OVERVIEW
Eculizumab

Introduction

Eculizumab is a humanized monoclonal antibody to complement factor 5 which acts to block complement activation and is used to treat paroxysmal nocturnal hemoglobinuria and hemolytic uremic syndrome. Eculizumab has been linked to several iinstances of serum enzyme elevations after repeated infusions and to rare instances of clinically apparent acute liver injury.

Background

Eculizumab (e" kue 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) and hemolytic uremic syndrome (HUS). In clinical trials in PNH, eculizumab was found to reduce hemolysis and the need for blood transfusions with subsequent improvement in symptoms and quality of life. Eculizumab was approved for use in PNH in the United States in 2007. The indications were later broadened to include atypical hemolytic uremic syndrome with complement-mediated thrombotic events in 2011. Eculizumab is available as a solution in single dose vials of 300 mg in 30 mL (10 mg/mL) under the commercial name Soliris. The recommended dose varies by body weight and indication, but it is typically given by intravenous infusion (over 35 minutes) weekly for 5 weeks and every two weeks thereafter. 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 eculizumab in patients with PNH and atypical HUS, serum enzyme levels were rarely mentioned and laboratory test results were described as being stable or unremarkable. In preregistration studies of eculizumab there were no reports of clinically apparent liver injury with jaundice. Indeed, in many studies, a steady improvement in ALT and AST values during treatment was described, perhaps reflecting the decrease in intravascular hemolysis that occurred. After approval and more widespread use of eculizumab, however, a case series of eculizumab therapy in 11 children with atypical HUS, reported that 5 children developed marked serum enzyme elevations during therapy that was accompanied by jaundice in three cases and led to discontinuation of

treatment in one patient after development of symptoms and jaundice (Case 1). The onset of injury was within the first 4 doses of eculizumab and tended to recur with subsequent doses, but to a lesser extent. Indeed, 4 children were able to continue eculizumab therapy without recurrence. The pattern of serum enzyme elevations was mixed. There was no mention of immunoallergic symptoms or autoantibody formation. Similar cases have not been reported in other case series or clinical trials. Thus, liver injury may occur with eculizumab therapy but it is typically mild, asymptomatic and self-limited in course, not requiring dose modification or discontinuation. There have been no reports of acute liver failure, chronic hepatitis or vanishing bile duct syndrome associated with eculizumab therapy.

Likelihood score: D (possible cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which eculizumab might cause liver injury is unknown. Eculizumab 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

Eculizumab therapy has been linked to rare instances of mild, transient serum enzyme elevations during therapy, typically arising 1 to 3 weeks after an initial or early infusion of the monoclonal antibody. Instances of jaundice and symptoms from liver injury with eculizumab therapy are rare and not well described, but there have been no reports of acute liver failure, chronic hepatitis, cirrhosis or vanishing bile duct syndrome associated with it use. In patients who develop persistent elevations of serum ALT or alkaline phosphatase or who develop jaundice and symptoms, therapy should be interrupted.

Drug Class: Monoclonal Antibodies, Hematologic Agents

Top of page

CASE REPORT
Eculizumab

Case 1. Mixed hepatocellular-cholestatic liver injury during eculizumab therapy.

[Modified from Case 1 in: Hayes W, Tschumi S, Ling SC, Feber J, Kirschfink M, Licht C. Eculizumab hepatotoxicity in pediatric aHUS. Pediatr Nephrol 2015; 30: 775-81. PubMed Citation]

A 9 year old boy with atypical hemolytic uremic syndrome was found to have marked elevations in serum aminotransferase and alkaline phosphatase levels 3 days after a second dose of eculizumab. All liver tests had been normal before treatment, and ALT values were normal on several occasions in the week after the initial dose and at the time of the second. The values fluctuated widely rising to a peak ALT of 908 U/L, AST 1107 U/L and alkaline phosphatase 1023 U/L. He had mild symptoms of right upper quadrant pain and liver tenderness, but serum albumin and INR remained normal (bilirubin not mentioned). Tests for viral hepatitis and autoimmune markers were negative and liver ultrasound showed hepatomegaly and an heterogenous liver texture, but no evidence of biliary obstruction. A liver biopsy showed minimal changes with mild hepatocellular cytoplasmic swelling and clearing, mild Kupffer cell hemosiderosis, mild pericentral sinusoidal dilation and fibrosis. Serum enzyme elevations soon fell into the normal range and he received a third infusion 3 weeks after the second. Three days later, his serum enzymes were again elevated and he was jaundiced with a direct bilirubin of 9.9 mg/dL (previously 0.0). Therapy was suspended and liver tests began to improve and were reportedly normal 4 weeks later.

Key Points

Medication:	Eculizumab (900 mg infusions)
Pattern:	Mixed (R=2.6 from peak values)
Severity:	3+ (jaundice, hospitalization)
Latency:	11 days
Recovery:	4 weeks
Other medications:	None mentioned

Comment

In a small case series, 5 of 11 children with atypical HUS treated with eculizumab developed evidence of liver injury after 1 to 4 doses of the monoclonal antibody. All five were known to have had normal serum enzymes before starting treatment and in several instances the elevations recurred with a

subsequent infusion. Nevertheless, all except the case described here recovered and were able to tolerate further doses of eculizumab without recurrence of liver injury. This article is the only description of liver injury from this monoclonal antibody and came as a surprise, because of the lack of hepatotoxicity noted in previous publications despite careful descriptions of several hundred patients with either HUS or PND who received eculizumab. The pattern of injury was "mixed" with marked elevations in aminotransferase as well as alkaline phosphatase and GGT levels. Also striking was the rapidity of onset and rapidity of resolution suggesting a direct effect on hepatic function rather than hepatocellular damage. A liver biopsy was performed, but at a time when the abnormalities had almost resolved. The biopsy showed hepatocellular swelling rather than necrosis and cell loss. Thus, the liver injury attributed to eculizumab is unusual and suggestive of a direct effect of the monoclonal antibody on hepatocyte pathways rather than direct cell damage.

Top of page

PRODUCT INFORMATION
Eculizumab

REPRESENTATIVE TRADE NAMES

Eculizumab – Soliris®

DRUG CLASS

Monoclonal Antibodies, Hematologic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

Top of page

CHEMICAL FORMULA AND STRUCTURE
Eculizumab

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Eculizumab	219685-50-4	Monoclonal Antibody	Not Available