Pediatr Nephrol (2011) 26:621–624
DOI 10.1007/s00467-010-1719-3

BRIEF REPORT

Efficacy of eculizumab in a patient with factor-H-associated atypical hemolytic uremic syndrome

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Received: 8 November 2010 / Accepted: 9 November 2010 / Published online: 15 December 2010

Abstract Atypical hemolytic uremic syndrome (aHUS) is a rare, chronic, life-threatening disease due to complement dysregulation. The use of early-onset plasma therapy is recommended, but optimal long-term treatment regimen is not well defined. Eculizumab, a monoclonal humanized anti-C5 antibody, has shown success in patients with aHUS. We report a 7-year-old girl with aHUS associated with factor H mutations successfully treated with eculizumab. Weekly plasma infusion (PI) of 25–30 ml/kg with short-term intensified PI during aHUS exacerbations was effective for 4.3 years. Progressive mild renal failure (stage 2) was attributed to chronic glomerular lesions. Subsequently, she exhibited aHUS exacerbation unresponsive to intensified PI. Eculizumab was initiated at 600 mg, resulting in immediate and complete inhibition of terminal complement activation. During the week following treatment, we observed a complete reversal of aHUS activity. She has been receiving 600 mg eculizumab every 2 weeks for the last 12 months. She had no aHUS exacerbation, and serum creatinine level returned to normal. In this patient, eculizumab led to control of PI-resistant aHUS exacerbation and chronic microangiopathic hemolytic activity. Clinical trials are ongoing to assess the safety and efficacy of this drug in the management of aHUS.

Keywords Atypical hemolytic and uremic syndrome · Genetic · Complement factor H · Plasma infusion · Plasma exchange · Eculizumab

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Introduction

Hemolytic uremic syndrome (HUS) is characterized by sudden onset of thrombocytopenia, hemolytic anemia, and acute renal failure. HUS not associated with enterobacterial infection is known as atypical HUS (aHUS). Atypical HUS is characterized by frequent relapses and carries a poor prognosis: 30–75% of cases progress to end-stage renal disease (ESRD) requiring long-term dialysis, and death occurs in 10% of patients [1, 2]. The use of plasma therapy (PT) immediately following aHUS onset is recommended; however, there is variable success and little consensus regarding long-term tolerance and effectiveness of PT [3, 4]. Further complicating the issue of treatment, some patients become unresponsive over long-term PT [5, 6]. Atypical HUS has been associated with defective regulation of the alternate complement pathway, leading to inappropriate chronic complement activation [7, 8]. Eculizumab (Soliris; Alexion Pharmaceuticals, Cheshire, CT, USA) is a humanized monoclonal anti-C5 antibody that targets the terminal complement system and blocks generation of proinflammatory C5a and the lytic C5b-9 complex. It has been approved for treating paroxysmal nocturnal hemoglobinuria [9]. Eculizumab may be an effective long-term option in managing aHUS patients [10–15]. Here we report the case of 7-year-old girl with aHUS associated with heterozygous combined de novo complement factor H gene

(*CFH*) mutations (S1191L and V1197A) that became resistant to PT and successfully treated with eculizumab.

Case report

This young girl presented with clinical features of aHUS (anemia, thrombopenia, acute renal failure requiring hemodialysis) at the age of 7 months. Laboratory investigations showed normal levels of C4, C3, and factor H, but genetic investigations showed heterozygous combined de novo complement factor H mutations on the same allele (S1191L and V1197A). During the first episode, daily plasma exchange (PEX) using cryosupernatant (Cr) as replacement fluid resulted in hemolysis resolution and renal function normalization. During the first year post diagnosis, two aHUS recurrences occurred and were treated with daily PEX (X5), which was subsequently weaned down to twice weekly. One year after the first exacerbation of aHUS, PEX regimen was terminated and weekly plasma infusion (PI) regimen (25–30 ml/kg) through a Port-a-cath was initiated and maintained for 4 years and 4 months. During this time, (Fig. 1), nine acute aHUS exacerbations occurred (thrombocytopenia, acute fall in haptoglobin level, and mild elevation of serum creatinine) and were managed by intensified PI three times weekly for 2 weeks. Significant acute renal failure occurred only once (relapse 5). Most reoccurences were triggered by viral infections (relapses 2–6, 8, 9); relapses 1 and 7 were precipitated by an attempt to increase the interval between PIs from 7 to 10 days. Over time, baseline plasma creatinine levels increased despite resolution of successive exacerbations. Four years and half after diagnosis, glomerular filtration rate (GFR) was at 63 ml/min/1.73 m^2. A renal biopsy was performed to avoid overlooking subclinical renal thrombotic microangiopathy (TMA), which could be a reason to increase plasma therapy by PEX regimen. The biopsy showed no sign of acute TMA but revealed chronic glomerular lesions with glomerulosclerosis (16/45 glomeruli) and ischemia (15/45). Five years and 5 months after initial presentation, while still on once-weekly PI, the patient developed severe aHUS exacerbation after a diarrheal episode [acute anemia (hemoglobin 9.4 g/dl) with undetectable haptoglobin level; thrombopenia; severe hypertension; acute renal failure with creatinine 1.2 mg/dl (108 μmol/l), and nephrotic proteinuria]. This acute exacerbation was unresponsive to PI intensification (30 ml/kg each 2 days for 10 days). Ten days after the beginning of this last acute exacerbation, PI was stopped and eculizumab was initiated at 600 mg weekly for three doses then 600 mg every 2 weeks. The patient has received no additional PI since initiation of eculizumab treatment. One week after the first dose of eculizumab, hypertension resolved, platelet count increased to 177×10^9/l, haptoglobin level normalized, and renal function recovered to baseline [plasma creatinine decreased to 0.8 mg/dl (73 μmol/l)] (Fig. 2). Three weeks after the first administration of eculizumab, plasma creatinine had decreased to 0.6 mg/dl (54 μmol/L) and proteinuria had disappeared. The patient has been receiving 600 mg eculizumab every 2 weeks for the last 12 months and shown no acute aHUS exacerbation despite viral infections. Plasma creatinine level is within normal range (0.4–0.5 mg/dl) and urine is protein free.

Discussion

Atypical HUS has a very poor prognosis, partly due to the lack of effective long-term treatment [1, 2]. Although the use of PT is recommended to manage acute aHUS exacerbation, there is little consensus on the optimal long-term treatment regimen [3]. PEX is often recommended to administer larger volumes of plasma [4], but it is an

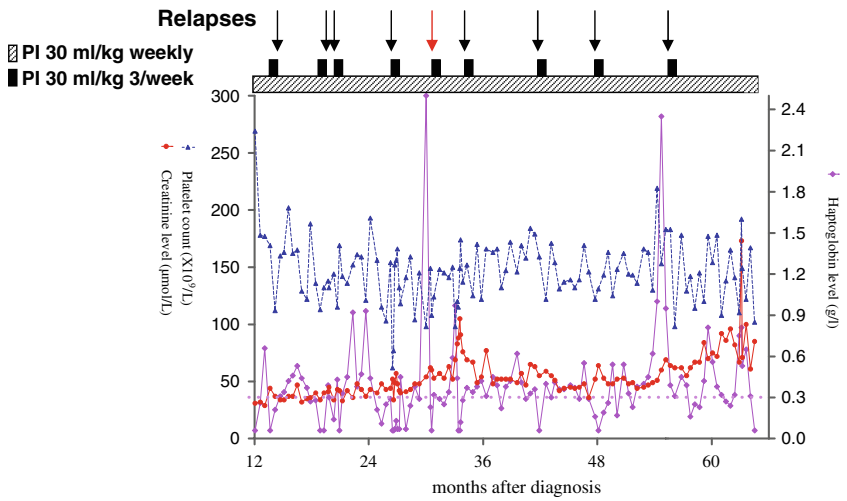

Fig. 1 Treatment evolution during plasma infusion (PI) regimen from 12 to 64 months after diagnosis. During this time, nine relapses occurred (*arrow*), which were successfully treated by PI intensification three times weekly for 2 weeks. Significant acute renal failure occurred only once (*red arrow*) but plasma creatinine returned to normal after PI intensification

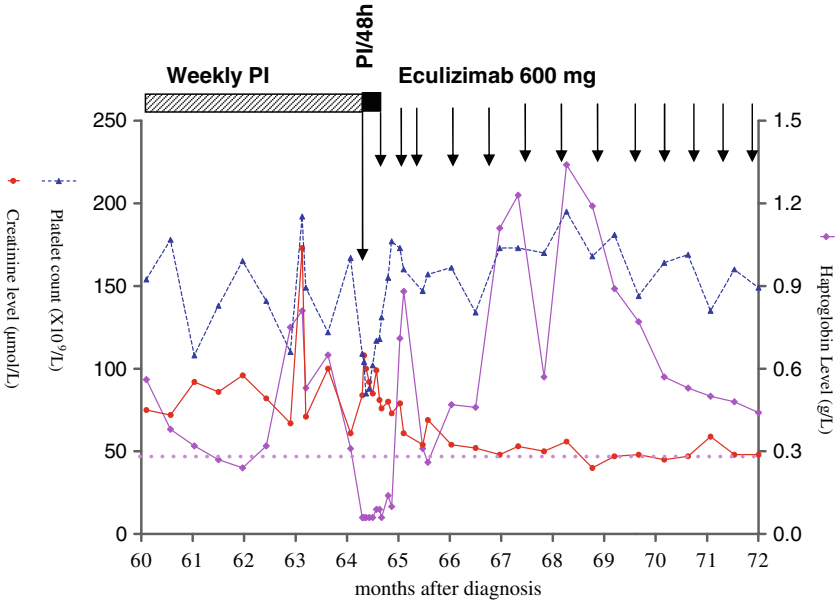

Fig. 2 Response to eculizumab following plasma-dependent atypical hemolytic uremic syndrome (aHUS) showing time course of platelet count and creatinine and haptoglobin level. After aHUS relapse 64 months after diagnosis (*long arrow*), plasma infusion (PI) was performed every 2 days for 10 days; aHUS persisted. Eculizumab was initiated at 600 mg weekly for three doses then 600 mg every 2 weeks. One week later, hypertension resolved, platelet count and haptoglobin level normalized, and plasma creatinine decreased, indicating successful aHUS reversal. Twelve months later, the patient was still in remission without any aHUS exacerbation

invasive procedure and requires a large central venous catheter, which carries potential infectious and thrombotic risks [16]. The outcome in cases of *CFH* S1191L mutation is poor. Seven other patients with *CFH* S1191L mutation have been reported in the literature. Two of them had aHUS recurrence posttransplant. Graft failure in occurred in one [5, 17], and the other developed ESRD despite PEX [18]. The two heterozygous mutations seen in our patient were identified in one family [19] (S1197L and V1197A). In that family, the mother died from HUS, and her daughter's outcome has not yet been reported.

In our patient, PI regimen was initially thought to be effective because she responded favorably at each acute exacerbation to PI intensification. Haptoglobin seemed to be a good predictor of the next recurrence of aHUS, and in most instances, PI intensification was initiated before acute renal failure onset. PI was a valuable therapeutic option because it obviated the need for a large central catheter and was well tolerated (no blood hyperviscosity and normal cardiac function after 5 years). However, the inability of our patient to be weaned from weekly PI gave us the impression that she had become plasma dependant. Furthermore we note that prior to eculizumab treatment, serum creatinine continued to rise after each successive aHUS exacerbation. This suggested that the underlying mechanism of the disease was chronically active. A renal biopsy was performed to evaluate the subclinical activity of TMA. It showed chronic glomerular lesions with glomerulosclerosis without TMA-specific lesions, suggesting that weekly PI regimen was sufficient to control the disease and to avoid subclinical TMA.

Few months later, a more severe aHUS relapse occurred a few days after a diarrheal episode. Three weekly PI regimens did not stop aHUS relapse. Instead of PEX therapy, we decided to use eculizumab, a terminal complement inhibitor demonstrated to block terminal complement activity. This treatment affected complete reversal of aHUS activity despite PI cessation. Twelve months after eculizumab initiation, our patient remained free of aHUS recurrences despite upper respiratory tract viral infections. To our surprise, serum creatinine levels returned to normal after 2 months of treatment. In retrospect, these observations suggest that directly targeting the complement system instead of replacing regulatory protein through PT may provide better control of chronic complement activity and improve long-term TMA management. The treatment regimen also has the advantage that it can be administered once every 2 weeks and not via a central venous access. Also, no side effects have occurred to date. Caution is recommended, however, because this treatment can increase the risk of infection by *Neisseria meningitides*. Vaccination against these infections was undertaken in previously in our patient, and we also decided to initiate prophylactic penicillin G therapy.

In this patient, eculizumab successfully reversed one acute PI-resistant aHUS exacerbation, and led to control of chronic microangiopathic hemolytic activity, and prevented viral-infection-triggered aHUS relapses. Long-term safety and efficacy under this therapy is still unknown, and clinical trials are ongoing to assess these issues in the routine management of aHUS.

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