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Erenumab

Updated: August 8, 2018.

OVERVIEW

Introduction

Erenumab is a monoclonal antibody to the receptor for calcitonin gene related peptide which plays a role in inducing migraine headaches. Erenumab is used for prevention of migraine in patients with episodic or chronic migraine headaches. Erenumab therapy has not been associated with serum enzyme elevations during therapy nor has it been implicated in cases of clinically apparent drug induced liver injury with jaundice.

Background

Erenumab (e ren' ue mab) is a recombinant, human monoclonal IgG1 antibody to the calcitonin gene related peptide (CGRP) receptor which plays an important role in migraine headaches. CGRP is a neuropeptide found throughout the central and peripheral nervous systems which has potent vasodilator and pain signaling activities. Circulating levels of CGRP are elevated in patients with migraines, and the efficacy of migraine therapies (serotonin receptor agonists, ergot alkaloids) is associated with lowering of CGRP levels. Erenumab inhibits the CGRP receptor blocking the subsequent downstream activation of the intracellular signaling pathways. In several prospective controlled trials, erenumab given subcutaneously every 4 weeks was shown to decrease the migraine frequency in adult patients with frequent and poorly controlled migraine headaches. Erenumab was approved for use in the United States in 2018 as a means of prevention of migraine headaches. Erenumab in available in solution in single use prefilled syringes or autoinjectors of 70 mg under the brand name Aimovig. The recommended dose is 70 mg subcutaneously once monthly. Erenumab is not effective as therapy of acute migraine and lowers the frequency but typically does not abolish all episodes. Side effects of erenumab are uncommon but can include injection site reactions and constipation. Erenumab has not been associated with significant numbers of severe adverse events, however it has had limited general use and the effects of long term suppression of CGRP signaling are unknown but could theoretically increase the rate of serious cardiovascular or cerebrovascular ischemic events.

Hepatotoxicity

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

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

Mechanism of Liver Injury

Erenumab is a human monoclonal antibody and is unlikely to be inherently hepatotoxic. While most recombinant proteins are metabolized by the liver, the metabolism leads largely to small peptides and amino acids which may be reused to synthesize proteins and are unlikely to be toxic or immunogenic.

Drug Class: Migraine Headache Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Erenumab – Aimovig®

DRUG CLASS

Migraine Headache Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Erenumab	1582205-90-0	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 08 August 2018

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"; erenumab is not discussed).

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"; erenumab is not discussed).

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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Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, Sapra S, et al. A controlled trial of erenumab for episodic migraine. N Engl J Med 2017; 377: 2123-32. PubMed Citation (Among 955 patients with frequent migraine headaches treated with erenumab [70 or 140 mg] or placebo injections once monthly for 6 months, migraine frequency decreased more with erenumab therapy and there were no differences in adverse event rates among the 3 groups, including "no clinically meaningful differences…with regard to the results of hepatic-function testing…" with no patients developing ALT or AST elevations above 5 times ULN during therapy).

Tepper S, Ashina M, Reuter U, Brandes JL, Doležil D, Silberstein S, Winner P, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol 2017; 16: 425-34. PubMed Citation (Among 667 patients with chronic migraine treated with erenumab [70 or 140 mg] or placebo every 4 weeks for 12 weeks, monthly migraine days decreased more with erenumab [-6.6 vs -4.2 days] and adverse event rates were similar in all 3 groups, one person on erenumab had a transient mild elevation of serum aminotransferase levels, but there were "no clinically significant abnormalities in…laboratory values…").

Ashina M, Dodick D, Goadsby PJ, Reuter U, Silberstein S, Zhang F, Gage JR, et al. Erenumab (AMG 334) in episodic migraine: Interim analysis of an ongoing open-label study. Neurology 2017; 89: 1237-43. PubMed Citation (Among 472 patients enrolled in open label extension trials of erenumab demonstrated the frequency of migraine headache was reduced for more than a year without new safety concerns and "there were no clinically significant changes in viral signs, laboratory values or ECG findings").

Erenumab (Aimovig) for migraine prevention. Med Lett Drugs Ther 2018; 60 (1549): 101-3. PubMed Citation (Concise review of the mechanism of action, clinical efficacy, safety and costs of erenumab shortly after its approval for use in the US; mentions minor side effects of injection site reactions and constipation, but makes no mention of ALT elevations or hepatotoxicity).

Edvinsson L. The CGRP pathway in migraine as a viable target for therapies. Headache 2018; 58 Suppl 1: 33-47. PubMed Citation (Review of the calcitonin gene related peptide [CGRP] and its receptor including their relationship to migraine headaches and development of small molecular inhibitors and monoclonal antibody therapies based upon their inhibition).

Dodick DW, Ashina M, Brandes JL, Kudrow D, Lanteri-Minet M, Osipova V, Palmer K, et al. ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia 2018; 38: 1026-37. PubMed Citation (Among 577 patients with episodic migraine treated with erenumab or placebo, monthly migraine days decreased more with erenumab [-2.9 vs -1.8 days]; overall adverse event rates were similar [48% vs 55%] and there were no liver related serious adverse events; no mention of changes in ALT levels or hepatotoxicity).