Effect of eculizumab and recombinant human soluble thrombomodulin combination therapy in a 7-year-old girl with atypical hemolytic uremic syndrome due to anti-factor H autoantibodies

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Abstract Atypical hemolytic uremic syndrome (aHUS), which is defined as non-Shiga toxin-associated hemolytic uremic syndrome, is a type of thrombotic microangiopathy. This syndrome presents with hemolytic anemia, thrombocytopenia, and acute kidney injury. Excessive complement activation due to genetic disorders of the complement system or production of autoantibodies to factor H (FH) causes the disease. We report a successful treatment course using eculizumab and recombinant human soluble thrombomodulin (rTMD) for a 7-year-old girl with aHUS due to anti-FH autoantibodies. Although her chief complaints were abdominal pain and loose stools, we were finally able to diagnose her with aHUS because Shiga toxin-producing *Escherichia coli* was not detected in her feces and a hemolytic assay analyzing FH function was positive. We administered rTMD to our patient because of signs of disseminated intravascular coagulation. Soon after the therapeutic intervention, the platelet count began to increase and abdominal pain was moderately improved. Plasma exchange limited the efficacy of her disease. Therefore, we administered eculizumab, monoclonal humanized antibody against C5, 3 weeks after admission.

Platelet counts immediately increased and kidney function gradually recovered. Genetic disorders were not detected. However, anti-FH autoantibody was observed. There were no symptoms for recurrence of aHUS or kidney dysfunction for 15 months, as a result of the administration of eculizumab every other week. In conclusion, combination therapy of eculizumab and rTMD was effective for an aHUS patient. This therapy may be helpful for improving the prognosis and long-term kidney function of aHUS patients.

Keywords Atypical hemolytic uremic syndrome · Acute kidney injury · Thrombotic microangiopathy · Plasma exchange · Complement regulatory protein

Introduction

Hemolytic uremic syndrome (HUS) is characterized by the triad of hemolytic anemia, thrombocytopenia, and acute kidney injury. More than 90 % of HUS cases develop the disease by Shiga toxin (Stx)-producing bacteria (OMIM #235400) infection and they are often accompanied by diarrhea, which is defined as D+HUS. Atypical hemolytic uremic syndrome (aHUS) is a rare form of HUS, which is a type of thrombotic microangiopathy (TMA) that occurs without bacterial infection. Excessive activation of the alternative pathway of complement in the microvasculature contributes to the pathogenesis of aHUS. aHUS has a poor prognosis, with a high rate of either end-stage renal disease or death in 50–80 % of patients [1]. Approximately 60 % of aHUS is derived from abnormalities of the complement regulatory protein, factor H (CFH), factor I (CFI), membrane cofactor protein (CD46), and complement components C3, factor B or thrombomodulin, and the remaining

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40 % of genetic disorders are unknown. Genetic abnormalities in complement system proteins are often documented in the familial form of the disease [2]. Autoantibodies to factor H (FH), which are detected in 6–10 % of aHUS cases, have also been recognized as a cause of aHUS. This type of aHUS primarily affects children between 9 and 13 years of age [3].

The European Paediatric Study Group for HUS recommends that plasmapheresis should be performed within 24 h of the diagnosis of aHUS. One and a half plasma volumes (60–75 mL/kg) exchanged per session using fresh frozen plasma or Octaplas® is recommended [4]. Eculizumab is a humanized monoclonal antibody against complement protein 5, which stops intravascular hemolysis in paroxysmal nocturnal hemoglobinuria (PNH) by preventing activation of the terminal complement pathway [5–7]. Several case reports have indicated the efficacy of eculizumab in aHUS treatment. Licht et al. [8] reported that five of seven aHUS patients on dialysis could cease blood purification therapy after the administration of eculizumab. An open-label multicenter phase 2 eculizumab trial in pediatric aHUS patients aged from 1 month to 18 years has recently started ([9]; NCT01193348).

Thrombomodulin is an endothelial membrane protein that has anticoagulation and anti-inflammatory effects, including the suppression of complement activity, and is a novel therapeutic medicine for disseminated intravascular coagulation. Recently, Honda et al. [10] reported the efficacy of recombinant human soluble thrombomodulin (rTMD) infusion for typical HUS treatment. But as far as we know, there is no report that mentions the efficacy of rTMD for aHUS treatment, or the efficacy of eculizumab and rTMD combination therapy for aHUS.

We describe here the course of successful treatment with eculizumab and rTMD combination therapy for a 7-year-old girl, who suffered from aHUS due to anti-FH autoantibodies. We also examined the histological findings of a kidney biopsy in the acute and convalescence stages. To the best of our knowledge, this is the first case report on the combination therapy with eculizumab and rTMD for aHUS.

Case report

A 7-year-old girl, who is a mixture of Japanese and Filipino, was transferred to our hospital because of hemolytic anemia, thrombocytopenia, and acute kidney injury. She had no particular past history. Since 2 days before the hospitalization, she suffered from abdominal pain and vomiting. Her body weight decreased by 2 kg and dropped to 20 kg, her face was pale, and her lips were dry. Although she complained of upper abdominal pain, bloody stools

were not present. She presented with oliguria with significant macro-hematuria and proteinuria (urinary protein: 315 mg/dL; urinary creatinine: 29 mg/dL). In the first blood examination, hemoglobin was 7.0 g/dL, the platelet count was 70,000/ μ L, and there were a significant percentage of fragmented erythrocytes. Biochemical findings suggested severe acute kidney injury, with a blood urea nitrogen level of 136.7 mg/dL, creatinine level of 4.25 mg/dL, uremic acid level of 17.0 mg/dL, and potassium of 4.7 mEq/L. Her lactate dehydrogenase level was 2,988 IU/L and her haptoglobin level was below 10 mg/dL, which were symptoms for hemolysis. The complement C3 level was 45 mg/dL, which was lower than the normal range (normal range: 74–130 mg/dL), but complement C4 levels were within normal limits. Renal ultrasonography findings showed insignificant echogenic large kidneys. Because we recognized that our patient had typical HUS, we started treatment by fluid therapy and electrolyte management.

After upper abdominal pain disappeared and the serum amylase level elevated to 161 U/L, we observed the development of pancreatitis and complication of disseminated intravascular coagulation (thrombocytopenia, fibrinogen, 103 mg/dL; fibrinogen degradation products, 161 μ g/mL) 5 days after admission. Soon after we began to administer fresh frozen plasma and rTMD, the platelet count began to increase and abdominal pain was moderately improved (Fig. 1). Although these therapies had improved her condition, improvement was only temporarily observed, and serum creatinine levels increased again on the 13th day after admission. Shiga toxin-producing *Escherichia coli* was not detected in her stool, anti-nuclear autoantibody was negative. Therefore, we performed plasma exchange (PE) with fresh frozen plasma (1.5 plasma volumes) against probable aHUS on three consecutive days from days 16 to 18. Although urine color improved to normal during PE, it returned to gross hematuria several hours after PE. Her general condition and abdominal pain did not improve, and her serum amylase level ascended to 1,018 U/L on day 20. Moreover, hypertension and pulmonary edema developed after PE and we needed to perform hemodialysis to improve our patient's condition. At this time, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) levels were normal (>100 %), anti-ADAMTS13 antibody was not identified, and FH function was abnormal by hemolytic assay analysis. Because the effectiveness of the above-mentioned interventions was only transiently observed, we concluded that the final diagnosis of our patient must be aHUS and further therapy was essential.

We started to administrate eculizumab 600 mg on day 21, which is monoclonal humanized antibody against C5. There was no significant adverse event related to

Fig. 1 Clinical course. Abnormal laboratory data, especially the platelet count, improved immediately after the administration of eculizumab. PE plasma exchange, HD hemodialysis, rTMD

recombinant human soluble thrombomodulin, FFP fresh frozen plasma, RBC red blood cell, RBx renal biopsy, Hb hemoglobin, Plt platelets, Cre creatinine

eculizumab infusion. The platelet count began to increase from 24,000 to 36,000/ μL on the next day of infusion, and serum creatinine levels peaked and descended gradually. Then, her C3 level slowly ascended to normal range and CH50 decreased to a level under measurement sensitivity. Abdominal pain disappeared as data of TMA improved and the serum amylase level descended to under 100 U/L. Although our patient required blood transfusion three times after starting eculizumab administration, her hemoglobin levels gradually increased. A total of 600 mg of eculizumab was administered to our patient once a week in the first and second weeks, and then the same dose of eculizumab was administered every 2 weeks as a maintenance dose. We medicated with amoxicillin 30 mg/kg/day to prevent meningococcal meningitis until a meningococcal vaccine became available. Although a vaccine was administered 3 weeks after the first eculizumab treatment, our patient did not suffer from any infectious disease.

The first renal biopsy was performed 2 weeks after the first eculizumab infusion. In light of microscopy findings, 10 of 50 glomeruli showed atrophy, mesangiolysis, global mesangial cell proliferation, mesangial matrix hyperplasia, or periglomerular capillary narrowing. Severe interstitial edema was also observed (Fig. 2). Immunofluorescence staining was positive for IgG, IgM, C3, and C4 (Fig. 3). Electron microscopy showed thickening of the capillary walls and swelling of the endothelial cells.

Our patient was discharged from hospital 5 weeks after the first eculizumab administration. On discharge, her

hemoglobin level was 10.7 g/dL, platelet count was 303,000/ μL , and blood urea nitrogen and creatinine levels were 51.0 and 0.72 mg/dL, respectively. No other organ damage was recognized. After discharge, our patient received eculizumab 600 mg, every 2 weeks, with no side effects, except for extremely mild alopecia. Her kidney function recovered to an estimated glomerular filtration rate of 56 mL/min/1.73 m^2 , with mild proteinuria (urinary protein–creatinine ratio, 0.3–0.5 mg/g) and mild hematuria with normal blood pressure.

A second renal biopsy was performed 6 months after the first eculizumab administration. We found sclerosis in 13.3 % (4/30) and segmental adhesions in 16.6 % (5/30) of the glomeruli. Mesangiolysis was observed in only a small part of glomeruli. Vascular endothelial damage still partially remained. Most glomeruli showed minimal changes and tubular interstitial edema had improved. Mesangial cells and the matrix tended to be increased at segmental areas of glomeruli (Fig. 4). Immunofluorescence staining was positive for IgG, C3, C4, and C1q (Fig. 5).

We continue to administrate eculizumab every 2 weeks. Up until the time of writing of this report, she has not experienced aHUS relapse and enjoys an ordinary life without any restrictions for 24 months.

Analyses for the pathogenesis of aHUS

No genetic disorder was detected and no association of any particular polymorphism was identified by complete

Fig. 2 **a** Periodic acid methenamine silver staining. The *arrow* shows the double contour of a glomerular capillary. Several mesangial areas have vacuolar degeneration. **b** Periodic acid-Schiff staining. Marked glomerular atrophy and ischemic sign can be seen. **c** Masson's trichrome staining. Severe interstitial edema can be seen. **d** Elastica van Gieson staining. Swelling of vascular endothelial cells and occlusion of the subendothelial space of the arterial lumen can be seen

Fig. 3 Immunofluorescence staining. Positive deposit for IgG, IgM, C3, and C4 along the capillary walls

sequencing of all exons in the CFH, CFI, membrane cofactor protein, CFB, C3, THBD, and CFHR1-3 genes. In contrast, anti-FH antibody was found in both samples collected before and after starting eculizumab therapy.

Discussion

In aHUS patients, PE is recommended to be performed within 24 h after diagnosis [4]. Although PE appears to be

Fig. 4 **a** Periodic acid-Schiff staining in the recovery phase. A glomerulus showing mesangiolysis is surrounded by neutrophils. **b** Periodic acid methenamine silver staining. One glomerulus (*arrow*) shows collapsing change. **c** Periodic acid methenamine silver staining. A glomerulus shows mesangial cell proliferation, which indicates the recovery process. **d** Masson's trichrome staining. A small amount of interstitial fibrosis can be observed

Fig. 5 Immunofluorescence staining. Staining for IgG is still positive. Staining for C3, C4, and C1q is positive at the vascular pole area

effective in removing anti-FH autoantibodies [11, 12], its effectiveness is transient in some patients. PE was only partially effective in our patient with aHUS due to anti-FH autoantibodies. Because we required 2 weeks for the final diagnosis of aHUS, it was difficult to perform PE at the

onset of the disease. Additionally, PE might not be fully effective for all patients of anti-FH autoantibody-associated aHUS. Mache et al. described that, although PE (three times per week) was effective in inhibiting the progress of TMA for approximately 8 weeks and allowed temporary

improvement of renal function, disease progression of aHUS was unable to be further prevented and it did not prevent renal failure [13].

Eculizumab is a humanized monoclonal antibody that binds to complement protein 5 validated for PNH. Recently, many case reports have described that eculizumab is valid for aHUS due to various genetic abnormalities [5, 14, 15]. aHUS develops as a result of unregulated complement progression. Because eculizumab targets complement factor C5, it blocks activation of the terminal complement cascade associated with the generation of the proinflammatory and prothrombotic molecules C5a and C5b-9. In our case, C3 ascended gradually to the normal range and stopped all symptoms of TMA after eculizumab administration. Since the origin of our case was ascertained to be anti-FH autoantibodies, PE might have been effective by removing antibodies from plasma. But our patient's general condition deteriorated and her serum amylase and creatinine levels ascended after PE, that is, PE was not fully effective for our patient. Lee et al. [16] mentioned an aHUS case associated with anti-FH antibodies whose hemolytic process was not controlled by 10 sessions of PE followed by a week of intermittent PE (three times per week) and hemodialysis. Lapeyraque et al. reported three cases of severe Shiga toxin-associated HUS whose complement activity was high and spontaneous recovery seemed unlikely. Eculizumab was administered to three patients, and the disease activity of the patients improved gradually and finally recovered without sequel [17]. Collectively, if complement activity is considerably high, the disease activity of HUS might be difficult to improve spontaneously. We speculate that PE was not fully effective for our patient because complement activity was considerably high, and eculizumab was effective for controlling complement activity directly.

There are few controlled trials of eculizumab for aHUS because of the low rate of disease incidence and severity of the disease. Our patient complained of transient nausea in the second administration and mild alopecia 3 months after starting eculizumab therapy. Kanakura et al. investigated the safety and efficacy of eculizumab in 29 Japanese patients with PNH. They reported that frequent adverse events were headache (52 %), nasopharyngitis (41 %), and nausea (21 %) [18], and described that the majority of adverse events were mild or moderate. Such findings coincide with descriptions in case reports of aHUS [15, 19].

rTMD has therapeutic value against disseminated intravascular coagulation, based on a clinical trial [20]. rTMD inactivates coagulation by binding to thrombomodulin, and then thrombin-recombinant human soluble thrombomodulin complexes activate protein C. Activated protein C inactivates factors VIIIa and Va, which inhibit

further thrombin formation. By this mechanism, rTMD inhibits endothelial injury and protects the kidney from ischemic damage [21, 22]. Similarly, some case reports have demonstrated that rTMD contributes to improving TMA due to thrombotic thrombocytopenic purpura, lupus nephritis, and hepatic veno-occlusive disease after bone marrow transplantation [23–25]. In our case, treatment with rTMD before eculizumab might have contributed considerably to improving kidney function and coagulability. We speculate that preventing thrombus formation by rTMD prior to eculizumab infusion increased its effect. Although therapeutic success is recognized to depend on the early diagnosis and early commencement of appropriate treatment, this combination treatment was effective for our patient in spite of the relatively late therapeutic intervention.

We diagnosed our patient with typical HUS at first because she exhibited loose stools and abdominal pain at the onset of the disease. Dragon-Durey et al. [3] reported that 84 % of patients with anti-FH autoantibody-related HUS complained of gastrointestinal symptoms and 53 % exhibited diarrhea. Therefore, the term “diarrhea-negative HUS” is not appropriate for aHUS. In diagnosing aHUS, another important factor is C3 levels. If C3 levels are low, this indicates complement dysregulation. However, in some cases, although complement dysregulation exists, C3 levels are within normal limits. Therefore, C3 levels alone cannot be used for making diagnoses of aHUS [1, 4].

We examined kidney pathological findings of the acute and recovery phases of our patient. We believe that the prognosis of kidney function of our patient might have been poor because histological findings of the acute phase were severe. However, the glomerular filtration rate recuperated more than expected. Our speculation was that early rTMD prevented the glomerular microangiopathy and sclerosis, because its efficacy inactivated abnormal coagulation. Although eculizumab played an important role in improving the activity of aHUS, rTMD might have played a central role to protect glomerular function. Histological findings of the recovery phase, which was examined 6 months after disease onset, showed evidence of the recovery process, such as mesangial cell proliferation. Nevertheless, mild proteinuria was still detected, and there were still histological findings, suggesting inflammation. Light and electron microscopy findings of the glomeruli showed two different states. One finding was recovery phase, and another finding was inflammation phase. The reason why inflammation remained 6 months after the onset of the disease was not clear. But we presume that, because inflammation at the onset was extremely severe, local inflammation needs more time to improve [13, 14].

Whether to cease eculizumab treatment for aHUS patients is controversial. Dragon-Durey et al. [3] described

the progress of long-term follow-up of 45 anti-FH antibody-associated aHUS patients. Recurrence of the disease occurred in 58 % of these patients, and recurrence deteriorated renal prognosis. Moreover, they found that the anti-FH autoantibodies remained detectable in 29 (88 %) of the 33 documented patients, even during remission. Only one patient showed a spontaneous decrease in anti-FH autoantibodies 60 months after onset. Giordano et al. reported a case of aHUS due to a specific mutation in CFH. They attempted to stop eculizumab administration after 18 months of remission. However, after 45 days, the patient presented with progressive reduction in platelet count and recurrence of proteinuria, and they reintroduced eculizumab [14]. Collectively, it might be difficult to cease treatment with eculizumab for aHUS patients. However, the safety of the long-term use of eculizumab for aHUS treatment has not been determined. The optimum aHUS treatment using eculizumab requires further investigation.

Conclusion

Eculizumab and recombinant human soluble thrombomodulin (rTMD) combination therapy were employed in a 7-year-old-girl with anti-factor H (FH) autoantibody-related atypical hemolytic uremic syndrome (aHUS), and remission was induced immediately. Maintenance eculizumab therapy was effective for a long-term relapse-free period of our patient. This therapy appears to be more effective than conventional therapy, and can improve prognosis and retain kidney function in patients with aHUS.

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Conflict of interest None.

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