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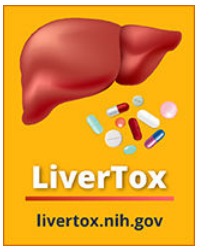

Lanadelumab

Updated: April 12, 2019.

OVERVIEW

Introduction

Lanadelumab is a human IgG1 monoclonal antibody to kallikrein which blocks the activation of bradykinin, a potent vasodilator responsible for the attacks of swelling, inflammation and pain in hereditary angioedema (HAE). Lanadelumab has been linked to a low rate of serum enzyme elevations during therapy, but has not been implicated in instances of clinically apparent acute liver injury.

Background

Lanadelumab (lan" a del' ue mab) is a human IgG1 monoclonal antibody to kallikrein, which inhibits its proteolytic activity, blocking the formation of bradykinin, a potent vasodilator, levels of which are increased during attacks of hereditary angioedema. HAE is a rare genetic disorder due to C1-inhibitor deficiency, an important mediator and regulator of plasma kallikrein activity. In clinical trials in patients with recurrent attacks of HAE, lanadelumab was found to reduce the frequency and severity of attacks and improve functional activity and quality of life. Lanadelumab was approved for use in HAE in the United States in 2018 and is currently available as a solution in single dose vials of 300 mg in 2 mL (150 mg/mL) under the commercial name Takhzyro. The recommended dose is 300 mg subcutaneously every 2 or 4 weeks. Side effects are not common, but can include injection site reactions, upper respiratory infections, headache, dizziness, myalgia, rash and diarrhea. Rare, but potentially severe adverse reactions include hypersensitivity reactions.

Hepatotoxicity

In preregistration trials in patients with HAE, serum ALT levels were elevated above 3 times the upper limit of normal in 6% of lanadelumab vs 0% of placebo recipients, but there were no instances of concurrent elevations in serum bilirubin and aminotransferase levels. The serum ALT and AST elevations generally arose after a month of therapy and continued to occur throughout treatment with no particular pattern. There were no hepatic serious adverse events, and only one patient discontinued lanadelumab early because of serum aminotransferase elevations (peak ALT 153 U/L), which resolved upon stopping. Since its approval, there have been no published cases of clinically apparent liver injury attributed to lanadelumab therapy, although the clinical experience with its use has been limited.

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

Mechanism of Injury

The mechanism by which lanadelumab might cause liver injury is unknown. Lanadelumab is a monoclonal antibody and, like other proteins, is metabolized into amino acids and is unlikely to have intrinsic toxicity. Inhibition of plasma kallikrein activity would not be expected to cause liver injury.

Outcome and Management

Lanadelumab therapy has been linked to rare instances of mild, transient serum enzyme elevations during therapy, typically arising at least a month after starting therapy. In patients who develop persistent elevations of serum ALT or alkaline phosphatase levels above 3 times ULN or who develop jaundice and symptoms, therapy should be interrupted.

Drug Class: Hematologic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Lanadelumab – Takhzyro®

DRUG CLASS

Hematologic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Lanadelumab	1426055-14-2	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 12 April 2019

Abbreviations used: HAE, hereditary angioedema.

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 monoclonal agents used in immunosuppressive regimens; mentions rituximab and problems of reactivation of hepatitis B, but also states that "the biological immunosuppressants are largely free

from hepatotoxicity, with the exception of the TNF alpha antagonists"; lanadelumab is not specifically mentioned).

Skidgel RA. Histamine, bradykinin, and their antagonists. In, Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 711-26.

(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; mentions that ALT elevations above 3 times ULN occurred in 6% of lanadelumab vs 0% of placebo treated subjects with HAE, but all elevations were transient, anicteric and asymptomatic, although in some cases, they led to treatment discontinuation).

(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; mentions that ALT elevations above 3 times ULN occurred in 6% of lanadelumab vs 0% of placebo treated subjects with HAE, but all elevations were transient, anicteric and asymptomatic, although in some cases, they led to treatment discontinuation).

Kenniston JA, Faucette RR, Martik D, Comeau SR, Lindberg AP, Kopacz KJ, Conley GP, et al. Inhibition of plasma kallikrein by a highly specific active site blocking antibody. J Biol Chem 2014; 289: 23596-608. PubMed PMID: 24970892.

(Description of a human monoclonal antibody with potent and specific affinity for plasma kallikrein, the serine protease that cleaves HMWK to release bradykinin, the proinflammatory peptide that mediates pain, swelling, vasodilation and inflammation and appears to be responsible for the acute attacks that occur in patients with HAE, who are deficient in serpin C1 inhibitor that regulates the kallikrein-kinin enzymatic pathway).

Banerji A, Busse P, Shennak M, Lumry W, Davis-Lorton M, Wedner HJ, Jacobs J, et al. Inhibiting plasma kallikrein for hereditary angioedema prophylaxis. N Engl J Med 2017; 376: 717-28. PubMed PMID: 28225674.

(Among 37 patients with HAE treated with 2 injections of lanadelumab [at 1 of 4 doses] or placebo 2 weeks apart, acute attacks were less in those given in highest doses [300 or 400 mg], adverse event rates were lower and there were no serious adverse events; no mention of ALT elevations or hepatotoxicity).

Banerji A, Riedl MA, Bernstein JA, Cicardi M, Longhurst HJ, Zuraw BL, Busse PJ, et al.; HELP Investigators. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. JAMA 2018; 320: 2108-21. PubMed PMID: 30480729.

(Among 125 patients with HAE in a placebo-controlled trial for 26 weeks, the mean monthly number of attacks was less with lanadelumab [0.26 and 0.48] than placebo [1.97], while adverse events that were more frequent were injection site reactions and headaches; one patient had elevations of ALT [140 U/L] and AST [143 U/L] during treatment that resolved with discontinuation).

Syed YY. Lanadelumab: first global approval. Drugs 2018; 78: 1633-7. PubMed PMID: 30267321.

(Review of the mechanism of action, history of development, pharmacology, clinical efficacy, safety and ongoing evaluation of lanadelumab as a means of prevention of HAE; mentions that aminotransferase elevations occurred with treatment but were "generally asymptomatic and transient, and were not serious").

Busse PJ, Farkas H, Banerji A, Lumry WR, Longhurst HJ, Sexton DJ, Riedl MA. Lanadelumab for the prophylactic treatment of hereditary angioedema with C1 inhibitor deficiency: a review of preclinical and phase I studies. BioDrugs 2019; 33: 33-43. PubMed PMID: 30539362.

(In phase 1 studies of lanadelumab there were "no clinically meaningful abnormalities or changes in laboratory parameters").