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BRIEF REPORT

# Eculizumab as rescue therapy for atypical hemolytic uremic syndrome with normal platelet count

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**Abstract**
*Background* Atypical hemolytic uremic syndrome (aHUS) in childhood is a rare disease with frequent progression to end-stage renal disease and a high recurrence after kidney transplantation. Eculizumab, a humanized monoclonal antibody that binds to complement protein C5, may be beneficial in the treatment of aHUS.
*Case-diagnosis/treatment* A 6-year-old girl developed aHUS with only slightly elevated C3d (4.4%), no mutations in complement factors, and no antibodies against factor H. Plasma exchange treatment was successful initially, until aHUS recurred. After reinitiating plasma exchange, normalization of the platelet count and improvement of hemolysis occurred, but renal function worsened. Renal function then improved dramatically promptly after the switch to eculizumab.
*Conclusions* This case demonstrates that platelet count is not always a reliable marker for improvement of aHUS and that eculizumab can prevent dialysis in plasma-resistant aHUS patients.

**Keywords** Eculizumab · Atypical hemolytic uremic syndrome · Acute kidney failure · Child

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## Introduction

Hemolytic uremic syndrome (HUS) is a severe disease characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney failure. In children, over 90% of HUS is caused by a Shiga toxin-producing *E. coli* (STEC) infection [1]. The remaining cases, termed atypical HUS (aHUS), concern a heterogeneous group of diseases, the majority having a dysregulation of the complement system. Atypical HUS has a poor prognosis: It frequently progresses to end-stage renal disease, often recurs after renal transplantation, and has a high mortality rate. Plasma therapy is the current treatment of choice. However, the latest case reports show the possible benefit of eculizumab, a humanized monoclonal antibody that binds to complement protein C5, thereby preventing activation of the terminal complement pathway [2–5]. Two phase II eculizumab trials in adults and adolescents with aHUS resistant to, or dependent on, plasmapheresis, showed promising results [6–8]. Five of the seven plasmapheresis-resistant dialysis patients became free of dialysis [6]. An open-label multicenter phase II eculizumab trial in children aged from 1 month to 18 years has recently started (NCT 01193348). Here we describe the successful treatment with eculizumab of a 6-year-old girl with aHUS, partially resistant to plasmapheresis.

## Case report

A formerly healthy 6-year-old girl presented with fever, vomiting, and lethargy without diarrhea. Laboratory tests revealed hemolytic anemia, thrombocytopenia, and severe renal insufficiency consistent with HUS. STEC and other bacterial and viral infectious agents were not detected.

Analysis of the complement system revealed only a slightly elevated C3d of 4.4% (reference value <3%). Although platelet count initially spontaneously increased to $195 \times 10^9$/l, the girl's kidney function progressively deteriorated and she developed severe hypertension. Plasmapheresis with fresh-frozen plasma (FFP) 80 ml/kg was initiated at the 7th day of admission for 3 days consecutively, followed by every other day for 3 weeks. Serum creatinine started to decline, platelet count further increased, and signs of hemolysis disappeared. After 3 weeks, plasmapheresis was replaced by plasma infusions.

Genetic work-up showed no mutations in complement factor H, I, B, complement C3, or MCP. Multiplex ligation-dependant probe amplification (MLPA) to detect the presence of homozygous deletions in the complement factor H-related 1 (CFHR1) gene was not performed. No factor H antibodies were detected. Lupus anticoagulins and antinuclear autoantibodies were negative and ADAMTS 13 activity was normal. In the 6th week after initial presentation, the girl developed an upper respiratory infection with recurrence of aHUS. Plasmapheresis was immediately reinstituted for 3 days consecutively, followed by an alternate day regimen. Although the platelet count promptly increased, renal function kept deteriorating and hypertension was hard to control with a four antihypertensive drug regimen. After renal biopsy confirmed severe thrombotic microangiopathy without globally sclerosed glomeruli (Fig. 1), plasma therapy was again intensified to daily exchanges. This had no effect on renal function; the girl became oliguric and needed dialysis. At that point, therapy was switched to eculizumab (Soliris®, 600 mg intravenously once weekly, followed by 600 mg every other week). Thereupon, renal function started to improve within 48 h (Fig. 2), diuresis increased and over weeks the four antihypertensive drugs could be reduced to ACE-inhibition monotherapy. Prophylactic therapy with feneticilline was started and the girl was vaccinated against *Neisseria meningococcus* with a quadrivalent vaccine

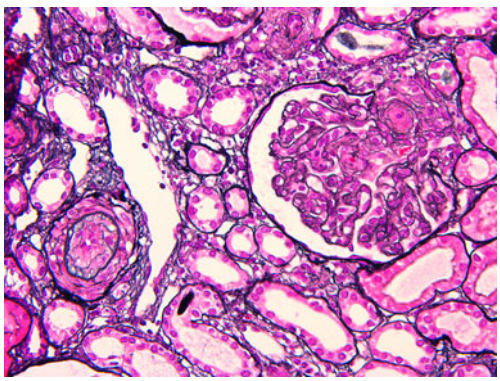

**Fig. 1** Renal histology before starting eculizumab. Magnification×400. Periodic acid Schiff (PAS)- and Jones-stained section showing obliterated arteriolae, mesangial infiltration, and narrowing of the capillary lumina

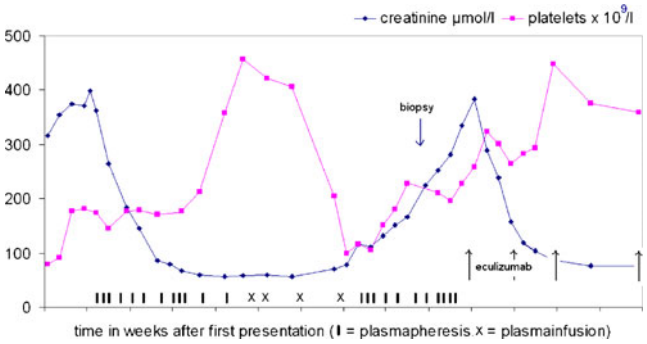


**Fig. 2** Serum creatinine and platelet count plotted with the used treatment modalities in atypical hemolytic uremic syndrome (aHUS) during the follow-up period

(Mencevax ACWY) and against *Streptococcus pneumoniae* (Pneumovax®, a 23-valent vaccine). There were no adverse events. Currently, 9 months after initiation of eculizumab treatment, renal function is normal, proteinuria minimal (urinary protein/creatinine 30 mg/mmol), and hypertension has disappeared. Alternate-week eculizumab infusions are continued.

## Discussion

Here we describe a child with relapsing aHUS with normalized platelet count during intensive plasmapheresis, but ongoing decline in renal function, whose renal function remarkably ameliorated with eculizumab treatment, thereby bypassing the need for renal replacement therapy.

Eculizumab is a humanized monoclonal antibody that binds to complement protein C5, thereby preventing the formation of the membrane attack complex (MAC). The fact that renal function of our patient promptly improved through blocking of the terminal pathway by eculizumab confirms the central role of complement in aHUS, despite almost normal complement analysis. Furthermore, we found no mutations in the complement system, although MLPA reaction of the CFHR1 gene was not performed, nor factor H antibodies.

As platelet counts had normalized, our patient was not eligible for the international study on effects of eculizumab in children with aHUS (NCT 01193348). However, this case clearly shows that a rise in platelet count is not always a reliable marker of disease recovery and the search for other biomarkers for disease activity management is still warranted. Fortunately, eculizumab treatment led to a recovery of the acute renal failure, by not only normalizing renal function but also hypertension and proteinuria. Eculizumab even seems to be more effective than plasmapheresis considering the lower amount of proteinuria at 4 weeks after plasma therapy compared to eculizumab treatment, shown

in Table 1. Eculizumab therapy is still being continued, at 600 mg IV every 2 weeks, with sustained remission. The optimal dose, dosing interval, and duration of treatment are unclear and need further study.

In conclusion, in this case, an adequate, intensive plasmapheresis schedule started immediately at relapse of aHUS restored the hematological parameters, but not kidney function. However, the switch to eculizumab saved this patient from dialysis treatment and even normalized the kidney function. Treatment with complement inhibitors has a high potential to become the standard therapy for aHUS, even in patients with no complement mutations identified.

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