

Eculizumab in the treatment of atypical hemolytic uremic syndrome in an infant leads to cessation of peritoneal dialysis and improvement of severe hypertension

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Received: 1 August 2014 / Revised: 10 September 2014 / Accepted: 11 September 2014 / Published online: 16 October 2014
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Abstract

Background Severe hypertension (HTN) and acute kidney injury frequently associated with atypical hemolytic uremic syndrome (aHUS) were refractory to various therapies in the pre-eculizumab era. Here we report the case of a 4-month-old boy who developed aHUS presenting with undetectable C3 protein, no predisposing mutations in complement factors, and no antibodies against factor H.

Methods Repeated plasma infusions and nine sessions of plasmapheresis were ineffective. The patient initially required continuous hemodiafiltration and thereafter peritoneal dialysis. Despite vigorous antihypertensive treatment and improved fluid overload with dialysis, HTN persisted. His low C3 level (<20 mg/dl) suggested unrestricted complement activation. Therefore, based on the suspicion of unrestricted complement cascade in the pathogenesis, treatment with

eculizumab, a human anti-C5 monoclonal antibody, was initiated with the aim of controlling disease activity.

Results Ecuzumab therapy resulted in the control of severe HTN and cessation of peritoneal dialysis.

Conclusions This infant with HTN and acute kidney injury associated with aHUS was treated successfully with ecuzumab.

Keywords Plasmapheresis-resistant · Meningococcal infection · Prophylactic antibiotics · Vaccination · Pathological findings · Atypical hemolytic uremic syndrome · Anti-C5 therapy

Introduction

Hemolytic uremic syndrome (HUS) is a rare disease with manifestations of microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment. There are two types of HUS: HUS which follows a diarrheal infection often caused by Shiga toxin-producing *Escherichia coli* (Stx-HUS) and atypical HUS (or non-Stx-HUS) caused by one or more genetic mutations. The latter type is extremely rare—accounting for less than 10 % of all HUS cases—and the clinical outcome is unfavorable, with up to one-half of cases progressing to end-stage renal failure and one-fourth of patients dying in the acute phase if they do not receive rigorous treatment [1]. Historically, the first-line therapy for aHUS has been plasma therapy, including plasmapheresis [2, 3]. However, approximately 80 % of patients with aHUS have only partial responses to short-term plasmapheresis with subsequent persistent tissue damage [4]. The main pathogenesis of aHUS is unrestricted overactivation of the alternative pathway of complement activation [5], which has led to ecuzumab, a human anti-C5 monoclonal antibody, being used for both

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plasmapheresis-resistant and plasmapheresis-dependent cases of aHUS [6–9].

We here report a 4-month-old male baby with plasmapheresis-resistant aHUS who was successfully treated with eculizumab. The results of this very effective therapy was control the patient's extremely severe hypertension and cessation of peritoneal dialysis.

Case report

A severely ill 4-month-old male baby weighing 7.1 kg presented with a 2-day history of fever and vomiting. His father and mother were alive and in good health; his maternal grandmother and grandaunt had died of cerebral infarction, but no details were available. Laboratory tests at a local hospital revealed anemia (8.9 g/dl), thrombocytopenia ($64 \times 10^9/l$), and acute renal insufficiency consistent with HUS. He was transferred to Hiroshima University Hospital where upon admission, schistocytes on the peripheral blood film, elevated levels of lactate dehydrogenase (LDH; 1,830 U/l), creatinine (1.95 mg/dl), and urea (38.8 mg/dl), and decreased platelets level ($41 \times 10^9/l$) were detected. Stool culture was negative, and immunoglobulin M (IgM) antibody for O-157 lipopolysaccharide was not detected. A tentative diagnosis of aHUS was made, which was later confirmed by a normal test result for ADAMTS13 (72 %) activity. After admission to the hospital, the patient received multiple blood transfusions, including fresh frozen plasma and continuous hemodiafiltration. However, his general condition remained poor, and hemolytic anemia, elevated LDH, and renal failure did not improve.

On day 26 he was transferred to the Hiroshima Prefectural Hospital for closer management of the renal failure. On admission, the serum complement of C3 and C4 was <20 and 14 (normal range 13–35) mg/dl, respectively. On the third day of admission, plasmapheresis with 60 ml/kg of fresh frozen plasma was initiated and performed for 3 consecutive days, in combination with hemodiafiltration, followed by plasmapheresis every other day for the next 2 weeks; however, there was no remarkable improvement of the hemolysis and renal failure. After nine sessions of plasmapheresis, the patient was not in remission from his disease according to the guideline of the European Pediatric Study Group for HUS [2]. Moreover, his severe hypertension (systolic blood pressure 140–150 mmHg), which initially did not respond to fluid removal by hemodiafiltration, was also refractory to the treatment with an intravenous large dose of nifedipine chloride, peroral enalapril, and losartan. At that time, eculizumab was not licensed for the treatment of aHUS in Japan. Therefore, after receiving approval from the institutional ethics committee, we started the patient on eculizumab, with an initial dose of 300 mg administered on day 48, followed by a second dose of 300 mg on day 55; thereafter and up to the present (17 months), the patient has been

receiving one 300-mg dose of eculizumab every 3 weeks in accordance with the manufacturer's recommendations, with sustained remission. For the prevention of infection after the treatment with eculizumab, the patient has received continuous antibiotic prophylaxis with cefdinir from the first administration of eculizumab, and on days 62 and 169 he received tetravalent conjugate meningococcal vaccine (Menactra®; Sanofi Pasteur, Lyon, France).

The severe hypertension gradually improved, and the patient was switched from intravenous nifedipine chloride to peroral nifedipine 11 weeks after the first administration of eculizumab. Plasma renin activity on days 40, 60, 84, and 123 was 18, 77, 5.7, and 1.2 ng/ml/h, respectively. Renal function improved, and peritoneal dialysis (PD) was stopped on day 117. On day 108 the patient presented with white stool and jaundice. Liver function tests were consistent with cholestatic jaundice with a total bilirubin of 2.5 mg/dl, direct bilirubin of 1.7 mg/dl, aspartate transaminase (AST) of 1,337 U/l, alanine transaminase (ALT) of 1,667 U/l, LDH of 954 U/l, and gamma-glutamyl transferase (GTP) of 1,093 U/l. Abdominal ultrasonography revealed dilatation of the common bile duct and some gallstones. Magnetic resonance cholangiopancreatography confirmed the diagnosis of cholelithiasis, which regressed spontaneously (Fig. 1).

Genetic work-up showed no predisposing mutations in complement factor (CF) H, CFI, CFB, C3, thrombomodulin, or membrane cofactor protein. At the initiation of the first session of plasmapheresis, protein level and CFH activity were normal, and antibodies to CFH were undetectable. Membrane cofactor protein expression on peripheral blood mononuclear cells was within the normal limit. Cobalamin-C disorder was ruled out based on the normal level of homocystine in the urine and negative tandem mass screening test.

A kidney ultrasound on admission to our hospital showed normal-sized kidneys for age with increased echogenicity in the renal cortex. A kidney biopsy performed on day 159 showed mild swelling of the glomerular endothelium and decrease in the size of the lumen, with approximately 10% of interstitial cell infiltration and fibrosis. A small number of fragmented erythrocytes were observed in a few glomeruli among the 47 glomeruli assessed (Fig. 2b). Only rarely were wrinkling, collapse, and/or thickening of the glomerular basement membranes, identical to that observed in ischemic lesions, observed in the biopsy specimen. However, a few glomeruli showed partial duplication of the peripheral basement membrane, which is a marker of chronic change. Moreover, several intralobular arteries and arterioles had a narrowed lumen due to myointimal hyperplasia (Fig. 2a). Juxtaglomerular apparatus hyperplasia was also observed in some glomeruli (Fig. 2a). Immunofluorescence findings showed weak C3, fibrinogen, and IgM depositions in glomerular capillaries.

Currently, 17 months after the initiation of eculizumab administration, the laboratory test results of our patient are

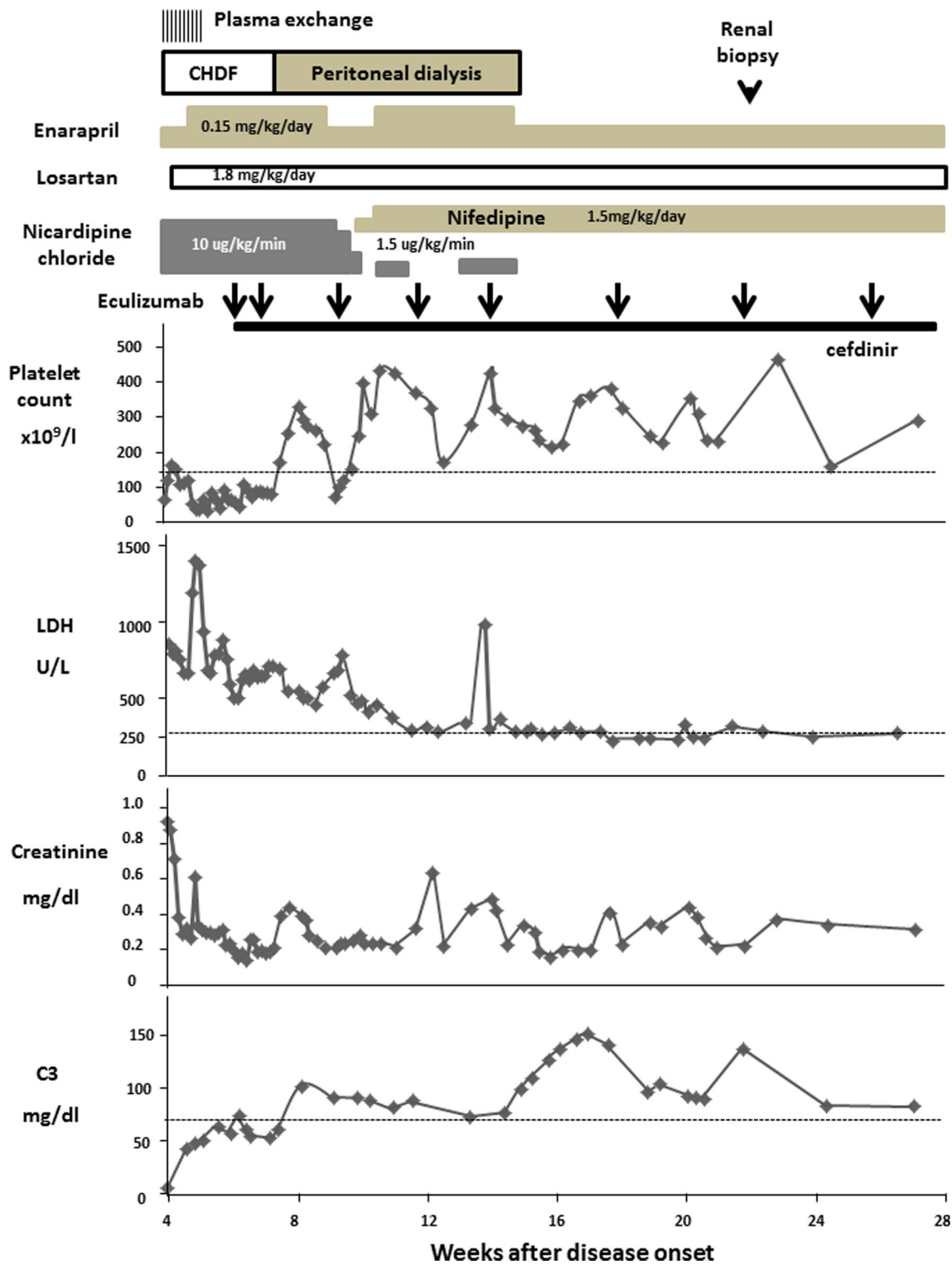
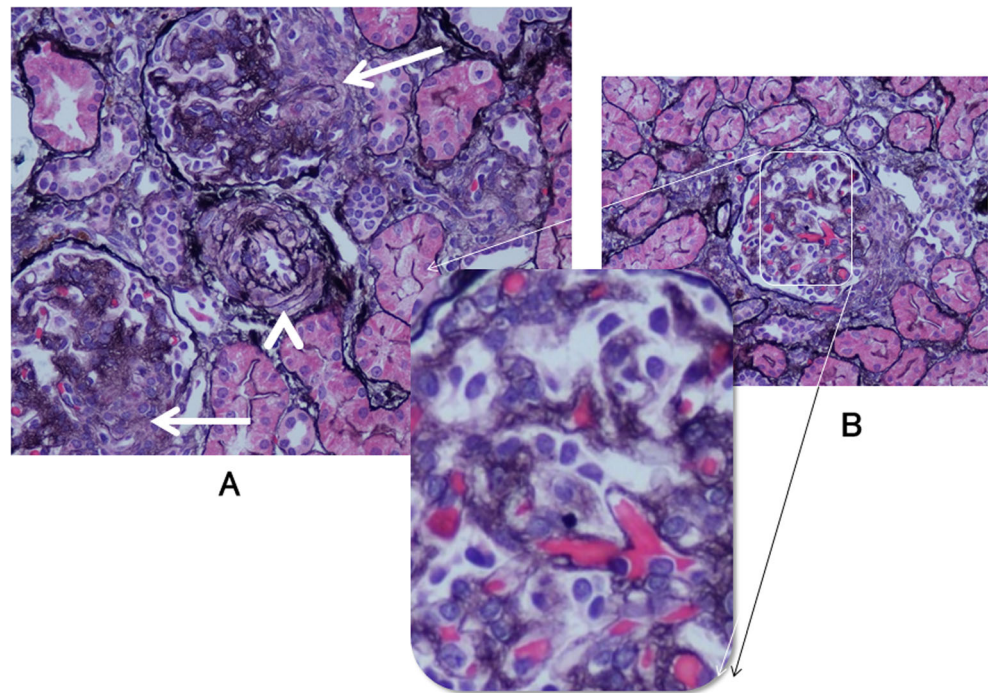


Fig. 1 Clinical course of the patient before and after eculizumab therapy. The patient received 9 sessions of plasmapheresis (vertical bars) in combination with continuous hemodiafiltration (CHDF) without clinical remission; severe hypertension continued despite vigorous antihypertensive treatment, including a high dose of nicardipine chloride. After 2 administrations of eculizumab (vertical arrows), the platelet count and complement 3 (C3) level increased and the lactate dehydrogenase (LDH)

level decreased. The therapy allowed cessation of peritoneal dialysis and nicardipine chloride administration. Renal biopsy (arrowhead) was performed on day 159 after disease onset. Dashed horizontal lines show the remission level for platelet count ($150 \times 10^9/l$), the upper limit of the reference range for LDH (260 U/l) in our institution, and the lower limit of the reference range for C3 (70 mg/dl)

Fig. 2 Pathological findings of renal specimens after hematological remission and cessation of peritoneal dialysis. **a** Periodic acid–methenamine silver (PAM) staining revealed an arteriole with a narrowed lumen due to myointimal hyperplasia (*arrowhead*) and juxtaglomerular apparatus hyperplasia (*arrows*). **b** PAM staining reveals thrombotic microangiopathy with intracapillary erythrocytes



as follows: hemoglobin, 11.4 g/dl; platelet count, $247 \times 10^9/l$; AST, 34 IU/l; ALT, 20 IU/l; LDH, 289 IU/l; gamma-GTP, 41 IU/l; total bilirubin, 0.1 mg/dl; urea nitrogen, 21.2 mg/dl; creatinine, 0.33 mg/dl {classified into chronic kidney disease (CKD) stage II according to diagnostic criteria of Japanese children [10]}; Na, 139 mEq/l; K, 4.4 mEq/l; Cl, 104 mEq/l; haptoglobin, 86 mg/dl; C3, 104 mg/dl; urinary protein negative; urine beta2 microglobulin, 172 ug/l.

Discussion

Eculizumab is emerging as an effective treatment for post-transplant aHUS recurrence [11] and may have a certain role in treating de novo aHUS [6–9, 12, 13], halting the hemolytic process. The complement pathway dysregulation that includes loss-of-function mutations in genes of the complement regulatory system and gain-of-function mutations in genes encoding the complement activators factor B and C3 seem to play a crucial role in the pathogenesis of aHUS. The low level of C3 in our patient indicated consumption due to unrestricted complement overactivation. This led us to initiate eculizumab treatment, and the disease activity of the patient subsequently subsided.

Three issues attracted our attention in light of these results. The first of these is the reason why the renal function of our patient improved after eculizumab therapy. Complement-induced endothelial injury might result in stenosis due to endothelial cell swelling and detachment, followed by inflammatory leucocyte recruitment, subendothelial expansion, and reactive smooth-muscle cell proliferation. Moreover, thrombus

formation on the injured endothelium also contributes to the stenotic process, leading to renal hypoperfusion and clinical renal failure. The late initiation of eculizumab therapy—not as a first-line therapy—has been shown in previous studies to result in a partial or complete recovery of renal function in patients with aHUS. To date, however, limited data on pathological findings following the improvement of renal function by treatment with eculizumab are available. Pathological data from a few large-scale studies have not provided further insights into the mechanism and process of recovery of renal function [14, 15]. The degree of vascular involvement is well correlated with the ultimate prognosis of thrombotic microangiopathy [16]. In our study, renal biopsy on day 159 showed very mild glomerular intracapillary thrombosis with 10 % of interstitial changes. Moreover, there were few ischemic changes, such as collapse of the capillary tuft with wrinkling and thickening of the capillary basement membranes, which is unlikely due to involvement of relatively large-sized vessels. The narrow extent of arterial and arteriolar damage in this case seems to allow a nearly complete improvement of renal function.

The second issue is the timing that the therapy should be initiated. The switch from plasma therapy to eculizumab has been shown to improve renal function even in patients with long-lasting and stable CKD. Kim et al. [7] reported a 7-month-old girl with aHUS dependent on plasmapheresis and PD who was able to stop PD after eculizumab therapy. This patient received eculizumab 15 weeks after the initiation of PD. In prospective phase 2 trials in which aHUS patients aged ≥ 12 years received eculizumab for 26 weeks, a number of dialysis-dependent patients were ultimately able to

stop dialysis [14]. In these trials, eculizumab inhibited complement-mediated thrombotic microangiopathy and was associated with significant time-dependent improvement in renal function in patients with aHUS [14, 15]. Despite the lack of evidence from randomized controlled studies, data from published studies indicate that eculizumab is likely to achieve better control of aHUS than dose plasma therapy. Based on these data, Zuber J et al. [5] recommended that eculizumab therapy should be initiated in patients with aHUS—particularly pediatric patients—as early as possible.

The third issue is the susceptibility to infection induced by eculizumab therapy. At the time of writing—17 months after we initiated eculizumab therapy—our patient has remained free of aHUS recurrences despite upper respiratory tract infection and gastrointestinal infection, without any adverse events of this medication. However, the therapy puts all patients at a high risk of neisserial infection because the membrane attack complex plays a crucial role in the elimination of the infection. Therefore, before the administration of eculizumab, the prevention of *Neisseria meningitidis* infection is mandatory. As a general rule, patients receiving eculizumab therapy require a tetravalent meningococcal vaccination. However, the tetravalent vaccines currently available do not cover serogroup B strains, which are the most prevalent *N. meningitidis* strains in Japan, as well as in Europe and America [17]. Moreover, because our patient urgently needed the emergent treatment with eculizumab, he has received continuous antibiotic prophylaxis from the first administration of this medication. The need for prophylactic antibiotics during continuous eculizumab treatment remains controversial. In a prospective and single-arm study involving 41 patients had been vaccinated against *N. meningitidis*, two patients suffered from meningococcal infection during the 26-week study period [15]. Because severe infection by *N. meningitidis* is frequently life-threatening in patients with a late complement component deficiency [18], we recommend antibiotic prophylaxis until the time that quadrivalent conjugate meningococcal vaccines that cover serotype B strains can be launched.

In summary, our patient, who was assumed to have an extremely poor prognosis, responded rapidly to eculizumab therapy, resulting in longitudinal complete remission, improvement of life-threatening hypertension, and cessation of PD. In the near future, eculizumab might be first-line therapy for aHUS if long-term complement blockade can be proved to be safe with meningococcal vaccination. However, the issue of the optimal duration of eculizumab therapy also remains unsettled [5].

Acknowledgments We thank Dr. Camille L. Bedrosian of Alexion Pharmaceuticals Inc. for helpful comments and Alexion Pharmaceuticals Inc. for providing eculizumab (Soliris) without charge prior to the approval of the use of eculizumab for the treatment of aHUS by Health, Labor and Welfare Ministry in Japan. Medical writing support was provided by Dr. John Kincaid (Alexion Global Medical Affairs).

Financial disclosure None.

Conflict of interest None.

References

1. Waters AM, Lichts C (2011) aHUS caused by complement dysregulation: new therapies on the horizon. *Pediatr Nephrol* 26:41–57
2. Ariceta G, Besbas N, Johnson S, Karpman D, Landau D, Licht C, Loirat C, Pecoraro C, Taylor CM, Van de Kar N, Vandewalle J, Zimmerhackl LB; European Paediatric Study Group for HUS (2009) Guideline for the investigation and initial therapy of diarrhea-negative-hemolytic uremic syndrome. *Pediatr Nephrol* 24: 687–696
3. Taylor CM, Machin S, Wigmore SJ, Goodship THJ (2009) Clinical practice guideline for the management of atypical haemolytic uremic syndrome in the United Kingdom. *Br J Haematol* 148:37–47
4. Noris M, Remuzzi G (2009) Atypical hemolytic-uremic syndrome. *N Engl J Med* 361:1676–1687
5. Zuber J, Fakhouri F, Roumenina LT, Loirat C, Fremeaux-Bacchi V (2012) Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. *Nat Rev Nephrol* 8:643–657
6. Lapeyraque AL, Fremeaux-Bacchi V, Robitaille P (2011) Efficacy of eculizumab in a patient with factor-H-associated atypical hemolytic uremic syndrome. *Pediatr Nephrol* 26:621–624
7. Kim JJ, Waller SC, Reid CJ (2012) Eculizumab in atypical haemolytic-uraemic syndrome allows cessation of plasma exchange and dialysis. *Clin Kidney J* 5:34–36
8. Vilalta R, Lara E, Madrid A, Chocron S, Munoz M, Casquero A, Nieto J (2012) Long-term eculizumab improves clinical outcomes in atypical hemolytic uremic syndrome. *Pediatr Nephrol* 27:2323–2326
9. Nummerger J, Witzke O, Opaza Saez A, Vester U, Baba HA, Kribben A, Zimmerhackl LB, Janecke AR, Nagel M, Kirschfink M (2009) Eculizumab for atypical hemolytic-uremic syndrome. *N Eng J Med* 360:542–544
10. Ishikura K, Uemura O, Ito S, Wada N, Hattori M, Ohashi Y, Hamasaki Y, Tanaka R, Nakanishi K, Kaneko T, Honda M; Pediatric CKD Study Group; Japan Committee of Measures for Pediatric CKD of the Japanese Society of Pediatric Nephrology (2013) Pre-dialysis chronic kidney disease in children: results of a nationwide survey in Japan. *Nephrol Dial Transplant* 28: 2345–2355
11. Ariceta G, Arrizabalaga B, Auirre M, Morteruel E, Lopez-Trascasa M (2012) Eculizumab in the treatment of atypical hemolytic uremic syndrome in infants. *Am J Kidney Dis* 59:707–710
12. Dorresteijn EM, van de Kar NCAJ, Cransberg K (2012) Eculizumab as rescue therapy for atypical hemolytic uremic syndrome with normal platelet count. *Pediatr Nephrol* 27:1193–1195
13. Garjan M (2012) Early treatment with eculizumab may be beneficial in atypical hemolytic uremic syndrome. *Clin Kidney J* 5:31–33
14. Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, Bedrosian C, Bingham C, Cohen DJ, Delmas Y, Douglas K, Eitner F, Feldkamp T, Fouque D, Furman RR, Gaber O, Herthelius M, Hourmant M, Karpman D, Lebranchu Y, Mariat C, Menne J, Moulin B, Nümberger J, Ogawa M, Remuzzi G, Richard T, Sberro-Soussan R, Severino B, Sheerin NS, Trivelli A, Zimmerhackl LB, Goodship T (2013) Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Eng J Med* 368:2169–2181
15. Fakhouri F, Hourmant M, Campistol JM, Catalana SR, Espinosa M, Gaber AO, Menne J, Minetti EE, Provot F, Rondeau E, Ruggenenti P, Weelers LE, Ogawa M, Bedrosian CL, Legendre CM (2013)

- Eculizumab inhibits thrombotic microangiopathy and improves renal function in adult atypical hemolytic uremic syndrome patients. *J Am Soc Nephrol* 24:49A–50A
16. Laszik Z (1996) Thrombotic microangiopathies. In: Silva F, D'Agati V, Nadasdy T (eds) *Renal biopsy interpretation*. Churchill Livingstone, New York, pp 283–308
 17. Bouts A, Monnens L, Davin JC, Struijk G, Spanjaad L (2011) Insufficient protection by *Neisseria meningitides* vaccination alone during eculizumab therapy. *Pediatr Nephrol* 26:1918–1920
 18. Ram S, Lewis LA, Rice PA (2010) Infections of people with complement deficiencies and patients who have undergone splenectomy. *Clin Microbiol Rev* 23:740–780