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CASE REPORT

Renal outcome with eculizumab in two diarrhea-associated hemolytic–uremic syndrome cases with severe neurologic involvement



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Summary The kidney and brain are the two target organs in patients with Shiga toxin-producing *Escherichia coli*-associated hemolytic–uremic syndrome (STEC-HUS). Activation of the alternative complement pathway occurs in patients with STEC-HUS. A monoclonal antibody (eculizumab) directed against C5 has been reported to be effective against severe neurologic involvement in patients with STEC-HUS. We report on two STEC-HUS children with severe neurologic involvement treated with eculizumab. Despite prompt resolution of initial neurologic findings upon treatment with eculizumab, proteinuria and hypertension persisted in these patients. The persistence of these two risk factors is particularly emphasized to discuss the long-term effects of eculizumab, especially on renal involvement.

產志賀毒素大腸桿菌相關溶血性尿毒症候群 (STEC-HUS) 的目標器官包括腎臟及腦部，在患者體內會出現補體替代途徑的活化。有報告指出，對於 STEC-HUS 所表現的重度神經學併發症，C5 單株抗體 (eculizumab) 具有若干效用。以下兩宗兒童個案，均為兼具重度神經學併發症的 STEC-HUS，且接受了 eculizumab 治療。治療期間神經學方面出現迅速改善，然而仍持續有蛋白尿及高血壓情形，因此必須注意 eculizumab 的長期影響特別是腎臟效應。

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Introduction

The recent outbreak of *Escherichia coli* O104:H4 (EHEC O104:H4) in Germany in May 2011 provided a great deal of new information for the management of Shiga toxin-producing *E. coli*-associated hemolytic–uremic syndrome (STEC-HUS) patients, especially for severely infected cases.^{1–3} The prompt resolution of neurologic findings in STEC-HUS patients upon treatment with eculizumab right at the peak of that outbreak had been reported from Canada.⁴ A total of 328 patients and 13 children were treated with eculizumab during the outbreak in Germany.^{1,2} There was also a limited outbreak of diarrhea-associated hemolytic–uremic syndrome (D + HUS) in Turkey in 2011.⁵ We had some experience in treating patients with eculizumab during that outbreak, and would like to discuss two of them from our experience to demonstrate the effectiveness of the drug and its safety.

Case reports

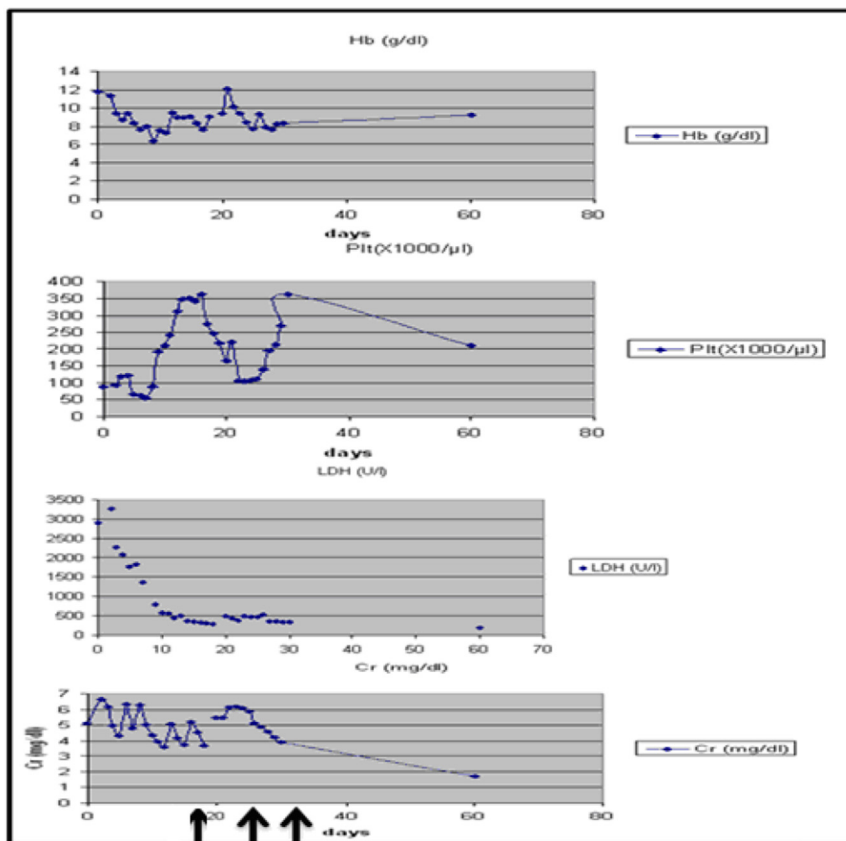
Case 1

A 9.5-year-old girl presented with visual hallucinations, lethargy, vomiting, and abdominal pain 3 days after experiencing watery diarrhea. The patient had watery diarrhea with vomiting that lasted for 2 days. Her urine output was decreased in the past 2 days and she was apathetic and hallucinating since that morning. On physical examination she had tremor in her hands, altered consciousness, and confusion with normal blood pressure (100/60 mmHg, <95th percentile). Based on low platelet count ($88.2 \times 10^3/\mu\text{L}$), low haptoglobin level (<8 mg/dL), fragmented erythrocytes in the blood smear, and high creatinine (5.02 mg/dL) and lactate dehydrogenase (LDH; 2902 U/L) levels, D + HUS was diagnosed. Leukocytosis was also present ($21.6 \times 10^3/\mu\text{L}$). Complement C₃ level was normal (93 mg/dL). *E. coli* O157:H7 serotype was isolated from her stool culture and polymerase chain reaction (PCR) detected Shiga toxin 2. The patient received plasma exchange (PE) therapy with a dose of 60 mL/kg fresh frozen plasma—five times initially on a daily basis and five times/week for the following 2 weeks together with hemodialysis. However, neurological disturbance including somnolence and hallucinations persisted. Because magnetic resonance imaging (MRI) device was temporarily unavailable at that time, noncontrast tomography was performed for cranial imaging and the result was normal. On the 19th day of hospitalization during the 15th PE session, the patient complained of blindness and then developed a generalized tonic–clonic convulsion and became unconscious. Her blood pressure, plasma calcium level (9.6 mg/dL), and electrolytes were within normal limits. Because of extreme agitation, midazolam infusion together with 2 L/minute oxygen was administered. She was vaccinated immediately against *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* infections (all at the same time) and a prophylactic antibiotic was prescribed. Eculizumab therapy (Soliris; Alexion Pharmaceuticals, Cheshire, CT, USA) was initiated immediately on the day of convulsion at a weekly dose of 600 mg for 3 weeks. Just before the eculizumab infusion was started, her hemoglobin level (9.05 g/dL), platelet count ($246 \times 10^3/\mu\text{L}$), and LDH level (280 IU/L) were stable but she was still anuric.

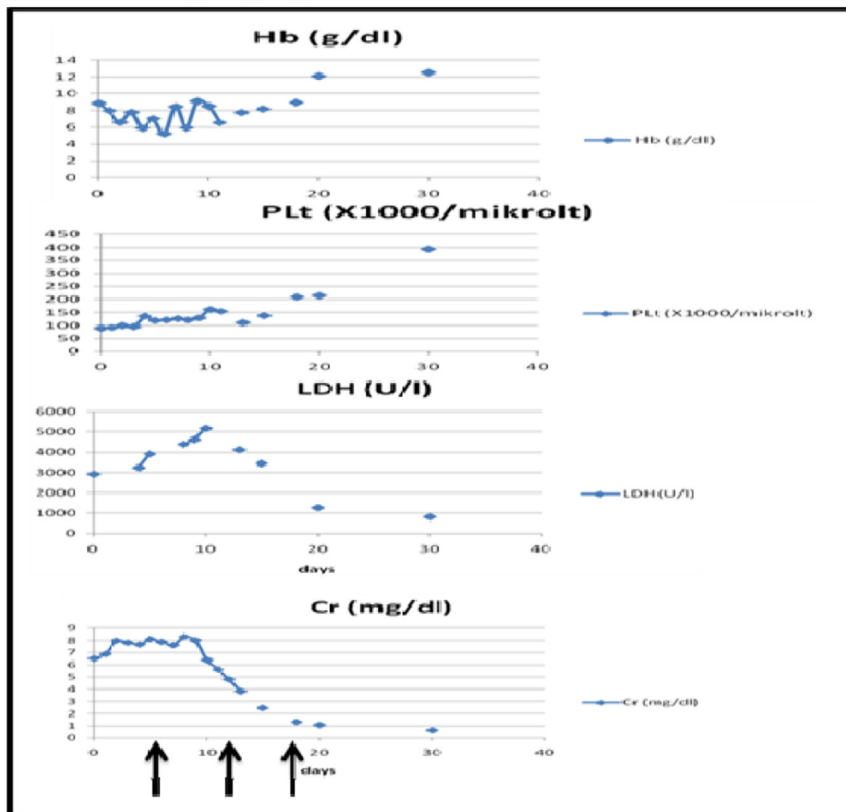
Following the first dose of eculizumab, the patient's neurological condition improved dramatically within 48 hours; however, anuria slowly resolved over 6 days after the first eculizumab infusion. The course of the laboratory findings are shown in Fig. 1 (Case 1). Nephrotic-range proteinuria (45.78 mg/m²/hour) and diminished renal functions [estimated glomerular filtration rate (eGFR): 44.93 mL/minute/1.73 m²] persisted on the 90th-day visit. The patient was hypertensive, and thus required treatment with ramipril. At the end of 1st year of treatment, her serum creatinine level was still above the normal limits (1.08 mg/dL, eGFR: 63.65 mL/minute/1.73 m²) and mild proteinuria was recorded (13.82 mg/m²/hour). The patient's blood pressure was under control with ramipril treatment. An analysis of *factor I*, *H*, and *MCP* genes did not identify any mutation.

Case 2

A 20-month-old girl was admitted with altered consciousness. She had a history of watery diarrhea for 4 days, which was treated with ceftriaxone. On the 4th day, the patient developed altered consciousness, weakness, and convulsion. An initial examination revealed an unconscious and pale child with normal blood pressure (90/60 mmHg, <95th percentile). Based on low platelet count ($89.10 \times 10^3/\mu\text{L}$), fragmented red blood cells in the blood smear, low hemoglobin (8.84 g/dL), low haptoglobin (<8 mg/dL), high creatinine (6.46 g/dL), and high LDH (2934 U/L) levels, D + HUS was diagnosed. Complement C₃ level was 75 mg/dL (90–180). During admission in the emergency department, her serum sodium level was 120 mEq/L and she was treated with 3% NaCl to control convulsions. In 48 hours, her serum sodium level was increased to 135 mEq/L and her consciousness was normal. Peritoneal dialysis (PD) was initiated on the day of admission. Neither Shiga toxins 1 and 2 could be shown with PCR nor could enterohemorrhagic *E. coli* be isolated from the stool, possibly because of the previous ceftriaxone treatment. On the 4th day of hospitalization while her serum sodium level was 137 mEq/L and blood pressure was normal, she presented with altered consciousness and dystonic movements. MRI revealed diffusion restriction in the right hemisphere. Laboratory evaluation on that day revealed the following measurements: hemoglobin, 7.79 g/dL; platelets, $95.20 \times 10^3/\mu\text{L}$; LDH, 3254 U/L; creatinine, 7.83 mg/dL; and haptoglobin level <8 mg/dL. The course of the laboratory findings is shown in Fig. 1 (Case 2). She was still anuric and thus PD was continued. Because of the difficulties involved in initiating PE therapy for infants and a previous report demonstrating the effectiveness of eculizumab in STEC-HUS patients with neurologic involvement, treatment with eculizumab was initiated at a dose of 600 mg/week for the 1st week on the day of altered consciousness and dystonic movements. The treatment was continued at a dose of 300 mg/week for the 2nd week and 300 mg every 2 weeks from the 3rd week onward. Vaccination against *H. influenzae* and *S. pneumoniae* infections was performed as previously described. Vaccination against *N. meningitidis* infections was performed immediately prior to treatment with eculizumab and prophylactic antibiotics were prescribed. Recovery of consciousness and dystonic movements were observed after 48 hours. Platelets increased immediately on the 1st day.



Case 1



Case 2

Figure 1 Course of laboratory findings of patients during the eculizumab therapy period (black arrows are days of eculizumab treatment). Case 1 received 15 sessions of plasma exchange before eculizumab therapy was initiated. Cr = creatinine; Hb = hemoglobin; LDH = lactate dehydrogenase; Plt = platelet.

Creatinine level began to decrease 5 days later. The LDH level began to decrease 9 days later. The need for transfusion ended 10 days later and haptoglobin level returned to normal limits after 3 weeks. The patient developed hypertension at the end of 2 weeks and required ramipril therapy. However, proteinuria persisted in the nephrotic range, and at the end of 8 months urine protein-to-creatinine ratio was still 2.46 mg/mg. The patient's blood pressure was normalized with ramipril therapy. An analysis of *factor I*, *H*, and *MCP* genes did not identify any mutation.

Discussion

Activation of the alternative complement pathway may contribute to the pathogenesis of STEC-HUS and further clinical research is needed to determine whether blockade of this pathway can attenuate the disease.⁶ Lapeyraque et al⁴ reported dramatic resolution of symptoms upon treatment with eculizumab in three STEC-HUS patients with central nervous system involvement who did not respond to PE therapy during the outbreak in Germany in May 2011. Following the publication of this report, a multicentre, single-arm, open-label 28-week clinical study was initiated in Germany and a total of 328 patients received eculizumab therapy.¹ Currently, there are three published reports on the experience of using eculizumab during the outbreak in Germany.^{2,3,7} In the pediatric series of Loos et al,³ it was reported that even in STEC-HUS cases with O104:H4, there is no need for novel treatments besides intensive supportive care. Menne et al² reported no demonstrable benefit of either eculizumab or plasmapheresis. In the study by Kielstein et al,⁷ 193 patients were treated in combination with PE and eculizumab (PE+Ecu). They were more severely ill patients compared with the patients treated who received supportive care ($n = 57$) or PE ($n = 241$) alone. Because of this, a direct comparison of the three treatment groups was not possible. At the study end point, the median creatinine level was higher in the PE+Ecu group. However, the need for dialysis and total hospital mortality did not significantly differ between the PE and the PE+Ecu groups. Because of limitations in available data, these results are insufficient to support the notion that PE+Ecu in comparison with PE offers a marked short-term benefit in the treatment of STEC-HUS.

Although we could only show *E. coli* O157:H7 in one of these patients we think that the girls were STEC-HUS cases because of the history of self-limited watery diarrhea and the normal *factor H*, *I*, and *MCP* genes (i.e., no mutations were observed in these genes). Both of the cases presented with neurologic involvement and showed dramatic improvement of neurologic findings with eculizumab therapy. Both of the cases also had chronic renal disease with proteinuria and hypertension after 3 months of follow up. One of them also showed low eGFR. We think that our cases show a great resemblance to the three eculizumab-treated STEC-HUS patients reported by Lapeyraque et al⁴ in terms of renal involvement. In addition, administration day, dosage, interval, and the number of times the drug was administered (twice and 4 times in Lapeyraque et al's⁴ cases, and 3 times in

our cases) are quite similar. The common features observed between our cases and those reported by Lapeyraque et al⁴ in terms of long-term renal involvement were particularly interesting for us. This made us think that the long-term renal effect of the drug, especially for persistent proteinuria and hypertension, is not as favorable as in resolving acute neurologic findings. Considering these well-known risk factors for renal disease progression, we believe that they warrant special attention in the follow up of these patients.

The high cost of the drug and ongoing doubts about its safety lead to a considerable delay in deciding whether the drug should necessarily be prescribed. Even in our patients, the drug could have been used during the late phase of the disease, probably after the cessation of the alternative complement pathway activation. In this context, the residual renal damage can be attributed to the late prescription of the drug. However, it is obvious that only randomized clinical trials (RCTs) can prove or disprove this hypothesis. It is also clear that acute nature and varying severity of the disease render such RCTs very difficult to be designed. Therefore, it seems that sharing personal clinical experience will continue to be important in order to develop treatment initiatives until such studies become available. For this reason, we considered important to report the clinical course of these two cases.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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