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Bezlotoxumab

Updated: September 28, 2017.

OVERVIEW

Introduction

Bezlotoxumab is a human monoclonal antibody to the Clostridium difficile toxin B that is used to reduce the risk of recurrence in high risk patients being treated for C. difficile infection. Bezlotoxumab has not been associated with serum enzyme elevations during therapy or with instances of clinically apparent liver injury.

Background

Bezlotoxumab (bez" loe tox' ue mab) is a human monoclonal antibody to the C. difficile toxin B that has high affinity for the toxin, blocking its binding to host cells. In several large clinical trials, bezlotoxumab given at the time of antibacterial therapy was found to decrease the rate of recurrence of C. difficile infection. In these same studies, a companion molecule, actoxumab, a human monoclonal antibody to the C. difficile toxin A, was found to be ineffective. Bezlotoxumab was approved for use in the United States in 2016 and current indications are for prevention (not therapy) of recurrence of C. difficile infection in persons receiving antibiotic therapy who are at high risk for recurrence. Bezlotoxumab is available in single use vials of 1,000 mg in 40 mL (25 mg/mL) under the brand name Zinplava. The recommended regimen is a single infusion of 10 mg/kg given intravenously over 60 minutes during antibacterial treatment of C. difficile infection. Side effects are not common, but can include nausea, fever and headache. Rare, but potentially severe adverse events include hypersensitivity reactions and worsening of congestive heart failure.

Hepatotoxicity

In large clinical trials, bezlotoxumab 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 bezlotoxumab therapy. Thus, liver injury from bezlotoxumab must be rare, if it occurs at all.

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

Mechanism of Injury

Bezlotoxumab 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

Bezlotoxumab – Zinplava®

DRUG CLASS

Antiinfective Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Bezlotoxumab	1246264-45-8	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 28 September 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"; bezlotoxumab is not specifically mentioned).

Orth P, Xiao L, Hernandez LD, Reichert P, Sheth PR, Beaumont M, Yang X, et al. Mechanism of action and epitopes of Clostridium difficile toxin B-neutralizing antibody bezlotoxumab revealed by X-ray crystallography. J Biol Chem 2014; 289: 18008-21. PubMed PMID: 24821719.

(X-ray crystallography demonstration of binding of bezlotoxumab to C. difficile toxin B).

Hussack G, Tanha J. An update on antibody-based immunotherapies for Clostridium difficile infection. Clin Exp Gastroenterol 2016; 9: 209-24. PubMed PMID: 27536153.

(Review of the mechanisms of action of bezlotoxumab in prevention of recurrent C. difficile infection).

Mullard A. FDA approves antitoxin antibody. Nat Rev Drug Discov 2016; 15: 811. PubMed PMID: 27895330.

(News report of the FDA announcement of approval of bezlotoxumab for prevention of recurrence [but not treatment] of C. difficile infection).

Wilcox MH, Gerding DN, Poxton IR, Kelly C, Nathan R, Birch T, Cornely OA, et al.; MODIFY I and MODIFY II Investigators. Bezlotoxumab for prevention of recurrent Clostridium difficile infection. N Engl J Med 2017; 376: 305-317. PubMed PMID: 28121498.

(Among 2655 adults with C. difficile infection given bezlotoxumab or actoxumab or both or placebo during antibiotic therapy in 2 prospective randomized controlled trials, recurrence was less with bezlotoxumab [16-17%] compared to placebo [26-28%], while rates of adverse events were similar and there was no mention of ALT elevations or any liver related serious adverse events or deaths).

Bartlett JG. Bezlotoxumab - a new agent for Clostridium difficile infection. N Engl J Med 2017; 376: 381-382. PubMed PMID: 28121509.

(Editorial in response to Wilcox [2017] providing an overview of the history, epidemiology and burden of C. difficile infection and summarizing its current management).