

# Ecuzumab as First-Line Therapy for Atypical Hemolytic Uremic Syndrome

**AUTHORS:** Martin Christmann, MD, PhD,<sup>a</sup> Matthias Hansen, MD, PhD,<sup>b</sup> Carsten Bergmann, MD, Prof,<sup>c</sup> Dirk Schwabe, MD, Prof,<sup>a</sup> Jörg Brand, MD, PhD,<sup>a</sup> and Wilfried Schneider, MD, PhD<sup>a</sup>

<sup>a</sup>Klinik für Kinder- und Jugendmedizin, Pädiatrische Intensivstation, Goethe-Universität, Frankfurt/Main, Germany;

<sup>b</sup>Clementine Kinderkrankenhaus, Pädiatrische Nephrologie, Frankfurt/Main, Germany; and <sup>c</sup>Bioscientia Institut für Medizinische Diagnostik GmbH, Humangenetik, Ingelheim, Germany

## KEY WORDS

atypical hemolytic uremic syndrome, complement, ecuzumab, infant

## ABBREVIATIONS

ADAMTS13—a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13

aHUS—atypical hemolytic uremic syndrome

CFB—complement factor B

CFH—complement factor H

CFHR—complement factor H-related

CFI—complement factor I

DGKE—diacylglycerol kinase  $\epsilon$

HUS—hemolytic uremic syndrome

LDH—lactate dehydrogenase

PE—plasma exchange

PI—plasma infusion

STEC—Shiga toxin-producing *Escherichia coli*

TMA—thrombotic microangiopathy

Dr Christmann was involved in the treatment of the patient and composed the initial manuscript; Dr Hansen, Prof Dr Schwabe, and Drs Brand and Schneider were involved in the treatment of the patient and reviewed and revised the manuscript; Prof Dr Carsten Bergmann performed the genetic analysis in this case and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to Martin Christmann, MD, PhD, Klinik für Kinder- und Jugendmedizin, Pädiatrische Intensivstation, Goethe-Universität, 60590 Frankfurt/Main, Germany. E-mail: [martin.christmann@kispi.uzh.ch](mailto:martin.christmann@kispi.uzh.ch)

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## abstract

Atypical hemolytic uremic syndrome (aHUS) is a genetic, life-threatening, chronic disease that can affect patients of all ages. aHUS is caused by uncontrolled complement activation due to genetic defects of complement regulation. Plasma exchange or infusion has been used to manage aHUS and may transiently maintain hematologic variables in some patients, but as the underlying complement dysregulation persists, end-stage renal disease or death occurs in 33% to 40% of patients during the first clinical manifestation. Here we present a pediatric case showing that first-line ecuzumab treatment successfully blocked the progression of thrombotic microangiopathy in aHUS. *Pediatrics* 2014;133:e1759–e1763

Atypical hemolytic uremic syndrome (aHUS), so called to distinguish it from hemolytic uremic syndrome (HUS) caused by Shiga-like toxin producing *Escherichia coli* (STEC; STEC-HUS) or other bacteria such as *Streptococcus pneumoniae*, is a rare, severe genetic disease.<sup>1,2</sup> aHUS is the result of defects in complement regulation. Consequently, constitutively activated complement attacks vascular endothelium, leading to systemic thrombotic microangiopathy (TMA) and the classic signs and symptoms of HUS: thrombocytopenia, hemolytic anemia, and reduced renal function.<sup>3</sup> In the absence of Shiga-like toxin, or bacteria producing Shiga toxin, and with no severe deficiency in the activity of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), this triad often suggests a diagnosis of aHUS.<sup>2-4</sup> The prognosis of aHUS is generally worse than that of STEC-HUS, with end-stage renal disease in 30% to 50% of cases and a marked increase in mortality.<sup>2,5</sup>

Approximately 20% of aHUS cases are the result of mutations in the gene coding for complement factor H (CFH). Other known genetic abnormalities resulting in aHUS include defects in complement factor I (CFI), membrane cofactor protein, complement factor B (CFB), and C3. It has been shown that mutations in the CFH gene lead to impaired complement activation and regulation on the surface of endothelial cells, with subsequent endothelial cell destruction, platelet aggregation, hemolysis, and renal insufficiency. However, causative mutations exhibit variable and incomplete penetrance.<sup>2,5</sup>

In the past, the mainstay of treatment of aHUS has been plasma exchange (PE) or plasma infusion (PI). Even with PE/PI, however, 65% of patients with aHUS require dialysis, have permanent kidney damage, or die within 1 year of

diagnosis.<sup>4,6,7</sup> Eculizumab is a monoclonal antibody against C5, designed to suppress terminal complement activation and prevent TMA. In prospective clinical trials, eculizumab has been shown to inhibit TMA progression and prevent or reverse organ damage.<sup>4</sup> Here we present the first reported case of an infant in whom eculizumab was initiated as first-line therapy without previous PE/PI.

## PATIENT PRESENTATION

We report on a 5.5-month-old girl who presented with pallor, fatigue, and nonbloody diarrhea. On admission, she was jaundiced, with elevated lactate dehydrogenase (LDH), progressive anemia, and thrombocytopenia, indicating TMA.

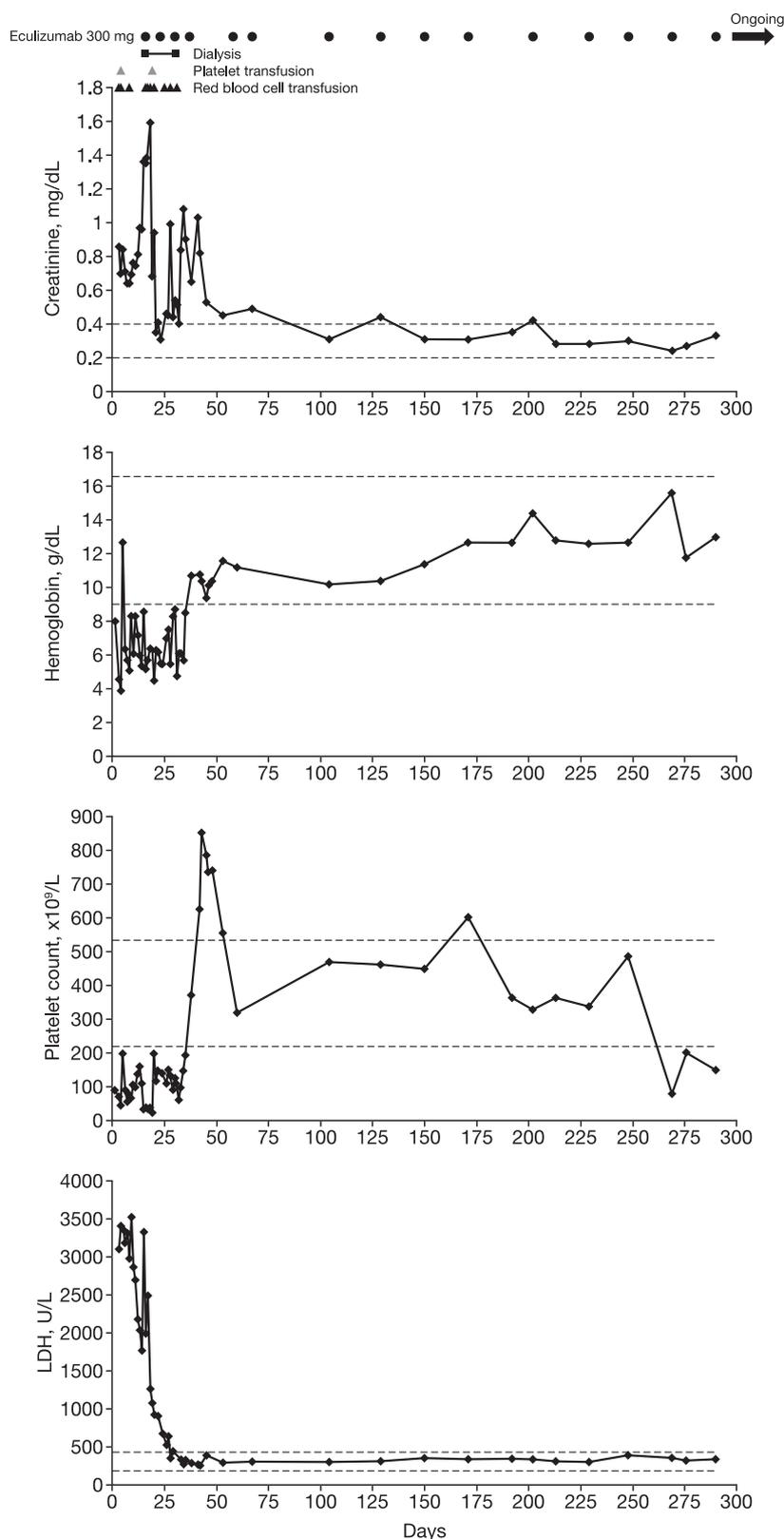
The patient was admitted to the ICU at our center with severe arterial hypertension that was treated with enalapril ( $2 \times 1$  mg/day), metoprolol ( $4 \times 2$  mg/day), hydrochlorothiazide ( $2 \times 10$  mg/day), and furosemide ( $3 \times 2$  mg/day). Her hypertension improved after 2 days, and because there appeared to be no major impairment in renal function, she was transferred to a regular ward. Seven days later, uncontrolled hypertension developed and, despite starting continuous furosemide therapy, urine production ceased. Treatment with nitroprusside was initiated back in the ICU.

An investigation for HUS revealed that the patient was negative for STEC, with normal ADAMTS13 activity, C4 in the normal range (11.8 mg/dL; normal: 10–40 mg/dL), and decreased C3 levels (61.5 mg/dL; normal: 90–180 mg/dL). This impairment in an infant <6 months of age, together with high LDH (3099 U/L; normal: 180–430 U/L), low hemoglobin levels (4.6 g/dL; normal: 9.0–16.6 g/dL), thrombocytopenia ( $71 \times 10^9/L$ ; normal:  $217\text{--}533 \times 10^9/L$ ), schistocytes, and a negative Coombs test and renal impairment (creatinine:

0.86 mg/dL; normal: 0.2–0.4 mg/dL), supported a preliminary diagnosis of aHUS. Ten days after referral, peritoneal dialysis was initiated but was switched to hemodialysis 3 days later. At the same time, eculizumab treatment was started at 300 mg per week for 4 weeks, and decreased thereafter to 300 mg every 3 weeks. In addition to the mandatory vaccinations against meningococci, pneumococci, and *Haemophilus influenzae* required in children receiving eculizumab,<sup>4</sup> antibiotic prophylaxis with oral penicillin was also provided.

After the third day of eculizumab therapy there was a marked decrease in hemolysis, as shown by a decrease in LDH levels (Fig 1). Ten days after eculizumab and dialysis were initiated, nitroprusside treatment was stopped, although the patient subsequently started treatment with enalapril (2 mg/day) and amlodipine (3 mg/day). Two weeks after the first eculizumab infusion, the patient no longer required dialysis. The glomerular filtration rate continued to increase, from 42 mL/minute at 3.5 weeks after starting treatment to 115 mL/minute at 9 months. She continues to receive 300 mg of eculizumab every 3 weeks, as well as 2 mg of enalapril and 1.3 mg of amlodipine per day, and her condition is very good. Oral antibiotic prophylaxis with penicillin is ongoing due to a lack of effective antimeningococcal vaccine (serogroup B).

Genetic analysis later revealed a previously unreported heterozygous CFH mutation in the patient, her 3- and 5-year-old siblings, and her father (c.2242\_2245delGATA [p.Asp748AsnfsX10]), none of whom have experienced any HUS symptoms to date. No other mutations known to be associated with aHUS have been found (CFH-related [CFHR] 1 [CFHR1], CFHR2, CFHR3, CFHR5, membrane cofactor protein (MCP), CFB, C3, CFI, THBD [thrombomodulin], and CFHR5 were analyzed).



**FIGURE 1**

Response to eculizumab, as shown by creatinine level, hemoglobin level, platelet count, and LDH level, in a 5.5-month-old girl with atypical hemolytic uremic syndrome. The x-axis represents days since first hospital admission. The dashed lines show the normal range for each measure.

## DISCUSSION

aHUS is now known to be the result of defects in genes associated with the complement cascade.<sup>8–10</sup> The resulting lack of inhibition leads to uncontrolled complement activation, TMA, endothelial lesions, and platelet aggregation leading to the typical triad of HUS symptoms: hemolytic anemia, thrombocytopenia, and renal insufficiency.<sup>5</sup> Distinguishing aHUS from STEC-HUS, particularly in infants, is often difficult and may take several days, which may be detrimental to outcomes.<sup>2</sup> Bloody diarrhea as an early symptom does not always mean typical or STEC-HUS, especially in children <6 months of age, because only 5% of STEC-HUS cases occur in this age group.<sup>2</sup> Therefore, an alternative cause of HUS may be suspected.<sup>11,12</sup> In contrast, diarrhea due to a gastroenteritis might be a trigger for an aHUS episode. Several groups of clinicians have presented diagnostic approaches to differentiate between aHUS and typical HUS forms.<sup>1,4,11,13</sup> The first diagnostic steps should start with a thorough medical history, with a focus on bloody diarrhea, the age of the patient, and family history of aHUS or renal disease. If an infection with enterohemorrhagic *E coli*, *Shigella dysenteriae*, or invasive *S pneumoniae* has been excluded, a full investigation of alternative HUS forms is necessary. This investigation includes the measurement of ADAMTS13 activity as well as C3, C4, CFB, CFH, and CFI levels.<sup>1,4,13</sup> A useful diagnostic algorithm was presented by Zuber et al.<sup>4</sup> In addition to the above-mentioned complement factors and regulatory proteins, recessive mutations in diacylglycerol kinase  $\epsilon$  (DKGE) and deficiency in cobalamin metabolism can cause aHUS-like symptoms, especially before the age of 1 year.<sup>14</sup>

Standard management of aHUS has been PE/PI, which aims to replace the missing complement regulatory

factors. PE/PI does not effectively block complement-mediated TMA in patients with aHUS; 65% of patients with aHUS require dialysis, have permanent kidney damage, or die within 1 year of diagnosis.<sup>4,6,7</sup> More recently, treatment with the monoclonal antibody eculizumab has become available. Eculizumab blocks the final pathway of the complement cascade by targeting C5, thereby preventing formation of the terminal complement complex C5b-9. To date, 3 case reports of treatment with eculizumab in infants have been published.<sup>9,10,13</sup> They describe the use of eculizumab after unsuccessful PE/PI in the neonatal period or in very young infants, in contrast to our case, in which eculizumab was used as first-line therapy in an infant for the first time. In all 3 cases, eculizumab therapy led to sustained recovery of renal function. Several case studies have also been published in older children, revealing the benefits of eculizumab after unsuccessful PE/PI.<sup>8,15–18</sup>

Because our patient had a very high probability of aHUS, even without having results of genetic testing, and given these positive reports of eculizumab, we decided to use eculizumab as first-line therapy without previous plasmapheresis. Our decision was also encouraged by the need to initiate treatment quickly to avoid TMA progression and permanent organ damage,

because other studies have shown a negative effect of treatment delay to recovery of renal function.<sup>19,20</sup>

As described above, positive effects on hemolysis and microangiopathy appeared rapidly (within a few days), and the patient has remained free of TMA symptoms for 9 months. A short episode of thrombocytopenia not associated with anemia, hemolysis, or renal insufficiency was interpreted as a side effect of a viral infection. Thrombocyte count normalized quickly. Eculizumab treatment is ongoing because previous experience has shown that interruption of treatment can lead to detrimental consequences for the patient. Giordano et al<sup>9</sup> reported the case of an 8-month-old boy with aHUS in whom eculizumab treatment was stopped after 18 months of remission. Forty-five days later, the patient experienced progressive reduction in platelet count and recurrence of proteinuria, despite the lack of systemic TMA symptoms. Eculizumab was restarted, with immediate normalization of biochemical variables.

A final recommendation as to how long eculizumab treatment should be continued, or which clinical or laboratory signs suggest that treatment may be discontinued, cannot be made. Also, it remains unclear whether aHUS is a disease to be treated homogeneously

despite different genetic causes. The recent finding of DGKE mutations may have important implications in the management of aHUS patients aged <1 year. Because safe discontinuation of eculizumab is possible if the unique cause of TMA is identified as mutations in DGKE or a deficiency in cobalamin metabolism, we nevertheless recommend that eculizumab treatment be started as soon as aHUS is suspected. It will be essential to design prospective clinical studies to assess in which patient group discontinuation of therapy should be considered. Designing these studies will be very challenging: randomly assigning eculizumab or placebo may be difficult because of ethical reasons.

In conclusion, the benefits of eculizumab in this case suggest that first-line eculizumab therapy should be recommended to stop TMA progression and to avoid irreversible organ damage in patients in whom, according to the aforementioned diagnostic criteria, aHUS is suspected. Eculizumab has been well tolerated in this patient, with no safety concerns becoming apparent.

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