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Emicizumab

Updated: November 29, 2019.

OVERVIEW

Introduction

Emicizumab is a humanized bispecific monoclonal antibody to two human coagulation factors – factor IXa and factor X – that mimics the activity of factor VIII and is used to prevent bleeding episodes in patients with severe hemophilia A (which is caused by factor VIII deficiency). Emicizumab has not been linked to serum enzyme elevations during therapy or to instances of idiosyncratic acute liver injury.

Background

Emicizumab (e" mi ciz' ue mab) is a recombinant, humanized, bispecific monoclonal antibody to two human coagulation factors – factor IXa and factor X – that is used to prevent bleeding episodes in patients with severe hemophilia A. Hemophilia A is a serious genetic disease associated with deficiency in product of factor VIII leading to recurrent episodes of bleeding that result in major disability and premature death. Hemophilia A is typically treated with infusions of factor VIII isolated and concentrated from human plasma or produced by recombinant techniques. Some patients given factor VIII infusions, however, develop neutralizing antibodies which inhibit the anticoagulation activity of the infusions. Emicizumab is a recombinant bispecific monoclonal antibody that binds to both factor IXa and X, which mimics the co-factor function of factor VIII, bypassing its need in the coagulation cascade. In clinical trials, emicizumab was found to reduce bleeding episodes in patients with hemophilia A and antibodies to factor VIII. Emicizumab was approved for use for this indication in the United States in 2017. Emicizumab is available as a solution in single dose vials of 30, 60, 105 and 150 mg under the commercial name Hemlibra. The recommended dose is 3 mg/kg by subcutaneous injection once weekly for 4 weeks, followed by 1.5 mg/kg weekly. Side effects are not common, but can include headache, arthralgia and infection site reactions. Rare, but potentially severe adverse reactions may include hypersensitivity reactions and thromboembolic events.

Hepatotoxicity

In clinical trials of emicizumab in patients with hemophilia A serum enzyme levels were rarely mentioned and laboratory test results were described as being stable or unremarkable. In preregistration studies of emicizumab there were no reports of clinically apparent liver injury with jaundice. There have been no reports of acute liver failure, chronic hepatitis or vanishing bile duct syndrome associated with emicizumab therapy.

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

Mechanism of Liver Injury

The mechanism by which emicizumab might cause liver injury is unknown. Emicizumab is a monoclonal antibody and, like other proteins, is metabolized into amino acids and is unlikely to have intrinsic toxicity.

Drug Class: Hematologic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Emicizumab – Hemlibra®

DRUG CLASS

Hematologic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Emicizumab	1610943-06-0	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 20 October 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; 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"; eculizumab is not specifically mentioned).

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: ”No clinically significant changes in laboratory parameters were observed during treatment with emicizumab” and there were no instances of clinically apparent liver injury with jaundice).

Shima M, Hanabusa H, Taki M, Matsushita T, Sato T, Fukutake K, Fukazawa N, et al. Factor VIII-mimetic function of humanized bispecific antibody in hemophilia A. N Engl J Med 2016; 374: 2044-53. 27223146

(Among 18 Japanese patients with severe hemophilia A treated with 0.3, 1.0 or 3.0 mg/kg weekly for 12 weeks, bleeding rates decreased by 90% in all groups and 71-73% of patients had no bleeding episodes and there were no treatment related serious adverse events; no mention of ALT elevations or hepatotoxicity).

Shima M, Hanabusa H, Taki M, Matsushita T, Sato T, Fukutake K, Kasai R, et al. Long-term safety and efficacy of emicizumab in a phase 1/2 study in patients with hemophilia A with or without inhibitors. Blood Adv 2017; 1: 1891-9. 29296836

(Among 14 Japanese patients with severe hemophilia A who participated in a phase 1 trial [Shima 2016] and were continued on emicizumab for up to 33 months, bleeding rates remained low and therapy was "well tolerated" with no treatment related serious adverse events or thromboembolic events; no mention of ALT elevations or hepatotoxicity).

Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G, Santagostino E, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med 2017; 377: 809-18. 28691557

(Among 109 patients with hemophilia A and factor VIII inhibitors who were treated with weekly injections of emicizumab or placebo, bleeding events were 87% less in emicizumab treated subjects while side effects were similar except for injection site reactions [15% vs 8%] and thrombotic microangiopathy [2% vs none]; no mention of ALT elevations or hepatotoxicity).

Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, Mancuso ME, Schmitt C, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. N Engl J Med 2018; 379: 811-22. 30157389

(Among 152 patients with hemophilia A without factor VIII inhibitors who were treated with weekly or biweekly injections of emicizumab or no treatment, bleeding events were 958% less with emicizumab prophylaxis while side effects were similar except for injection site reactions, and there were on instances of thrombotic microangiopathy and no ALT elevations or hepatotoxicity).

Franchini M, Mannucci PM. Non-factor replacement therapy for haemophilia: a current update. Blood Transfus 2018; 16: 1-5. 29517971

(Review of efficacy and safety of non-factor VIII replacement therapy for hemophilia including use of emicizumab in patients with and without inhibitors; no mention of ALT elevations or hepatotoxicity).

Scott LJ, Kim ES. Emicizumab-kxwh: first global approval. Drugs 2018; 78: 269-74. 29357074

(Review of the development, mechanism of action, pharmacology, clinical efficacy and safety of emicizumab shortly after its approval for use in hemophilia A in the US; discusses adverse events of thromboembolism but does not mention ALT elevations or hepatotoxicity).