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Crizanlizumab

Updated: July 12, 2021.

OVERVIEW

Introduction

Crizanlizumab is a humanized monoclonal antibody to P-selectin which is used to prevent painful crises in sickle cell disease. Crizanlizumab is generally well tolerated and has not been associated with serum aminotransferase elevations during therapy or with instances of clinically apparent liver injury.

Background

Crizanlizumab (kriz an liz ue mab) is a humanized monoclonal IgG2 antibody directed against P-selectin, which is used to prevent painful, vaso-occlusive crises in patients with sickle cell disease. Sickle cell disease is caused by an inherited mutation in the β globin gene that creates hemoglobin S, which is prone to aggregation with deoxygenation resulting in deformation and sickling of red blood cells, hemolytic anemia, and recurrent painful crises involving different organs and tissues. Sickle cell disease affects at least 100,000 Americans and is most common in persons of African descent. Long term complications include disability due to recurrent painful crises, acute chest syndrome, pulmonary hypertension, stroke and cerebral infarcts, end-organ damage and early mortality. Binding of the monoclonal antibody to P-selectin inhibits its attachment to its glycoprotein ligand thereby inhibiting the adhesion of sickled red cells to endothelium, a critical step in the vaso-occlusive crises of sickle cell disease. Thus, crizanlizumab does not prevent sickling of red cells or increase hemoglobin levels or change the oxygen-binding characteristics of hemoglobin, but rather it inhibits the aggregation and binding of the sickled red cells to platelets, leukocytes and endothelial cells which mediates the vascular occlusions that underlie painful crises. In preregistration randomized, placebo-controlled trials, 48 weeks of crizanlizumab therapy resulted in a decrease in the number of painful crises and both duration and numbers of hospitalizations. Crizanlizumab was approved in the United States in 2019 as therapy for prevention of painful crises in sickle cell disease in adults and children above the age of 16 years. Crizanlizumab is available in single dose pre-filled syringes 100 mg in 10 mL (10 mg per mL) under the brand name Adakveo. The recommended dose is 5 mg/kg intravenously over 30 minutes at 0 and 2 weeks, followed by every 4 weeks thereafter. Crizanlizumab can be given with hydroxyurea, the standard therapy for sickle cell disease. Common side effects of crizanlizumab include mild local injection reactions, arthralgias, backpain, diarrhea, pruritus, nausea, vomiting and chest pain. Also reported have been rare instances of severe hypersensitivity reactions.

Hepatotoxicity

Mild-to-moderate serum aminotransferase elevations arise a small percentage of treated patients, but are generally asymptomatic and transient and rarely necessitate discontinuation of crizanlizumab injections. In registration trials of crizanlizumab 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 crizanlizumab there have been no reports of clinically significant liver injury attributed to its use.

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

Mechanism of Injury

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

Outcome and Management

Drug Class: Genetic Disorder Agents, Monoclonal Antibodies, Sickle Cell Disease Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Crizanlizumab – Adakveo®

DRUG CLASS

Sickle Cell Disease Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Crizanlizumab	1690318-25-2	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 12 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 crizanlizumab).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761128Orig1s000MultidisciplineR.pdf

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA multidisciplinary scientific review of the crizanlizumab application which mentions safety results in 175 patients treated with crizanlizumab for an average of 42 weeks, there were no treatment-related hepatobiliary adverse events or episodes of drug induced liver injury or jaundice).

Koh C, Turner T, Zhao X, Minniti CP, Feld JJ, Simpson J, Demino M, et al. Liver stiffness increases acutely during sickle cell vaso-occlusive crisis. Am J Hematol. 2013;88:E250–4. PubMed PMID: 23828202.

(Among 23 patients with sickle cell disease evaluated before and during an acute vaso-occlusive crisis, serum liver enzyme elevations did not change appreciably but hepatic stiffness increased [measured by ultrasound transient

elastography] as did serum total and indirect bilirubin and reticulocyte counts, while serum albumin and hemoglobin decreased).

Feld JJ, Kato GJ, Koh C, Shields T, Hildesheim M, Kleiner DE, Taylor JG 6th, et al. Liver injury is associated with mortality in sickle cell disease. Aliment Pharmacol Ther. 2015;42:912–21. PubMed PMID: 26235444.

(Among 247 patients with sickle cell disease, liver disease was common, elevations in ALT were present in 16% and alkaline phosphatase in 33%; factors associated with mortality during follow up were iron indices [serum ferritin, transferrin, and iron] and liver abnormalities [direct bilirubin, albumin and alkaline phosphatase levels]; liver biopsy done in 40 patients revealed nodular regenerative hyperplasia in 36% and portal venopathy in 23%).

Ataga KI, Kutlar A, Kanter J, Liles D, Cancado R, Friedrisch J, Guthrie TH, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. N Engl J Med. 2017;376:429–39. PubMed PMID: 27959701.

(Among 198 patients with sickle cell disease treated with crizanlizumab [2.5 or 5.0 mg/kg] or placebo subcutaneously in 14 injections over 48 weeks, the number of pain crises and duration of hospitalizations decreased with crizanlizumab, while hemoglobin levels and reticulocyte counts did not change and adverse events were more frequent with active therapy but usually mild-to-moderate in severity [arthralgia, diarrhea, vomiting, pruritus and chest pain]; no mention or listing of ALT elevations or hepatotoxicity).

Two drugs for sickle cell disease. Med Lett Drugs Ther. 2020;62(1595):51–2. PubMed PMID: 32324178.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of crizanlizumab and voxelotor shortly after their approval for use in sickle cell disease in the US; no mention of ALT elevations or hepatotoxicity).

Blair HA. Crizanlizumab: first approval. Drugs. 2020;80:79–84. PubMed PMID: 31933169.

(Review of the mechanism of action, history of development, pharmacology, clinical efficacy and adverse side effects of crizanlizumab shortly after its approval for use in sickle cell disease in the US, mentions adverse events of arthralgia, back pain, diarrhea, nausea, pruritus, fever and chest pain, but not ALT elevations or hepatotoxicity; infusion reactions arose in 3% of cases).

Osunkwo I, Manwani D, Kanter J. Current and novel therapies for the prevention of vaso-occlusive crisis in sickle cell disease. Ther Adv Hematol. 2020;11:2040620720955000. PubMed PMID: 33062233.

(Review of the pathogenesis of vaso-occlusive crises in sickle cell disease and drugs that target different components of the multifactorial process including increasing fetal hemoglobin [hydroxyurea], decreasing oxidative stress [L-glutamine], increasing oxygen affinity of hemoglobin [voxelotor], and decreasing adhesion of sickled cells to platelets, neutrophils and endothelium [crizanlizumab]; no mention of ALT elevations with therapy or hepatotoxicity).

Darbari DS, Sheehan VA, Ballas SK. The vaso-occlusive pain crisis in sickle cell disease: definition, pathophysiology, and management. Eur J Haematol. 2020;105:237–46. PubMed PMID: 32301178.

(Extensive review of the pathogenesis of vaso-occlusive crisis in patients with sickle cell disease and therapies that target different steps in the process including inflammation, adhesion, oxygen affinity and stability of hemoglobin, and oxidative stress; discusses efficacy of L-glutamine, voxelotor and crizanlizumab, mentioning that all three are well tolerated; no mention or discussion of hepatotoxicity).

Ali MA, Ahmad A, Chaudry H, Aiman W, Aamir S, Anwar MY, Khan A. Efficacy and safety of recently approved drugs for sickle cell disease: a review of clinical trials. Exp Hematol. 2020;92:11–18.e1. PubMed PMID: 32841705.

(Review of randomized controlled trials of 3 recently approved drugs for sickle cell disease focusing upon L-glutamine, voxelotor, and crizanlizumab states that all three are "well tolerated without any alarming adverse effects"; no mention of ALT elevations or hepatotoxicity).

Gardner RV. Crizanlizumab in vaso-occlusive crisis caused by sickle cell disease. Drugs Today (Barc). 2020;56:705–14. PubMed PMID: 33332478.

(Review of clinical efficacy and safety of crizanlizumab; no mention of ALT elevations or hepatotoxicity).

Tisdale JF, Thein SL, Eaton WA. Treating sickle cell anemia. Science. 2020;367(6483):1198–9. PubMed PMID: 32165573.

(Review of mechanism of action and efficacy of current and the promise of future therapies of sickle cell anemia, mentions that prevention of adhesion may prevent sickle crises by delaying the time to vasculature obstruction relative to the time of transit of the red cells through the capillaries).

Pace BS, Starlard-Davenport A, Kutlar A. Sickle cell disease: progress towards combination drug therapy. Br J Haematol. 2021;194(2):240–51. PubMed PMID: 33471938.

(Review of the pathophysiology of sickle cell disease and vaso-occlusive crises and mechanism of action of drugs used to treat sickle cell disease and drugs currently under investigation for efficacy in decreasing the microvascular occlusive crises that mediate much of the morbidity and mortality of this disease).