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Ravulizumab

Updated: April 12, 2019.

OVERVIEW

Introduction

Ravulizumab is a humanized monoclonal antibody to complement factor 5 which acts to block complement activation and is used to treat paroxysmal nocturnal hemoglobinuria. Ravulizumab has not been linked to serum enzyme elevations during therapy or to instances of idiosyncratic acute liver injury.

Background

Ravulizumab (rav" ue liz' ue mab) is a recombinant, humanized IgG monoclonal antibody to complement factor 5, which inhibits its enzymatic cleavage and activation. Activated complement is an important mediator of immune damage including hemolysis of red blood cells and plays an essential role in the hemolysis and tissue damage that accompanies paroxysmal nocturnal hemoglobinuria (PNH). In clinical trials in PNH, ravulizumab was found to reduce hemolysis and the need for blood transfusions with subsequent improvement in symptoms and quality of life. Ravulizumab was approved for use in PNH in the United States in 2018. Ravulizumab is available as a solution in single dose vials of 300 mg in 30 mL (10 mg/mL) under the commercial name Ultomiris. Ravulizumab is given by intravenous infusion, the dose varying by body weight, with a recommended loading dose of 2,400 to 3,000 mg followed 2 weeks later by maintenance dose of 3,000 to 3,600 mg every 8 weeks thereafter. Ravulizumab was engineered to have a prolonged half-life allowing for an every-8-week maintenance regimen in contrast to the every-2-week regimen required for eculizumab, a similar monoclonal antibody to complement factor 5 that was approved for use in PNH in 2007. Side effects are not common, but can include headache, diarrhea, nausea, fatigue and upper respiratory tract infections. Rare, but potentially severe adverse reactions include serious infections, including meningococcal infections, for which reason eculizumab is available only as a part of a risk evaluation and mitigation strategy (REMS) that requires physician training in its use and enrollment of the patient in a surveillance program.

Hepatotoxicity

In clinical trials of comparing ravulizumab and eculizumab in patients with PNH, serum enzyme levels were rarely mentioned, and laboratory test results were described as being stable or unremarkable. Summaries of preregistration trials of ravulizumab vs eculizumab commented that there were “no notable differences in changes in clinical chemistry or hematology parameters” and no patient discontinued therapy because of adverse events. Clinical use of ravulizumab has been limited, but there have been no reports of clinically apparent liver injury associated with its use. Acute self-limited liver injury with jaundice has, however, been reported with eculizumab (a similar monoclonal antibody to complement factor 5) therapy of hemolytic uremic syndrome in children. Affected children were able to continue or resume the monoclonal therapy after

resolution of the injury without recurrence, and neither ravulizumab or eculizumab have been linked to cases of acute liver failure or chronic liver injury.

Likelihood score: E* (unproven but suspected rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which ravulizumab might cause liver injury is unknown. Ravulizumab is a monoclonal antibody and, like other proteins, is metabolized into amino acids and is unlikely to have intrinsic toxicity. Because it blocks the activation of complement, it might predispose to conditions that depend on complement activation for resolution (such as meningococcemia), but it is not clear whether this applies to any liver diseases.

Outcome and Management

Ravulizumab therapy has been linked to rare instances of mild, transient serum enzyme elevations, but cases of jaundice and symptoms from liver injury with ravulizumab therapy have not been described. In patients who develop persistent, marked elevations of serum ALT or alkaline phosphatase or who develop jaundice and symptoms, therapy should be interrupted.

Drug Class: Hematologic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ravulizumab – Ultomiris®

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
Ravulizumab	1803171-55-2	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 12 April 2019

Abbreviations used: HUS, hemolytic uremic syndrome; PNH, paroxysmal nocturnal hemoglobinuria.

Zimmerman HJ. 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 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"; ravulizumab is not specifically mentioned).

Krensky AM, Azzi JR, Hafler DA. Immunosuppressants and tolerogens. 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. 637-53.

(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 clinical trials comparing therapy with ravulizumab to eculizumab found "no notable differences in changes in clinical chemistry or hematology parameters").

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Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med 1995; 333: 1253-8. PubMed PMID: 7566002.

(Among 80 patients with PNH seen at a single London referral center between 1940 and 1970, ages 16 to 73 at diagnosis, the median survival was 10 years and causes of death were often hemorrhage or serious thrombotic events).

Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood 2014; 124: 2804-11. PubMed PMID: 25237200.

(Review of the pathophysiology, genetic causes, diagnosis, classification, clinical features and treatment of PNH; no mention of adverse effects of eculizumab).

Hayes W, Tschumi S, Ling SC, Feber J, Kirschfink M, Licht C. Eculizumab hepatotoxicity in pediatric aHUS. Pediatr Nephrol 2015; 30: 775-81. PubMed PMID: 25416628.

(Among 11 children with atypical HUS treated with eculizumab, liver test abnormalities above 3 times ULN arose in 5 children after 1-4 doses [peak direct bilirubin 0.5-9.9 mg/dL, ALT 129-908 U/L, AST 244-1039 U/L, Alk P 173-1023, all values having been normal before treatment], which resolved despite continuing therapy in 4 who were asymptomatic, but required discontinuation in one who became jaundiced and symptomatic but recovered upon stopping after a third dose).

Röth A, Rottinghaus ST, Hill A, Bachman ES, Kim JS, Schrezenmeier H, Terriou L, et al. Ravulizumab (ALXN1210) in patients with paroxysmal nocturnal hemoglobinuria: results of 2 phase 1b/2 studies. Blood Adv 2018; 2: 2176-85. PubMed PMID: 30171081.

(Among 39 patients with PNH treated with ravulizumab with varying doses and frequencies [every 2, 4, 6 ,8 or 12 weeks], adverse events were common but well tolerated, most commonly headache, and two subjects developed meningococcal infections; no mention of ALT elevations or hepatotoxicity).

Lee JW, Sicre de Fontbrune F, Wong Lee L, Pessoa V, Gualandro S, Füreder W, Ptushkin V, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood 2019; 133: 530-9. PubMed PMID: 30510080.

(Among 246 treatment-naïve patients with PNH treated with either ravulizumab [every 8 weeks] or eculizumab [every 2 weeks] for 6 months, response rates were similar in the two groups as were adverse events including headache [36% and 33%], serious infections [16% vs 3.3%], and discontinuations [0% vs 1.6%], and there were no serious hepatic adverse events or discontinuations because of serum enzyme elevations).

Kulasekararaj AG, Hill A, Rottinghaus ST, Langemeijer S, Wells R, Gonzalez-Fernandez FA, Gaya A, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood 2019; 133: 540-9. PubMed PMID: 30510079.

(Among 195 patients with PNH on long term eculizumab therapy, need for transfusions and rates of hemolysis remained low both in those who remained on eculizumab and those who were switched to ravulizumab and adverse event rates are similar; no mention of ALT elevations or hepatotoxicity).