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# Eculizumab

Updated: March 25, 2017.

# OVERVIEW

## 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 instances 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: Hematologic Agents, Monoclonal Antibodies

# CASE REPORT

## 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

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|---|---|
| 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.

## PRODUCT INFORMATION

**REPRESENTATIVE TRADE NAMES**

Eculizumab – Soliris®

**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 |
|---|---|---|---|
| Eculizumab | 219685-50-4 | Monoclonal Antibody | Not Available |

## ANNOTATED BIBLIOGRAPHY

References updated: 25 March 2017

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

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).*

Krensky AM, Vincenti F, Bennett WM. Immunomodulators. In, Brunton LL, Lazo JS, Parker KL, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill, 2006, pp. 1405-88.

*(Textbook of pharmacology and therapeutics).*

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).*

Hillmen P, Hall C, Marsh JC, Elebute M, Bombara MP, Petro BE, Cullen MJ, et al. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med 2004; 350: 552-9. PubMed PMID: 14762182.

*(Among 11 patients with transfusion dependent PNH treated with eculizumab, transfusion requirements, episodes of hemolysis and LDH levels decreased and quality of life improved; no adverse events were attributed to therapy except for rare infusion reactions).*

Hillmen P, Young NS, Schubert J, Brodsky RA, Socié G, Muus P, Röth A, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med 2006; 355: 1233-43. PubMed PMID: 16990386.

*(Among 87 patients with PNH treated with eculizumab or placebo by iv infusion every 1-2 weeks for 26 weeks, median transfusion numbers were less with eculizumab compared to placebo [0 to 10], LDH levels decreased [86%] and quality of life improved significantly, while adverse events were more common including headache, body pain, and fatigue while serious adverse events were less common with eculizumab vs placebo, and none were liver related or considered related to therapy).*

Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. N Engl J Med 2009; 361: 1676-87. PubMed PMID: 19846853.

*(HUS occurs most commonly in children after E. coli 0157:H7 infection and is marked by bloody diarrhea followed by hemolysis, thrombocytopenia and renal dysfunction; about 10% of cases of HUS are considered "atypical", occurring without known bacterial infection and having a poor prognosis, some being genetic and some sporadic, marked by abnormalities in complement activation and its regulation).*

Röth A, Hock C, Konik A, Christoph S, Dührsen U. Chronic treatment of paroxysmal nocturnal hemoglobinuria patients with eculizumab: safety, efficacy, and unexpected laboratory phenomena. Int J Hematol 2011; 93: 704-14. PubMed PMID: 21611719.

*(Among 19 patients with PNH treated with eculizumab for 6-46 months, LDH levels decreased by 85% and transfusion requirements by 86%, but other indices of hemolysis changed little [haptoglobin and bilirubin levels, reticulocytes] while ferritin levels rose [mean levels from 104 to 528 μg/L]; no discussion of adverse events).*

Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, Bingham C, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med 2013; 368: 2169-81. PubMed PMID: 23738544.

*(Among 37 children with atypical HUS treated with eculizumab, symptoms and signs of disease improved in most children and no serious infection related events occurred; no mention of ALT elevations or hepatotoxicity).*

Kanakura Y, Ohyashiki K, Shichishima T, Okamoto S, Ando K, Ninomiya H, Kawaguchi T, et al. Long-term efficacy and safety of eculizumab in Japanese patients with PNH: AEGIS trial. Int J Hematol 2013; 98: 406-16. PubMed PMID: 23934275.

*(Among 27 Japanese patients with PNH treated with eculizumab for up to 2 years, intravascular hemolysis and transfusion requirements decreased and adverse events were uncommon, but included headache and diarrhea, usually early in treatment; no mention of ALT elevations or hepatotoxicity).*

Hillmen P, Muus P, Röth A, Elebute MO, Risitano AM, Schrezenmeier H, Szer J, et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol 2013; 162: 62-73. PubMed PMID: 23617322.

*(Among 195 patients with PNH treated with eculizumab long term, there were 4 deaths, but none considered related to therapy; there were no liver related serious adverse events and no mention of ALT elevations or hepatotoxicity).*

Reiss UM, Schwartz J, Sakamoto KM, Puthenveetil G, Ogawa M, Bedrosian CL, Ware RE. Efficacy and safety of eculizumab in children and adolescents with paroxysmal nocturnal hemoglobinuria. Pediatr Blood Cancer 2014; 61: 1544-50. PubMed PMID: 24777716.

*(Among 7 children or adolescents with PNH treated with eculizumab for 12 weeks, there were no hepatic serious adverse events and no mention of ALT elevations).*

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).*

Licht C, Greenbaum LA, Muus P, Babu S, Bedrosian CL, Cohen DJ, Delmas Y, et al. Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. Kidney Int 2015; 87: 1061-73. PubMed PMID: 25651368.

*(Among 37 patients with atypical HUS enrolled in two open label studies of eculizumab, clinical improvements in hematologic features and renal function occurred in both studies and there were "no new safety concerns or meningococcal infections"; no mention of ALT elevations or hepatotoxicity).*

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 after 1 to 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 acutely symptomatic but recovered upon stopping after a third dose).*

Mallett A, Hughes P, Szer J, Tuckfield A, Van Eps C, Cambell SB, Hawley C, et al. Atypical haemolytic uraemic syndrome treated with the complement inhibitor eculizumab: the experience of the Australian compassionate access cohort. Intern Med J 2015; 45: 1054-65. PubMed PMID: 26247170.

*(Among 10 patients with atypical HUS treated with eculizumab for an average of 3 years, all had a beneficial clinical response; no mention of ALT elevations or liver related adverse events).*

Greenbaum LA, Fila M, Ardissino G, Al-Akash SI, Evans J, Henning P, Lieberman KV, et al. Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome. Kidney Int 2016; 89: 701-11. PubMed PMID: 26880462.

*(Among 22 children with atypical HUS treated with eculizumab for 26 weeks, 14 had a complete resolution of thrombotic microangiopathy and several more had a hematologic response; most adverse events were considered unrelated to treatment and "elevated levels of ALT and AST were noted in some patients before and after receiving eculizumab", but these normalized by week 26).*

Ninomiya H, Obara N, Chiba S, Usuki K, Nishiwaki K, Matsumura I, Shichishima T, et al. Interim analysis of post-marketing surveillance of eculizumab for paroxysmal nocturnal hemoglobinuria in Japan. Int J Hematol 2016; 104: 548-558. PubMed PMID: 27464489.

*(Among 319 Japanese patients with PNH treated with eculizumab and enrolled in postmarketing surveillance, the most common adverse events reported were headache [22%] and there were 20 deaths, none of liver failure, but one attributed to liver cancer).*

Fakhouri F, Hourmant M, Campistol JM, Cataland SR, Espinosa M, Gaber AO, Menne J, et al. Terminal complement inhibitor eculizumab in adult patients with atypical hemolytic uremic syndrome: a single-arm, open-label trial. Am J Kidney Dis 2016; 68: 84-93. PubMed PMID: 27012908.

*(Among 41 adults with atypical hemolytic uremic syndrome treated with eculizumab in two prospective, open label studies, there were significant improvements in hematologic, renal and quality of life features; two patients developed meningococcal infections and ALT levels were elevated in 34% of patients before and "transient liver enzyme level elevations were observed during the study", but most values were abnormal in only 8% of patients by the end of treatment).*