Eculizumab as First-Line Therapy for Atypical Hemolytic Uremic Syndrome

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**KEY WORDS**
atypical hemolytic uremic syndrome, complement, eculizumab, 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 ε
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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**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 eculizumab 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.1,2 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.3 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 of symptoms to date. No other mutations were found (CFH-related [CFHR] 1 [CFHR1], CFHR2, CFHR3, CFHR5, membrane cofactor protein [MCP], CFB, C3, CFI, THBD [thrombomodulin], and CFHR5 were analyzed).
aHUS is now known to be the result of defects in genes associated with the complement cascade. 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. Distinguishing aHUS from STEC-HUS, particularly in infants, is often difficult and may take several days, which may be detrimental to outcomes. 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. Therefore, an alternative cause of HUS may be suspected. 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. 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. A useful diagnostic algorithm was presented by Zuber et al. In addition to the above-mentioned complement factors and regulatory proteins, recessive mutations in diacylglycerol kinase ε (DKGE) and deficiency in cobalamin metabolism can cause aHUS-like symptoms, especially before the age of 1 year. Standard management of aHUS has been PE/PI, which aims to replace the missing complement regulatory
After unsuccessful PE/PI, revealing the benefit as other studies have shown a negative effect of treatment delay to recovery of renal function. 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 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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