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ORIGINAL ARTICLE

Eculizumab hepatotoxicity in pediatric aHUS

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Abstract
Background Eculizumab is a humanized anti-C5 antibody approved for the treatment of atypical hemolytic uremic syndrome (aHUS). Its use is increasing in children following reports of its safety and efficacy.
Methods We reviewed biochemical and clinical data related to possible drug-induced liver injury in 11 children treated with eculizumab for aHUS in a single center.
Results Elevated aminotransferases were observed in 7 children aged 6 to 11 years following eculizumab treatment for aHUS. Internationally accepted liver enzyme thresholds for drug-induced liver injury were exceeded in 5 cases. In all cases, liver injury was classified as mixed hepatocellular and cholestatic. Infectious and other causes were excluded in each case. One patient with no pre-existing liver disease developed tender hepatomegaly and liver enzyme derangement exceeding 20 times the upper limit of normal following initiation of eculizumab. Recurrent liver injury following re-challenge with eculizumab necessitated its discontinuation and transition to plasma therapy.
Conclusions Hepatotoxicity in association with eculizumab is a potentially important yet previously unreported adverse event. We recommend monitoring liver enzymes in all patients receiving eculizumab. Further research is required to clarify the impact of this adverse event, to characterize the mechanism of potential hepatotoxicity, and to identify which patients are most at risk.

Keywords Atypical hemolytic uremic syndrome · Thrombotic microangiopathy · Complement · Eculizumab · Transaminitis · Hepatotoxicity

Introduction

Eculizumab is a first-in-class humanized anti-C5 antibody approved for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) in adults and children. It was first established as a treatment for PNH, for which it is reported to be safe and effective [1–3]. Its use in treating aHUS is increasing in children following case series and recent treatment trials reporting safety and efficacy in inducing thrombotic microangiopathy (TMA) response [4–8].

In treatment trials of aHUS, various nonspecific side effects have been reported in association with eculizumab [8]. Other adverse events reported to date, but likely unrelated to eculizumab treatment, include septic shock [9], photodermatosis [10], melanoma [11], and a case of desquamating rash and hyperammonemia [12]. No hepatic side effects have been reported to our knowledge.

We report a series of 5 children with aHUS who experienced hepatotoxicity following eculizumab treatment. Two further children experienced transient liver enzyme

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derangement, which did not reach the threshold for liver injury as defined by Aithal et al. [13]. Recurrent symptoms necessitated discontinuation of eculizumab and transition to plasma therapy for aHUS in one patient. In each case, workup for infective and autoimmune causes of hepatitis was non-explanatory, including hepatitis A, B, C, Epstein-Barr virus (EBV), cytomegalovirus (CMV), parvovirus, adenovirus, HHV6, HHV7, alpha-1-antitrypsin, ceruloplasmin, copper, total immunoglobulin G (IgG), antinuclear antibodies, smooth muscle cell antibodies, and liver–kidney microsomal antibodies.

Materials and methods

Eculizumab was dosed according to a standardized weight-based regimen. The induction schedule comprised four weekly doses of 900 mg for patients weighing 40 kg or more, and two weekly doses of 600 mg for patients weighing 30–39.9 kg. The maintenance regimen comprised 1,200 mg every 2 weeks for patients weighing 40 kg or more, and 900 mg for patients weighing 30–39.9 kg (Table 1).

Investigations for genetic mutations in complement proteins CFI, CFH, MCP/CD46, THBD/CD141, C3, and CFB and anti-CFH antibodies were performed in all patients. No known pathogenic mutations were identified. Variants of unknown significance were found in C3 and CFH in cases 2 and 4 respectively. One patient tested positive for anti-CFH antibodies (case 5).

Drug-induced liver injury was defined by internationally accepted criteria of a greater than 5-fold increase in alanine transaminase (ALT) or aspartate aminotransferase (AST) above the upper limit of normal (ULN) or an increase in hepatic alkaline phosphatase (ALK) above two times the ULN [13]. Liver injury was further classified as mixed hepatocellular and cholestatic in each case [13].

Case reports

We observed derangement in liver enzymes in association with eculizumab therapy in 5 of the 11 patients receiving eculizumab for aHUS in our center. Transient mild liver enzyme disturbance was observed in 2 further cases. The time course of liver enzyme derangement was similar in each case with fluctuation in ALT, AST, ALK and gamma-glutamyl transpeptidase (GGT) 10–29 days following the first eculizumab dose with resolution within 14–21 days (Fig. 1).

In 4 of the 5 affected patients, the biochemical derangement was asymptomatic and maintenance eculizumab was continued. In 1 patient (case 1), the magnitude of elevation in liver enzymes was more marked; concern about progressive elevation in transaminases and clinical symptoms of tender hepatomegaly and jaundice necessitated discontinuation of eculizumab.

The pattern of liver injury was classified as mixed hepatocellular/cholestatic in each case with R values ranging from 2.8 to 4.9 [13].

The time course of transaminitis relative to eculizumab dosing for cases 1 and 3 is illustrated in Fig. 1. Patient characteristics and patterns of liver enzyme dysfunction are summarized in Table 2.

Case 1

A boy aged 8 years and 11 months with hereditary spherocytosis and previous splenectomy developed aHUS for which eculizumab was commenced. Three days following the second dose, markedly elevated liver enzymes were noted (Fig. 1). ALT, AST, and GGT rose to over 20 times the ULN; the international normalized ratio (INR) and albumin remained within normal limits. Clinical symptoms of right upper quadrant pain and signs of tender hepatomegaly were evident. Right upper quadrant abdominal pain in the context of spherocytosis can be reflective of gall bladder disease; however, ultrasound imaging showed a normal gall bladder, mild hepatomegaly with a coarse parenchymal appearance, and normal hepatic and portal vasculature. Investigations for underlying causes of liver disease were normal, including viral hepatitides, autoimmune workup, alpha-1-antitrypsin, copper, ceruloplasmin, and creatinine phosphokinase.

Liver enzyme abnormalities fluctuated following the second dose of eculizumab with two further significant peaks in ALT (Fig. 1). A third dose was suspended pending normalization of liver enzymes. A liver biopsy taken after the second dose when liver enzymes had normalized showed mild minimal pathological change, with mild hepatocellular cytoplasmic swelling and clearing, mild Kupffer cell hemosiderosis, mild pericentral sinusoidal fibrosis, and mild sinusoidal

Table 1 Induction and maintenance regimens according to patient weight

Patient weight (kg)	Induction regimen	Maintenance regimen
≥ 40	900 mg weekly×4	1,200 mg week 5; 1,200 mg every 2 weeks
30–39.9	600 mg weekly×2	900 mg week 3; 900 mg every 2 weeks
20–29.9	600 mg weekly×2	600 mg week 3; 600 mg every 2 weeks
10–19.9	600 mg weekly×1	300 mg week 2; 300 mg every 2 weeks
5–9.9	300 mg weekly×1	300 mg week 2; 300 mg every 3 weeks

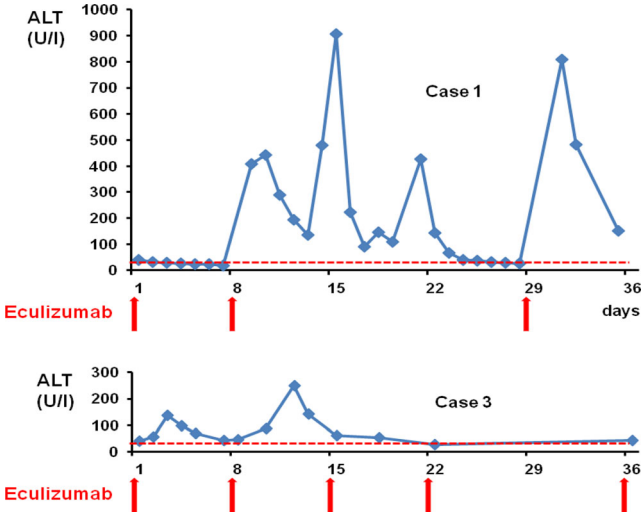

Fig. 1 Time course of alanine transaminase (ALT) in cases 1 and 3 in relation to eculizumab dosing. *Dashed lines* represent the upper limit of normal

dilatation. There was no evidence of autoimmune or infectious hepatitis. The presence of sinusoidal eosinophils and hepatocellular cytoplasmic changes raised concerns with regard to a drug effect.

The third eculizumab dose was then given, after which marked liver enzyme elevation recurred (Fig. 1). Eculizumab was therefore discontinued, with transition to plasma therapy. Follow-up to 4 weeks revealed no further abnormalities in liver biochemistry.

Case 2

A boy aged 10 years and 3 months with a background of Evans syndrome and recurrent thrombocytopenia developed marked hemolysis and thrombotic microangiopathy consistent with aHUS. Plasma exchange was initiated with partial remission, following which eculizumab was commenced. Asymptomatic elevation of ALT (maximum 175 IU/l) and AST (maximum 409 IU/l) were noted 7 days after the third eculizumab dose with spontaneous resolution over the subsequent 14 days. Whilst elevated liver enzymes can be observed in patients with Evans syndrome, such findings were not previously observed in this patient.

Case 3

An 11.5 year-old boy had a history of obesity, uniform hyperechogenicity of the liver parenchyma on ultrasound imaging, and normal liver biochemistry, thought to be consistent with non-alcoholic fatty liver disease. He developed aHUS and achieved remission with plasma therapy, following which he was transitioned to eculizumab. Three days following the first eculizumab dose, elevated liver enzymes were noted (Table 2). ALT rose again after a further dose but subsequently normalized (Fig. 1). Again, elevated liver enzymes can be observed in the context of the underlying disease, but were not previously observed in this patient.

Case 4

A boy aged 6.5 years had severe systemic sequelae from his initial presentation with thrombotic microangiopathy including end-stage renal disease (ESRD), limb ischemia with resulting loss, ischemic colitis requiring colectomy, testicular infarct, and skin necrosis requiring grafting. Following a period of partial remission on plasma therapy, he was transitioned to eculizumab.

Fluctuating asymptomatic elevations in ALT, AST, and ALK with spontaneous resolution were noted in association with eculizumab doses. One year following initial presentation the patient developed abdominal pain with elevated liver enzymes. ERCP showed a choledochal cyst. Liver biopsy showed mild chronic eosinophilic portal inflammation with mild fibrosis and moderate iron accumulation. Transaminitis was felt to be unlikely to be related to these findings.

Case 5

An 8-year-old boy with no pre-existing liver disease experienced derangement in ALT and AST exceeding internationally accepted thresholds for drug-induced liver injury following initiation of eculizumab for aHUS. Liver enzyme abnormalities were not associated with specific symptoms and resolved after 56 days.

Discussion

Hepatotoxicity in association with various biological therapies is rare but well recognized [14–25]. However, to our knowledge, this is the first report of potential hepatotoxicity in association with eculizumab therapy. Eculizumab is a humanized monoclonal anti-C5 antibody [26] that has been used for over a decade in patients with paroxysmal nocturnal hemoglobinuria (PNH) [1, 3] and aHUS [8] in patients of all age groups. The serious adverse event (SAE) profile of eculizumab is nonspecific; hepatotoxicity (including elevation in liver enzymes) has not been reported, yet was observed in two adult PNH patients, although it was clearly linked to an underlying liver disease preceding eculizumab treatment in these cases (Camille Bedrosian, personal communication, 8 October 2014). On the other hand, eculizumab was found to reverse progressive thrombosis and hepatic failure in a patient with PNH and Budd–Chiari syndrome unresponsive to anticoagulation therapy [27].

Table 2 Patient characteristics with peak values (baseline) for alanine aminotransferase (ALT, upper limit of normal 40 U/l), aspartate aminotransferase (AST, upper limit 45 U/l), gamma-glutamyl transpeptidase (GGT, upper limit 45 U/l), alkaline phospatase (ALK, upper limit 180 U/l) and conjugated bilirubin (upper limit 2 μmol/l) with platelet count, LDH and haptoglobin on the day of the first eculizumab dose

Case	1	2	3	4	5
Age at disease onset	8 years 11 months	10 years	11 years	4 years 1 month	8 years 4 months
Gender	Male	Male	Male	Male	Male
Diagnosis	aHUS	aHUS	aHUS	aHUS	aHUS
Complement mutation	None identified	Homozygous variant of unknown significance in C3 gene (c.304C>G(p.Arg102Gly))	None identified	Variant of unclear significance in CFH gene (c.245-7_245-8delinsTTCA)	None identified
Anti-CFH antibodies	Pending	Negative	Pending	Pending	Positive
Concomitant disease	Congenital spherocytosis	Evans syndrome	Increased cranial pressure	Ischemic complications of TMA (skin, intestinal, and limb)	None
Treatment prior to eculizumab	Plasma exchange	Plasma exchange	Plasma exchange	Plasma exchange	Plasma exchange
Duration of disease at first dose of eculizumab	1 ½ weeks	25 days	2 months	2 years 3 months	14 days
Eculizumab doses preceding changes in liver enzymes	2	1	2	4	1
Creatinine (μmol/l) at first dose of eculizumab	175	63	89	382	67
Dialysis at first dose of Eculizumab	No	No	No	Hemodialysis	No
ALT max (baseline)	908 (19)	175 (21)	249 (24)	360 (16)	129 (19)
AST max (baseline)	1107 (40)	491 (89)	244 (23)	373 (44)	262 (26)
GGT max (baseline)	1039 (26)	40 (24)	445 (29)	33 (14)	29 (19)
ALK max (baseline)	1023 (114)	240 (56)	229 (90)	571 (304)	173 (75)
Conjugated bilirubin max (baseline)	168 (0)	35 (0)	125 (0)	7 (0)	6 (0)
Platelets ($\times 10^9$/l) at first dose of eculizumab	561	202	176	282	243
LDH at first dose of eculizumab	3250	1034	650	1062	922
Haptoglobin at first dose of eculizumab	0.59	0.87	1.28	1.07	<0.10
Liver biopsy	Hepatocellular cytoplasmic swelling, Kupffer cell hemosiderosis, sinusoidal fibrosis	N/A	N/A	Mild chronic eosinophilic portal inflammation, mild fibrosis, moderate iron accumulation	N/A
Follow up on eculizumab without liver injury	0 months	11 months	8 months	2 months	17 months

A possible explanation for the observed liver injury in this series is the underlying disease process itself. Hepatitis was reported in 50 % of 27 patients with anti-CFH autoantibody-mediated aHUS, although the degree of liver enzyme derangement was not characterized [28]. In our case series, however, liver injury was temporally associated with eculizumab dosing rather than with aHUS disease presentation. We observed liver enzyme derangement 10 to 29 days following initiation of eculizumab, but 10 days to 2 years 3 months following presentation with aHUS.

In 4 of the 5 cases in this series, liver enzyme derangement was transient, asymptomatic, and did not compromise treatment. In one case, however, clinical symptoms of tender hepatomegaly coupled with recurrent liver enzyme derangement and jaundice led us to discontinue eculizumab and change to plasma therapy. Discontinuation of biological therapy for hepatotoxicity is relatively common in cancer treatment (e.g., discontinuation of erlotinib or imatinib for cytolytic hepatitis or gemtuzumab for cytolytic hepatitis); however, this is a novel complication in the treatment of aHUS [29].

The underlying mechanisms of hepatotoxicity associated with biological therapies remain incompletely understood [29]. Certain therapies are associated with specific patterns of hepatotoxicity, for example, sinusoidal obstruction syndrome secondary to gemtuzumab ozogamicin [30]. Specific targeting of hepatic Kupffer cells was initially thought to be the major mechanism responsible [30], but accumulation of antibody–toxin conjugates in hepatocytes causing calicheamicin-induced damage has subsequently been demonstrated [31].

The mechanism of hepatotoxicity potentially related to eculizumab in this case series has not yet been elucidated. A potential mechanism for our observations relates to the role of C5 in normal liver regeneration and its role in hepatocyte defense mechanisms during inflammation. C5 activity was found to be important in liver regeneration in a murine model of liver toxicity [32]. Further animal studies have demonstrated a potential role for C5 in defense reactions of Kupffer cells and hepatocytes [33]. Eculizumab may therefore disrupt hepatic regeneration and defense reactions.

Other possible mechanisms include a hypersensitivity reaction, off-target effects of the monoclonal antibody [34], and local hepatic side effects of C5 terminal complement blockade. Recent data from renal biopsies following long-term eculizumab therapy suggest direct antibody binding to tissue C5 [35]. If a similar process occurs in the liver, this may play a role in hepatotoxicity.

Some studies would lead one to hypothesize a hepatoprotective effect of eculizumab. Hillebrandt et al. found the Hc gene (which encodes complement C5) to be a significant modifier of liver fibrogenesis in animal studies. In addition, an association between genetic haplotypes associated with higher serum C5 levels and aggravated liver fibrogenesis in human patients with hepatitis C has been observed [36]. Given these findings, one could hypothesize that C5 blockade might slow the progression of liver fibrosis, as has been suggested in case reports [27].

The long-term consequence of recurrent subclinical hepatocellular injury, which may be related to maintenance eculizumab therapy, is not known. Reports of cirrhosis and chronic hepatitis following acute idiosyncratic drug-induced liver injury are concerning in this regard [37].

To our knowledge, hepatotoxicity in association with eculizumab has not previously been reported. This may be an effect that has escaped the attention of clinicians, as it was subclinical in all but one case in this series. The true prevalence of this side effect remains to be established as hepatic enzyme monitoring has not been part of routine clinical monitoring for patients receiving eculizumab to date.

In light of the consistent finding of hepatotoxicity in this series we recommend regular monitoring of hepatic enzymes in all patients receiving eculizumab and caution in its use in patients with pre-existing liver disease. In patients with excessive hepatic enzyme disturbance or clinical symptoms of hepatitis in association with eculizumab, plasma therapy may have to be considered as an alternative treatment. Further research is required to clarify the impact of this adverse effect, to characterize the mechanism of potential hepatotoxicity, and to identify which patients are most at risk.

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Conflict of interest The other authors declare no conflict of interest.

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