Prophylactic amoxicillin for the prevention of meningococcal infection in infants with atypical hemolytic uremic syndrome under treatment with eculizumab: a report of two cases

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Abstract

Eculizumab, a humanized monoclonal antibody to complement C5, is a therapeutic drug for atypical hemolytic–uremic syndrome (aHUS) that inhibits the terminal pathway of complement. Patients on eculizumab therapy may become more susceptible to infection with capsule-forming bacteria, including meningococci. Therefore, meningococcal vaccination is required for patients who are on eculizumab therapy. However, the means to prevent meningococcal infection in infants who cannot be vaccinated with the available meningococcal vaccine have not yet been established internationally. In two infants with aHUS at 4–5 months after birth, prophylactic oral amoxicillin was administered, and meningococcal infection was not detected during the period between the initiation of eculizumab therapy and the administration of meningococcal vaccine. Neither adverse events related to amoxicillin nor thrombotic microangiopathy occurred during the treatment. Thus, oral administration of amoxicillin may be effective for preventing meningococcal infection under treatment with eculizumab in infants who have not received meningococcal vaccination.

Keywords aHUS · Eculizumab · *Neisseria meningitidis* · Amoxicillin · Antibiotic prophylaxis · Vaccination

Introduction

Atypical hemolytic uremic syndrome (aHUS) is a form of thrombotic microangiopathy (TMA) caused by the abnormal activation of complement. A humanized monoclonal antibody to complement C5 (eculizumab) was approved as a therapeutic drug [1], making great progress in the treatment of aHUS. Eculizumab binds to C5 to inhibit the cleavage of C5 to C5a and C5b, thereby inhibiting the formation of the membrane attack complex (C5b-9) [1].

The membrane attack complex plays an important role in the defense mechanism against capsule-forming bacteria, including *Neisseria meningitidis*, and the administration of eculizumab may increase susceptibility to infection by encapsulated bacteria [1]. Of particular concern is the infection with *N. meningitidis*, which may cause invasive

meningococcal disease (IMD) accompanied by bacteremia, sepsis, or meningitis, showing rapid progression, ultimately resulting in a shock state or adrenal hemorrhage and possibly serious fatal symptoms (Waterhouse–Friderichsen syndrome). In Japan, the annual incidence (2014) for IMD was 0.028 per 100,000 and case fatality rate was 19% [2].

Therefore, the meningococcal vaccination is required 2 weeks before the initiation of eculizumab therapy, or the administration of antibiotics for the first 2 weeks after vaccination if eculizumab treatment needs to start immediately [1]. In the United States, the meningococcal vaccination is inoculated in infants aged ≥ 9 months [3–6]. At present, the only meningococcal vaccine approved in Japan is the quadrivalent meningococcal polysaccharide diphtheria toxoid conjugate vaccine (MCV4-DT; Menactra®). The safety and efficacy of this vaccine have not been established for infants aged < 2 years in Japan. The Japan Pediatric Society recommends meningococcal vaccination in infants aged ≥ 9 months when they are on eculizumab therapy [7].

However, no standard of care for preventing meningococcal infection before immunization with meningococcal vaccine has been established. Previous studies have shown that prophylactic antibiotics were administered to infants with

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aHUS before or in parallel with eculizumab therapy [8–13]. Here we report our recent experience in two blood relative infants, a 4-month-old and a 5-month-old, who developed aHUS and were managed with prophylactic amoxicillin (20 mg/kg/day) [14] to prevent meningococcal infection from the beginning of eculizumab therapy to immunization with meningococcal vaccine.

Case report

Case 1

The patient was a 4-month-old boy with no relevant medical family history. He was born at 40 weeks and 4 days of gestation with a bodyweight of 3268 g. No neonatal asphyxia or neonatal jaundice was noted after birth. No abnormalities were found on health checkups at 1 and 3 months after birth.

On day 5 of presentation, the third dose of Pneumococcal vaccine (PCV13, *Haemophilus influenzae* type b vaccine), and the second dose of diphtheria/pertussis/tetanus/inactivated poliovirus vaccine were inoculated. Four days later (day-1), intake of milk by the baby decreased at night. On the following day (day 0), he had a poor complexion and was brought to a local general hospital. The patient was referred to our center due to anemia, thrombocytopenia, and renal impairment.

On admission, the patient was 62.0 cm in height and 8.1 kg in weight. Although he reacted to pain stimulation, his activity was poor. His face was pale and colored slightly yellow, although there was no purpura in the trunk or extremities. Findings on hematological examination on admission included low hemoglobin (Hb) 4.3 g/dL, indicating anemia, elevated lactate dehydrogenase (LDH) 1977 IU/L and schistocytes suggesting hemolysis. Additional laboratory findings included low platelets (PLT) $2.8 \times 10^4/\mu\text{L}$, elevated creatinine (Cre) 0.68 mg/dL, eGFR 28.9 mL/min/1.73m² [15], and D-dimer 2.9 µg/mL, leading to a diagnosis of thrombotic microangiopathy (TMA). Coombs test was negative for autoimmune hemolytic anemia and stool analysis was also negative for STEC, and not detected cobalamin C deficiency. There was no decrease in complement levels: C3 was 119 mg/dL, C4 was 10 mg/dL, and CH50 was 64.7 U/mL.

The examination of complement-related factors revealed that the sC5b-9 level was high: 1615.1 ng/mL in the serum (normal range, 148.0–1243.6 ng/mL) and 342.8 ng/mL in the plasma (normal range, 37.0–260.6 ng/mL), suggesting that the terminal complement system was activated. Gene analysis showed no rare variant (allele frequency (AF) < 0.005 in Human Genetic Variation Database (HGVD)) in the 13 causative genes (CFH, CFHR1–CFHR5, C3, CFI, CFB, MCP, THBD, DGKE, and PLG) found in aHUS (Table 1).

Assuming aHUS or thrombotic thrombocytopenic purpura as the cause of TMA, three sessions of plasma-exchange therapy (days 0, 1, and 2) were performed, resulting in a prompt improvement in anemia, thrombocytopenia, and renal impairment. On day 2, ADAMTS13 activity was normal (78.2%), and the ADAMTS13 inhibitor level was also normal (< 0.5 Bethesda unit/mL). Stool analysis was negative for STEC. On day 9, aHUS was diagnosed based on the positive result of the sheep erythrocyte hemolysis test [16]. On day 10, intravenous drip infusion of eculizumab (300 mg) for the treatment of aHUS was started. One week later (day 17), another drip infusion of eculizumab (300 mg) was given, and the patient was discharged on the following day (day 18). Eculizumab drip infusion (300 mg), given every 3 weeks, was continued thereafter.

Oral administration of amoxicillin for the prevention of meningococcal infection was started on the same day as the beginning of eculizumab therapy (day 10). The first dose of meningococcal vaccine (MCV4-DT; Menactra®) was inoculated at 10 months after birth, and the second dose was inoculated 8 weeks later. Oral administration of amoxicillin (20 mg/kg/day) was continued until 14 days after the second dose of meningococcal vaccine.

The patient was monitored for TMA by evaluating reductions in Hb and PLT and increases in serum creatinine, LDH, and D-dimer in blood samples obtained at the time of eculizumab administration and at the onset of fever because of viral infection or other causes. Blood culture was to be performed to check for meningococcal infection at the time of fever of 38.0 °C or higher. No evidence of TMA or meningococcal infection was found between the beginning of eculizumab therapy and the end of amoxicillin administration. No adverse events related to amoxicillin were observed. In this patient, eculizumab therapy for the treatment of aHUS was continued for more than 3 years, and there was neither aHUS attack nor meningococcal infection during that period.

Case 2

The patient was a 5-month-old boy. In the patient's family history, there was a record of aHUS diagnosed in his cousin (Case 1) on his mother's side and treated with eculizumab. The patient was born at 37 weeks and 0 day of gestation with a bodyweight of 2876 g. There was no neonatal asphyxia or neonatal jaundice after birth. No abnormalities were found on health checkups at 1 and 3 months after birth.

The patient developed upper respiratory infection accompanied by coughing and nasal discharge (day 3). Three days after the onset of upper respiratory infection, there were decreases in the intake of milk and urinary volume; therefore, the patient was brought to a local general hospital. On the same day (day 0), he was found to have anemia,

Table 1 Characteristics, symptoms, laboratory, complement-related factor, and genetic results of both cases

	Case 1	Case 2
Age at onset	4 months	5 months
Sex	Male	Male
Trigger	Vaccination	Upper respiratory infection
Symptoms	Decreased intake of milk + poor complexion	Decreased intake of milk + decreased urine volume
Hb (mg/dL)	4.3	6.0
PLT ($10^4/\mu\text{L}$)	2.8	8.0
LDH (IU/L)	1977	2194
sCr (mg/dL)	0.68	1.17
eGFR (ml/min/1.73m ²)	28.9	18.4
D-dimer ($\mu\text{g/mL}$)	2.9	26.9
C3 (mg/dL)	119	120
C4 (mg/dL)	10	20
CH50 (U/mL)	64.7	85.8
sC5b-9 serum levels (148.0–1243.6 ng/mL) ^a	1615.1	1310.2
sC5b-9 plasma levels (37.0–260.6 ng/mL) ^a	342.8	362.3
Sheep hemolysis test	Positive	Negative
anti-CFH antibodies (AU/mL)	10.5	3.9
Genetic study	No rare variant	PLG:p.V342M (heterozygous variant) CFHR3–CFHR-1: gene deletion

Cr creatinine, Hb hemoglobin, LDH lactate dehydrogenase, PLT platelets

^aResults of eculizumab administration (measured before the next administration)

thrombocytopenia, and renal impairment and was referred and admitted to our center.

On admission, the patient was 60.6 cm in height and 7.7 kg in weight. His activity was poor, and his facial color was pale. There was no purpura in the trunk or extremities. Findings on hematological examination on admission included low hemoglobin (Hb) 6.0 g/dL, indicating anemia, elevated lactate dehydrogenase (LDH) 2194 IU/L and schistocytes suggesting hemolysis. Additional laboratory findings included low platelets (PLT) $8.0 \times 10^4/\mu\text{L}$, elevated creatinine (Cre) 1.17 mg/dL, eGFR 18.4 mL/min/1.73 m² [13], and D-dimer 26.9 $\mu\text{g/mL}$, leading to a diagnosis of thrombotic microangiopathy (TMA). Coombs test was negative for autoimmune hemolytic anemia and stool analysis was also negative for STEC, and not detected cobalamin C deficiency. There was no decrease in complement levels: C3 was 120 mg/dL, C4 was 20 mg/dL, and CH50 was 85.8 U/mL.

Although the sheep erythrocyte hemolysis test was negative, the examination of complement-related factors revealed that the sC5b-9 level was high, 1310.2 ng/mL in the serum (normal range, 148.0–1243.6 ng/mL) and 362.3 ng/mL in the plasma (normal range 37.0–260.6 ng/mL), suggesting that the terminal complement system was activated. Gene analysis showed no rare variant (AF < 0.005 in HGVD) in the 13 causative genes (CFH, CFHR1–CHFR5, C3, CFI, CFB, MCP, THBD, DGKE, and PLG) found in aHUS, but

there was a heterozygous rare variant of p.V342M in PLG, although its involvement in pathogenesis is unclear. In addition, there were CFHR3–CFHR-1 gene deletions (Table 1).

After admission, two sessions of plasma-exchange therapy (days 0 and 1) were performed, assuming aHUS or thrombotic thrombocytopenic purpura as cause of TMA. Since the patient had a relevant family history of aHUS diagnosis, intravenous drip infusion of eculizumab (300 mg) for the treatment of aHUS was started on day 1, and intravenous drip infusion of ampicillin (25 mg/kg/day) for the prevention of meningococcal infection was performed concurrently. However, bacterial pneumonia due to *Moraxella catarrhalis* was found on day 2, and ampicillin was switched to intravenous drip infusion of cefotaxime (200 mg/kg/day) for the treatment of bacterial pneumonia. The ADAMTS13 activity and ADAMTS13 inhibitor level were confirmed to be 25.7% and < 0.5 Bethesda unit/mL, respectively. Stool analysis was negative for STEC.

Intravenous drip infusion of eculizumab (300 mg) was given on day 8, i.e., 1 week after the initial eculizumab dose. On the following day (day 9), cefotaxime therapy for the treatment of pneumonia ended; instead, oral administration of amoxicillin for the prevention of meningococcal infection was started. The first dose of meningococcal vaccine (MCV4-DT; Menactra®) was inoculated at 9 months after birth, and the second dose was inoculated at 1 year after

birth. Oral administration of amoxicillin (20 mg/kg/day) was continued until 20 days after the second dose of meningococcal vaccine.

The patient was monitored for TMA by evaluating reduction in Hb and PLT and increases in serum creatinine, LDH, and D-dimer in blood samples obtained at the time of eculizumab administration and at the onset of fever because of viral infection or other causes. Blood culture was to be performed to check for meningococcal infection at the time of fever of 38.0 °C or higher. No evidence of TMA or meningococcal infection was found between the beginning of eculizumab therapy and the end of amoxicillin administration. No adverse events related to amoxicillin were observed. In this patient, eculizumab therapy for the treatment of aHUS was continued for more than 1 year, and there was neither aHUS attack nor meningococcal infection during that period.

Discussion

Thirteen serological groups of meningococci have been confirmed in terms of capsular polysaccharide antigens, and meningococcal infection is mainly caused by five serological groups (A, B, C, Y, and W) [17]. Although the number of cases of invasive meningococcal infection occurring per year in Japan is infrequent, as low as 40 cases [18], the risk of mass outbreak exists because this infection spread via human–human transmission. The risk of meningococcal infection is estimated to be 1000–2000 times higher among patients who are on eculizumab therapy. In the United States, 16 cases of IMD occurred among patients on eculizumab therapy in 2008–2016 [19]. Of these 16 patients, 10 had paroxysmal nocturnal hemoglobinuria and 5 had aHUS. Penicillin and cephem antibiotics are used for the treatment of IMD. The fatality rate of IMD is 10% to 15%, whereas the fatality rate of meningococcal bacteremia is about 40%, showing the seriousness of this condition [20].

Although the prevention of meningococcal infection is indispensable in patients on eculizumab therapy, there has been no established appropriate preventive strategy for patients not covered by immunization with meningococcal vaccine [21]. In the United States, there are several different meningococcal vaccines available, and vaccination can be administered to infants aged ≥ 2 months [4–6, 22–24]. In contrast, in Japan, MCV4-DT (Menactra[®]) [25] is the only meningococcal vaccine available in the market, and the use of this vaccine is not recommended for infants aged < 9 months after birth. Although MCV4-DT is effective for serotypes A, C, Y, and W-135, it does not cover serotype B. There is no approved vaccine effective for serotype B in Japan. In Japan, the meningococcal serotypes of 160 IMD patients reported from April 2013 to October 2017 were serotype Y in 75 patients (46.9%) and serotype B in 15

patients (9.4%) respectively [18], and the infants with aHUS on eculizumab therapy contracting meningococcemia after receiving preventive vaccinations were reported [26].

In this regard, prophylaxis with various antibiotics has been performed to prevent infection in infants with aHUS undergoing eculizumab therapy before meningococcal vaccination [8–13]. There are the following three reports on infants who are at least 2 months old and qualified for eculizumab therapy [1]: amoxicillin prophylaxis was implemented until 2 weeks after vaccination (MCV4-TT; Nimenrix[®]) in a 3-month-old infant [8]; in a 4-month-old infant, prophylactic administration of cefdinir was started at the beginning of eculizumab therapy, and vaccination (MCV4-DT; Menactra[®]) was performed 2 weeks later (6 months after birth) and 17 weeks later (9 months after birth) [9]; and prophylactic antibiotics such as ampicillin were given to five infants aged 3–6 months until at least 2 weeks after vaccination [10]. Based on the findings from previous reports [8–13], prophylactic antibiotics can be necessary at least until vaccination, although there still remains controversy. Because the current vaccine cannot cover all serotypes, prophylactic oral antibiotics may be continued after vaccination. This issue needs to be investigated in the future.

In conclusion, we experienced two very rare cases of aHUS in infants 4–5 months after birth treated by eculizumab; in those patients, meningococcal infection was successfully prevented by the administration of oral amoxicillin continued until immunization with meningococcal vaccination. Eculizumab therapy for the treatment of aHUS was continued safely in these infants, and there was no TMA attack during treatment. Therefore, we consider that prophylactic administration of amoxicillin may be effective for preventing meningococcal infection after eculizumab therapy in infants aged < 9 months who are not vaccinated with meningococcal vaccine.

Limitation

Both cases underwent long-term administration of AMPC, but we did not check changes of bacterial species in feces.

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Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors. The publication of this report was approved by our institutional review board (no. 2019078).

Informed consent Oral consent was obtained from the parents of the patients for the publication of this case report.

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