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Evinacumab

Updated: July 8, 2021.

OVERVIEW

Introduction

Evinacumab is a human monoclonal antibody to angiopoietin-like protein 3 which is approved for use in patients with homozygous familial hypercholesterolemia. Evinacumab is given intravenously every 4 weeks and is generally well tolerated, and has not been associated with serum aminotransferase elevations during therapy or with instances of clinically apparent liver injury.

Background

Evinacumab (e" vin ak' ue mab) is a human monoclonal IgG4 antibody directed against angiopoietin-like protein 3 (ANGPTL3) which is a protein expressed largely in the liver that inhibits lipoprotein lipase and endothelial lipase activity, two endogenous lipases which break down lipids in serum. Inhibition of ANGPTL3 by evinacumab causes preservation of full activity of both lipases resulting in a decrease in serum cholesterol and triglycerides levels. In preregistration randomized, placebo controlled trials, evinacumab resulted in a 45% to 55% decrease in total and LDL-cholesterol in patients with severe homozygous familial hypercholesterolemia who were already receiving maximum tolerated amounts of lipid lowering agents. Therapy also decreased serum triglyceride levels to a similar extent. Evinacumab was approved for use as an adjunct to cholesterol lowering therapy of familial hypercholesterolemia in adults and children 12 years of age or older the United States in 2021. It continues to be evaluated as therapy for hypertriglyceridemia and for refractory forms (both familial and non-familial) of hypercholesterolemia. Evinacumab is available in single use vials of 345 mg in 2.3 mL or 1200 mg in 8 mL (both 150mg/mL) under the brand name Evkeeza. The recommended dose is 15 mg/kg given intravenously over 60 minutes every 4 weeks. It can be administered with other lipid lowering oral agents including statins, ezetimibe, niacin and anti-PCSK9 monoclonal antibodies. Common side effects of evinacumab include mild local injection reactions, rhinorrhea, nasopharyngitis, dizziness, nausea, fatigue, and pain in the extremities. Rare instances of severe hypersensitivity reactions including anaphylaxis was been reported.

Hepatotoxicity

In preregistration randomized controlled studies, mild serum aminotransferase elevations arose a small percentage of treated patients but were generally asymptomatic and transient and did not require discontinuation or modification of dose. In addition, there were no reported instances clinically apparent liver injury or severe hepatic adverse events attributed to the therapy. Since approval and more general use of evinacumab there have been no reports of clinically significant liver injury attributed to its use, but the number of patients treated has been limited.

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

Mechanism of Injury

Possible mechanisms of liver injury due to evinacumab are not apparent. Monoclonal antibodies and immunoglobulins are generally taken up and metabolized intracellularly to short peptides and amino acids.

Drug Class: Monoclonal Antibodies, Antilipemic Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Evinacumab – Evkeeza®

DRUG CLASS

Antilipemic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Evinacumab	1446419-85-7	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 08 July 2021

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 before the availability of evinacumab).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761181Orig1s000MedR.pdf

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA clinical scientific review of the evinacumab application which mentions that there was "no evidence of CK, ALT, or AST elevation" with evinacumab and only ALT elevation above 5 times ULN occurred in a patient who had stopped therapy 3 months previously).

Dewey FE, Gusarova V, Dunbar RL, O'Dushlaine C, Schurmann C, Gottesman O, McCarthy S. Vet al. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. N Engl J Med. 2017;377:211–21. PubMed PMID: 28538136.

(Exon sequencing in large populations demonstrated rare loss-of-function mutations in the ANGPTL3 gene that was associated with lower levels of serum triglycerides and cholesterol and lower risk for coronary artery disease; inhibition of ANGPTL3 using evinacumab reduced triglyceride and cholesterol levels in a mouse model of dyslipidemia, and with similar effects were noted in a phase 1 trial in 83 patients with dyslipidemia, in which 7 of 62 subjects receiving evinacumab had transient serum ALT elevations).

Gaudet D, Gipe DA, Pordy R, Ahmad Z, Cuchel M, Shah PK, Chyu KY, et al. ANGPTL3 Inhibition in homozygous familial hypercholesterolemia. N Engl J Med. 2017;377:296–7. PubMed PMID: 28723334.

(Among 9 adults with homozygous familial hypercholesterolemia treated with evinacumab for 4 weeks, LDL cholesterol levels decreased by 49%, HDL cholesterol by 36%, and triglycerides by 47%; no mention of adverse events).

Ahmad Z, Banerjee P, Hamon S, Chan KC, Bouzelmat A, Sasiela WJ, Pordy R, et al. Inhibition of angiopoietin-like protein 3 with a monoclonal antibody reduces triglycerides in hypertriglyceridemia. Circulation. 2019;140:470–86. PubMed PMID: 31242752.

(Among 139 adults with hypertriglyceridemia enrolled in 2 studies of different single or multiple doses of evinacumab, there were no serious treatment related adverse events; serum ALT levels rose in 0-30% of evinacumab treated versus 0-8% of placebo recipients, but all elevations were self-limited and none required dose modification or were associated with clinically apparent liver injury).

Raal FJ, Rosenson RS, Reeskamp LF, Hovingh GK, Kastelein JJP, Rubba P, Ali S, et al. ELIPSE HoFH Investigators. Evinacumab for homozygous familial hypercholesterolemia. N Engl J Med. 2020;383:711–20. PubMed PMID: 32813947.

(Among 65 patients with homozygous familial hypercholesterolemia treated with intravenous evinacumab [15 mg/kg] vs placebo every 4 weeks for 24 weeks, changes in LDL cholesterol averaged -47% vs +1.9%, while adverse event rates were similar in both groups and ALT or AST elevations [all less than 5 times ULN] arose in 5% vs 10% and there were no treatment related serious adverse events).

Kersten S. Bypassing the LDL receptor in familial hypercholesterolemia. N Engl J Med. 2020;383:775–6. PubMed PMID: 32813955.

(Editorial on Raal et al [2000] stressing the rapid and dramatic decreases in total cholesterol and triglycerides that occur with evinacumab which has the advantage of acting independently of the LDL-receptor which makes it appropriate as therapy for homozygous familial hypercholesterolemia).

Rosenson RS, Burgess LJ, Ebenbichler CF, Baum SJ, Stroes ESG, Ali S, Khilla N, et al. Evinacumab in patients with refractory hypercholesterolemia. N Engl J Med. 2020;383:2307–19. PubMed PMID: 33196153.

(Among 272 patients with refractory [non-familial] hypercholesterolemia treated with different dose regimens of sc or iv evinacumab or placebo for 16 weeks, optimal doses reduced LDL cholesterol levels by 47-50%, and adverse events were common but generally mild except for a single instance of acute anaphylaxis; no mention of ALT elevations or hepatotoxicity).

Evinacumab (Evkeeza) for homozygous familial hypercholesterolemia. Med Lett Drugs Ther. 2021;63(1623):66–7. PubMed PMID: 33976097.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of evinacumab shortly after its approval for use in homozygous familial hypercholesterolemia in the US mentions common adverse events of nasopharyngitis, rhinorrhea, dizziness, nausea, infusion reactions, and rare instances of anaphylaxis; no mention of ALT elevations or hepatotoxicity).

Markham A. Evinacumab: first approval. Drugs. 2021;81:1101–5. PubMed PMID: 34003472.

(Review of the mechanism of action, history of development, pharmacology, clinical efficacy and safety of evinacumab shortly after its approval for use in familial hypercholesterolemia in the US, mentions adverse events of nasopharyngitis, rhinorrhea, dizziness, nausea, asthenia, pain in extremities and infusion reactions but does not mention ALT elevations or hepatotoxicity).