Long-term Eculizumab Treatment Contributes to Recovery from End-stage Renal Disease Caused by Atypical Hemolytic Uremic Syndrome

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Abstract

We experienced a favorable outcome in an adult case of atypical hemolytic uremic syndrome (aHUS) after long-term eculizumab treatment. A 38-year-old Japanese man with a history of central retinal vein occlusion was admitted to our hospital with progressive dyspnea. He was found to have non-immune hemolytic anemia, thrombocytopenia, and acute renal failure two weeks after an episode of the common cold. Plasma exchange was ineffective; therefore, we initiated eculizumab after we excluded other thrombotic microangiopathies. Although long-term peritoneal dialysis was required, we successfully discontinued dialysis 18 months after the onset of aHUS with eculizumab.

Key words: atypical hemolytic uremic syndrome, eculizumab, peritoneal dialysis, thrombotic microangiopathy

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Introduction

Atypical hemolytic uremic syndrome (aHUS) is characterized by three major components: microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and acute kidney injury. This syndrome is known to be caused by the abnormal activation of the complement cascade (1). In Japan, the number of new patients with aHUS is estimated to be around 100 cases per year. aHUS was certified as an intractable disease by a new law in January 2015, and its medical expenses are covered by the Japanese government. This syndrome was treated previously with plasma exchange, which is a standard treatment for thromboembolic thrombocytopenic purpura (TTP), but its prognosis was poor (2). When patients with aHUS are treated with plasma exchange, a reported approximately 10% die and approximately 50% progress to end-stage renal disease 1 year after the onset of aHUS (2). Anti-complement factor 5 antibody, eculizumab, which has been used for the treatment of paroxysmal nocturnal hemoglobinuria, was recently reported effective for aHUS (3). Following that trial and US Food and Drug Administration approval, eculizumab was approved for the treatment of aHUS in Japan in 2013.

We herein report a case of aHUS, for which we successfully discontinued dialysis 18 months after initiation of eculizumab. Our case suggests that long-term treatment with eculizumab may gradually recover kidney damage and ultimately lead to discontinuation of dialysis.

Case Report

The patient was a 38-year-old man who presented with a 1-week history of dyspnea. Two weeks prior to presentation, the patient developed a cough and a fever, which resolved quickly. One week later, the patient started experiencing progressive dyspnea while walking and decided to visit our hospital. He denied having any episodes of bloody diarrhea. His medical history revealed central retinal vein occlusion at the age of 36 years. He had no family history of thrombosis.
Admission was negative for Shiga-toxin-producing Escherichia coli (STEC); therefore, STEC-HUS was ruled out. We confirmed activation of the complement cascade. We sent the patient’s plasma to the Department of Transfusion, Nara Prefectural University, for a quantitative hemolysis assay using sheep blood cells (4). The patient’s plasma revealed severe hemolysis that was 1.6 times that of the positive control, and addition of recombinant complement factor H (CFH) suppressed the hemolysis, indicating the presence of CFH-related complement amplification (data not shown). However, anti-CFH antibody in the patient’s plasma was negative by Western blotting. In addition, genetic testing conducted at the National Cerebral and Cardiovascular Center in Osaka, Japan, did not reveal any abnormalities, including levels of CFH, component 3 (C3), membrane cofactor protein (MCP), complement factor I (CFI), complement factor B (CFB), and thomboomodulin. Around half of cases of aHUS do not have mutations in the complement regulatory proteins (5); therefore, we clinically diagnosed this case as aHUS.

The clinical course of our case is shown in Figure. A decrease in the LDH levels and improvement in the hemoglobin and platelet count were observed after eculizumab was initiated. However, the renal function continued to worsen, the creatinine level rose to 10 mg/dL, and hemodialysis was started shortly after the initiation of eculizumab. Hemodialysis was transitioned to peritoneal dialysis around three months after onset, based on the patient’s request.

We continued eculizumab, which gradually improved his renal function, and at 18 months after onset of aHUS, we successfully discontinued dialysis. Up to 36 months after onset, the patient has had no signs of recurrence, with continuation of eculizumab.

**Discussion**

TMA is a syndrome of MAHA, thrombocytopenia, and organ dysfunction, which has a variety of causes (6). aHUS is one of those causes (7), and the Japanese guidelines for aHUS were first published in 2016. It is thought that genetic abnormalities of complement regulatory factors or anti-CFH

| **CBC** | **Chemistry** | **Serology** |
|--------|--------------|--------------|
| WBC 9.53x10⁹/μL | Alb 4.2 g/dL | Direct Coomb’s (-) |
| Neu 81.0 % | LDH 2,470 IU/L | Indirect Coomb’s (-) |
| Eo 0.0 % | T-bil 2.7 mg/dL | ADAMTS13 |
| Baso 0.0 % | D-bil 0.6 mg/dL | activity 72.9 % |
| Mono 4.0 % | BUN 58 mg/dL | inhibitor <0.5 BU/mL |
| Lym 14.0 % | Cre 6.8 mg/dL | |
| RBC 268x10⁶/μL | CRP 0.25 mg/dL | Urinalysis |
| Hb 7.4 g/dL | Haptoglobin 11 mg/dL | Protein (3+) |
| Ht 21.6 % | | Occult blood (3+) |
| MCV 80.6 fl | Coagulation | |
| MCH 27.6 pg | PT-INR 1.07 | Stool |
| MCHC 34.3 % | aPTT 27.3 sec | Occult blood (-) |
| Plt 7.6x10⁴/μL | Fibrinogen 131.0 mg/dL | STEC (-) |
| Ret 81.1 % | FDP 194.0 μg/mL | |

FDP: fibrin degradation product, Plt: platelet, RBC: red blood cell, Ret: reticulocyte, STEC: Shiga toxin-producing Escherichia coli, WBC: white blood cell
antibody lead to uncontrollable activation of complement, which results in endothelial damage, intravascular microthrombosis, and eventually organ dysfunction (1, 8). Approximately 25% of cases of aHUS have resulted in death from thrombosis or acute renal failure (9). Even if death in the acute phase can be avoided by plasmapheresis, around half of the surviving cases eventually develop end-stage renal disease that requires dialysis (9). Kidney transplantation has been performed in such cases, but the recurrence rate was around 50%, and the rate of post-transplant kidney loss was 30% (10). Simultaneous liver and kidney transplantation has also been attempted (11), but the number of applicable cases is limited, and it is still a controversial treatment. About 40% of cases of aHUS are in young patients, including pediatric cases (12); therefore, lifelong dialysis can markedly reduce the quality of life. However, based on previous reports, eculizumab is expected to improve chronic kidney disease by more than 1 stage and meaningfully improve the health-related quality of life in more than half of all aHUS cases (3).

Based on the three major components of TMA—normal activity of ADAMTS13 and exclusion of STEC infection and other clear causes of TMA—our case met the diagnostic criteria of aHUS under the current guidelines (13), and these findings led us to the clinical diagnosis. A hemolytic analysis using sheep blood cells suggested a CFH-related abnormality, which also supported the diagnosis of aHUS. Subsequently, further genetic tests were conducted, but we did not detect any abnormalities of complement genes. To date, genetic abnormalities of C3, CFB, CFH, CFI, MCP, and thrombomodulin are reported to be related to aHUS (14-17). In Japan, several cases of abnormal C3 have also been reported (18). However, previous reports have shown that genetic abnormalities can be detected in around half of cases (5), as with the present case, which suggests that there are still several unknown genetic abnormalities causing aHUS. Considering his history of retinal vein thrombosis, we suspect that our patient might have an underlying genetic abnormality. Other experimental tests, such as measurements of C5a and C5b-9 complex in serum and urine samples by enzyme-linked immunosorbent assay (ELISA) (19), observation of deposits of C5b-9 protein on the endothelial cells in vitro using immunofluorescence microscopy (20), a modified Ham test using a genetically modified complement-sensitive cell line (21), and a skin biopsy (22), have been reported as possible diagnostic tools. However, further investigations are necessary to apply the findings from those tests in a clinical setting.

Eculizumab was not approved in Japan in 2013; thus, we initially treated the patient only with plasma exchange, which was insufficient to control disease progression. We started eculizumab 29 days after onset, following thorough discussion regarding the benefits and risks of off-label use of self-imported eculizumab. It has been reported that delayed initiation of eculizumab is associated with a worse outcome of the renal function (3, 23). Eventually, our case required long-term dialysis. However, long-term treatment with eculizumab resulted in our patient discontinuing dialysis 18 months after onset. This case suggests that it is worth considering long-term eculizumab, even for cases with delayed admission requiring dialysis, as the renal function can still be recovered and slowly improved by eculizumab.

Eculizumab is estimated to cost in the range of US $600,000 per year (24); thus, we need to avoid the overuse of eculizumab by performing careful diagnosis and treatment decision-making. An observational study revealed that around 70% of cases in other countries were able to successfully discontinue eculizumab without recurrence (25).
However, there are no prospective studies on the discontinuation of eculizumab in Japan. Therefore, in the present case, we are continuing treatment with eculizumab in the expectation of further, gradual improvement of the renal function.

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Author’s disclosure of potential Conflicts of Interest (COI).
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References
1. Noris M, Mescia F, Remuzzi G. STEC-HUS, atypical HUS and TTP are all diseases of complement activation. Nat Rev Nephrol 8: 622-633, 2012.
2. Kaplan BS, Meyers KE, Schulman SL. The pathogenesis and treatment of hemolytic uremic syndrome. J Am Soc Nephrol 9: 1126-1133, 1998.
3. Legendre CM, Licht C, Miuus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med 368: 2169-2181, 2013.
4. Yoshiida Y, Miyata T, Matsumoto M, et al. A novel quantitative hemolytic assay coupled with restriction fragment length polymorphisms analysis enabled early diagnosis of atypical hemolytic uremic syndrome and identified unique predisposing mutations in Japanese patients with atypical hemolytic uremic syndrome. Pediatr Int 56: 1085-1088, 2017 DOI: 10.2169/internalmedicine.56.7862