Prophylactic Eculizumab after Renal Transplantation in Atypical Hemolytic–Uremic Syndrome

TO THE EDITOR: Atypical hemolytic–uremic syndrome is a rare microangiopathic hemolytic condition characterized by thrombocytopenia and acute renal failure.[1] The prognosis for patients with atypical hemolytic–uremic syndrome with a factor H mutation is poor; 60% have end-stage renal disease or die within a year.[2] The expected rate of graft failure due to recurrent atypical hemolytic–uremic syndrome among patients with a factor H or factor I mutation is 80% within 1 to 2 years.[3] Here, we describe a child with atypical hemolytic–uremic syndrome and a known factor H mutation who had normal renal function 1 year after high-risk kidney transplantation with prophylactic dosing of the terminal complement inhibitor eculizumab.

Our patient received a diagnosis of atypical hemolytic–uremic syndrome and a factor H mutation at 4 years of age. During the following 6 years, his renal function remained abnormal, necessitating intermittent peritoneal dialysis and later, continuous cycling peritoneal dialysis. At 9 years of age, severe septicemia developed in association with catheter use, rapid deterioration of renal function ensued, and additional hemodialysis was needed, ultimately resulting in transplantation of a kidney from a deceased donor.

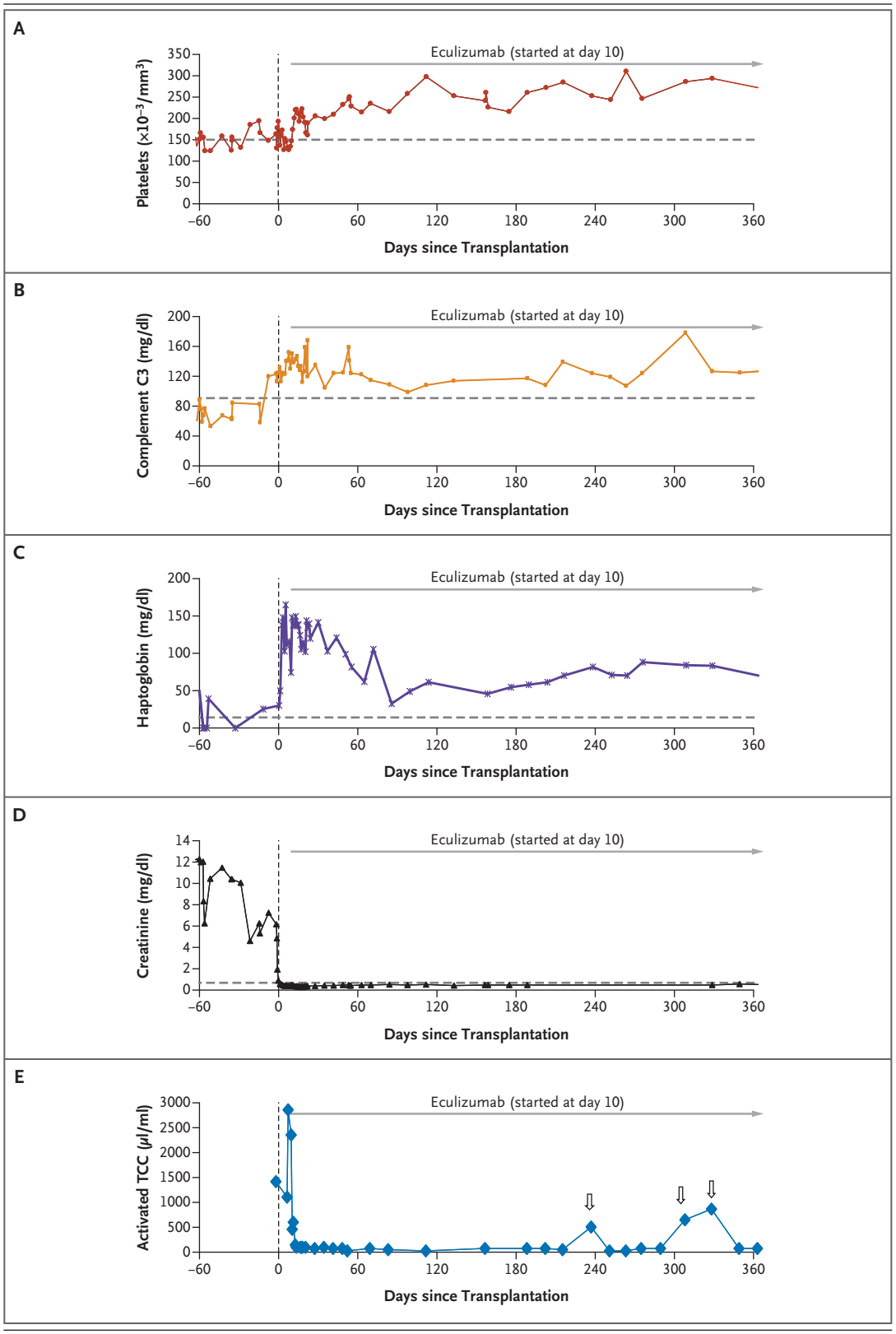
Within 48 hours after transplantation, urine output was high, and the creatinine level decreased to within the normal range. Plasma exchange was performed on a daily basis until 9 days after transplantation. On day 10, the patient received the first dose (600 mg) of eculizumab. No plasma exchange was performed thereafter. Subsequent doses of 600 mg were given every 2 weeks. Peak and trough levels of the drug were measured after each of the first four doses were given, to ensure sufficient drug levels. With ongoing treatment with 600 mg of eculizumab every 2 weeks, there was no evidence of active disease for over 1 year after transplantation. During this period, the patient's complement component 3 values, platelet counts, and haptoglobin levels all stabilized in the middle of the normal range (Fig. 1).

Terminal complement is necessary to prevent and limit the severity of infection with *Neisseria meningitidis*. Owing to the mechanism of action of eculizumab, our patient was vaccinated against meningococcal infection before the initiation of eculizumab treatment.[5]

Unabated complement activation due to the production of mutant factor H may explain the high rate of recurrence of atypical hemolytic–uremic syndrome, and overall lack of success of renal transplantation, in patients with factor H mutation. Recent reports have shown that treatment with eculizumab during recurrence can improve renal function.[5,6] However, we began prophylactic treatment before there was any evidence of recurrence, to maintain chronic suppression of complement activity in an attempt to reduce the risk of progression to graft failure in our high-risk patient with factor H mutation. To date, the patient shows no signs of graft rejection or recurrence of atypical hemolytic–uremic

Figure 1 (facing page). Response to Eculizumab Therapy after Renal Transplantation in a Patient with a Factor H Mutation and Atypical Hemolytic–Uremic Syndrome.

Ten days after renal transplantation, the patient received the first dose of eculizumab. No plasma exchange was performed thereafter. Within 24 to 48 hours after the first dose, platelet counts increased (Panel A). The patient's platelet counts, complement component 3 (C3) values (Panel B), and haptoglobin levels (Panel C) all stabilized in the middle of the normal range during the year since transplantation. Serum creatinine levels have been maintained within the normal range. The gray horizontal lines in Panels A through D represent the lower limit of the normal ranges for platelets (155,000 to 425,000 cells per cubic millimeter), complement C3 (90 mg per deciliter), and haptoglobin (14 mg per deciliter) and the upper limit of the normal range for serum creatinine (0.64 mg per deciliter [57 μmol per liter]), respectively. After the commencement of eculizumab treatment, activation of serum terminal complement complex (TCC)[4] was blocked within 1 day, and the blocking was maintained with the regimen of a dose given every 14 days. An attempt to increase the interval between doses to 21 days (arrows) resulted in an increase in the activated TCC level, indicating that the eculizumab level under this regimen was insufficient to maintain blocking. Dosing every 14 days was resumed. The normal range (5th to 95th percentile) for serum TCC is 3.0 to 22.9 μl per milliliter. To convert values for creatinine to micromoles per liter, multiply by 88.4.


A
Platelets (×10⁻³/mm³)
350
300
250
200
150
100
50
0
Eculizumab (started at day 10)
–60
0
60
120
180
240
300
360
Days since Transplantation
B
Complement C3 (mg/dl)
200
160
120
80
40
0
Eculizumab (started at day 10)
Days since Transplantation
C
Haptoglobin (mg/dl)
200
150
100
50
0
Eculizumab (started at day 10)
Days since Transplantation
D
Creatinine (mg/dl)
14
12
10
8
6
4
2
0
Eculizumab (started at day 10)
Days since Transplantation
E
Activated TCC (μl/ml)
3000
2500
2000
1500
1000
500
0
Eculizumab (started at day 10)
Days since Transplantation

syndrome and has received no plasma therapy since eculizumab therapy was started.

Lothar Bernd Zimmerhackl, M.D., Ph.D.
Johannes Hofer, M.D.
Gérard Cortina, M.D.
Walter Mark, M.D.
Reinhard Würzner, M.D., Ph.D.
Therese C. Jungraithmayr, M.D.
Medical University Innsbruck
Innsbruck, Austria
lothar.zimmerhackl@i-med.ac.at

Gus Khursigara, Ph.D.
Kay O. Kliche, M.D.
Alexion Pharmaceuticals
Cheshire, CT

Wolfgang Radauer, M.D.
Children's Hospital Salzburg
Salzburg, Austria

Drs. Zimmerhackl and Jungraithmayr contributed equally to this letter.

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1. Noris M, Remuzzi G. Atypical hemolytic–uremic syndrome. N Engl J Med 2009;361:1676-87.
2. Sellier-Leclerc AL, Fremeaux-Bacchi V, Dragon-Durey MA, et al. Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. J Am Soc Nephrol 2007;18:2392-400.
3. Zimmerhackl LB, Scheiring J, Prüfer F, Taylor CM, Loirat C. Renal transplantation in HUS patients with disorders of complement regulation. Pediatr Nephrol 2007;22:10-6.
4. Prüfer F, Scheiring J, Sautter S, et al. Terminal complement complex (C5b-9) in children with recurrent hemolytic uremic syndrome. Semin Thromb Hemost 2006;32:121-7.
5. Chatelet V, Frémeaux-Bacchi V, Lobbedez T, Ficheux M, de Ligny BH. Safety and long-term efficacy of eculizumab in a renal transplant patient with recurrent atypical hemolytic-uremic syndrome. Am J Transplant 2009;9:2644-5.
6. Nürnberger J, Witzke O, Opazo Saez A, et al. Eculizumab for atypical hemolytic–uremic syndrome. N Engl J Med 2009;360:542-4. [Erratum, N Engl J Med 2009;360:2487.]

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CORRECTIONS

Effect of Nateglinide on the Incidence of Diabetes and Cardiovascular Events (10.1056/NEJMoa1001122; published on March 14, 2010, at NEJM.org). In Table 1 (page 7), all values in the Baseline and Last study visit rows under Angiotensin-receptor blocker were incorrect. The article has been corrected at NEJM.org.

Effect of Valsartan on the Incidence of Diabetes and Cardiovascular Events (10.1056/NEJMoa1001121; published on March 14, 2010, at NEJM.org). In Table 1 (page 7), all values given for Lipids and for Ratio of urinary albumin to creatinine were incorrect in the Valsartan and Placebo columns, and all values given for Angiotensin-receptor blocker, including the P values, were incorrect. In the Statistical Analysis subsection of Methods (page 3), the first sentence should have begun, "On the assumption that the study would continue until the extended cardiovascular outcome occurred in 1374 patients in the two study groups combined" rather than "... in 1774 patients in the placebo group." The article has been corrected at NEJM.org.

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus (10.1056/NEJMoa1001282; published on March 14, 2010, at NEJM.org). The third sentence of the Plasma Lipids subsection of Results (page 7) should have read, "Median plasma triglyceride levels decreased from 164 to 122 mg per deciliter (1.85 to 1.38 mmol per liter) in the fenofibrate group and from 160 to 144 mg per deciliter (1.81 to 1.63 mmol per liter) in the placebo group" rather than "... from 189.0 to 147.0 mg per deciliter (2.13 to 1.66 mmol per liter) in the fenofibrate group and from 186.2 to 170.0 mg per deciliter (2.10 to 1.92 mmol per liter) in the placebo group." We regret the error. The article has been corrected at NEJM.org.

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