. The approval was based upon the efficacy of raxibacumab in animal models of anthrax and on data on safety and pharmacokinetics in healthy human volunteers. Human anthrax is exceeding rare, but has occurred in the United States as a result of acts of terrorism. Raxibacumab is available in single use vials of 1700 mg in 34 mL (50 mg/mL) under the brand name Raxibacumab. The recommended dose is 40 mg/kg by slow (135 minute) intravenous infusion in adults and children above 40 kg in weight. Side effects were assessed in studies done in several hundred healthy adult volunteers. While described as "generally well tolerated" and similar in rate to that in placebo recipients, adverse events included rash, pain, somnolence, and local infusion and hypersensitivity reactions. Premedication with diphenhydramine (an antihistamine) is recommended.

Hepatotoxicity

In human volunteer studies, raxibacumab was associated with local infusion and general hypersensitivity reactions, but clinical laboratory results remained unchanged. There have been no reports of hepatotoxicity associated with administration of raxibacumab.

Likelihood score: E (unlikely cause of liver injury, but it has had very limited use in humans).

Mechanism of Injury

Raxibacumab is a human monoclonal antibody and is unlikely to be inherently hepatotoxic. Recombinant proteins are often 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.

Drug Class: Antiinfective Agents, Antitoxins; Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Obiltoxaximab – Anthim®

Raxibacumab – Raxibacumab®

DRUG CLASS

Antiinfective Agents

COMPLETE LABELING (Obiltoxaximab)

COMPLETE LABELING (Raxibacumab)

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Obiltoxaximab	1351337-07-9	Monoclonal Antibody	Not Available
Raxibacumab	565451-13-0	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 27 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).

Migone TS, Subramanian GM, Zhong J, Healey LM, Corey A, Devalaraja M, Lo L, et al. Raxibacumab for the treatment of inhalational anthrax. N Engl J Med. 2009;361:135–44. PubMed PMID: 19587338.

(In both rabbits and monkeys exposed to lethal doses of B. anthracis spores, raxibacumab increased the survival rate, and antibody levels associated with protection in animals were readily achieved in humans given intravenous infusions of raxibacumab; adverse events included headache, upper respiratory tract infection, nausea, arm and leg pain, cough, and arthralgia, all of which were no more frequent with raxibacumab than with placebo).

Raxibacumab for anthrax. Med Lett Drugs Ther. 2013;55(1413):27–8. PubMed PMID: 23545582.

(Concise review of the mechanism of action, efficacy in animal studies and safety in human volunteer studies of raxibacumab shortly after its approval for use in the United States; mentions mild-to-moderate adverse effects, but does not mention ALT elevations or hepatoxicity).

Hendricks KA, Wright ME, Shadomy SV, Bradley JS, Morrow MG, Pavia AT, Rubinstein E, et al; Workgroup on Anthrax Clinical Guidelines. Centers for disease control and prevention expert panel meetings on prevention and treatment of anthrax in adults. Emerg Infect Dis. 2014;20(2):e130687. PubMed PMID: 24447897.

(Summary of recommendations on the prevention and treatment of anthrax from a symposium held by the CDC).

Huang E, Pillai SK, Bower WA, Hendricks KA, Guarnizo JT, Hoyle JD, Gorman SE, et al. Antitoxin treatment of inhalation anthrax: a systematic review. Health Secur. 2015;13:365–77. PubMed PMID: 26690378.

(Systematic review of the literature on animal studies of the efficacy of antitoxin therapy for anthrax).

Tsai CW, Morris S. Approval of raxibacumab for the treatment of inhalation anthrax under the US Food and Drug Administration "Animal Rule". Front Microbiol. 2015;6:1320. PubMed PMID: 26648915.

(Review of the animal and clinical data that supported the FDA approval of raxibacumab based upon the Animal Rule; no mention of ALT elevations or hepatotoxicity).

Huang B, Xie T, Rotstein D, Fang H, Frucht DM. Passive immunotherapy protects against enteric invasion and lethal sepsis in a murine model of gastrointestinal anthrax. Toxins (Basel). 2015;7:3960–76. PubMed PMID: 26426050.

(In a mouse model, administration of raxibacumab at the same time as gastrointestinal exposure to anthrax spores prevented lethal sepsis in over 90% of cases).

Migone TS, Bolmer S, Zhong J, Corey A, Vasconcelos D, Buccellato M, Meister G. Added benefit of raxibacumab to antibiotic treatment of inhalational anthrax. Antimicrob Agents Chemother. 2015;59:1145–51. PubMed PMID: 25487792.

(In rabbits exposed to lethal doses of anthrax spores, addition of raxibacumab to ciprofloxacin therapy improved the survival rate at 28 days [82% vs 65%]).

Nagy CF, Leach TS, Hoffman JH, Czech A, Carpenter SE, Guttendorf R. Pharmacokinetics and tolerability of obiltoxaximab: a report of 5 healthy volunteer studies. Clin Ther. 2016;38:2083–97.e7. PubMed PMID: 27568215.

(Among 340 healthy volunteers who received one or several doses of obiltoxaximab in phase 1 pharmacokinetic studies, adverse events included headache, itch, rash, urticaria and hypersensitivity reactions including anaphylaxis in 3 patients, while "clinical laboratory test results… were unremarkable and stable over time").

Yamamoto BJ, Shadiack AM, Carpenter S, Sanford D, Henning LN, Gonzales N, O'Connor E, et al. Obiltoxaximab prevents disseminated Bacillus anthracis infection and improves survival during pre- and postexposure prophylaxis in animal models of inhalational anthrax. Antimicrob Agents Chemother. 2016;60:5796–805. PubMed PMID: 27431219.

(In studies done in rabbits and macaques challenged with active anthrax spores, obiltoxaximab was highly effective in preventing overt disease and death when administered with antibiotics and prevented disease when administrated before onset).

Yamamoto BJ, Shadiack AM, Carpenter S, Sanford D, Henning LN, O'Connor E, Gonzales N, et al. Efficacy projection of obiltoxaximab for treatment of inhalational anthrax across a range of disease severity. Antimicrob Agents Chemother. 2016;60:5787–95. PubMed PMID: 27431222.

(Prediction of the efficacy of obiltoxaximab in humans based upon antibody levels achieved in animal studies).

Greig SL. Obiltoxaximab: First global approval. Drugs. 2016;76:823–30. PubMed PMID: 27085536.

(Review of the clinical features of anthrax in humans and the challenges of developing therapy and FDA criteria under the Animal Rule whereby efficacy can be established by studies in animals alone; in human volunteer studies, obiltoxaximab was "generally well tolerated", the major adverse events of concern being hypersensitivity reactions which arose in 5-10% of recipients of obiltoxaximab administered intravenously and occasionally qualified as being anaphylaxis).