

Preemptive Use of Eculizumab for Living-Donor Kidney Transplantation in a Child with Atypical Hemolytic Uremic Syndrome

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Eculizumab is an anti-complement C5 monoclonal antibody that has recently been reported as an effective therapy for atypical hemolytic uremic syndrome. However, few data are available on the preemptive use of this medication in pediatric kidney transplantation. This report describes a successful preemptive use of eculizumab in combination with living unrelated kidney transplantation in a 10-year-old child with end-stage renal disease

secondary to atypical hemolytic uremic syndrome who has a complement factor H mutation that has not been previously reported. Further observations and clinical trials are required to address the challenges and areas of uncertainty related to preemptive eculizumab therapy for kidney transplantation in children and adults with atypical hemolytic uremic syndrome.

INTRODUCTION

Atypical hemolytic uremic syndrome (aHUS) is a rare thrombotic microangiopathy characterized by overactivation of the alternative complement pathway. This syndrome is associated with severe clinical manifestations, a tendency to recur, and, until recently, a poor long-term prognosis (Noris & Remuzzi, 2009). With conventional supportive therapy, the expected rate of graft failure after kidney transplantation due to recurrent aHUS among patients with a mutation in a complement gene ranges from 50% to 80% within the first five years post transplant (Le Quintrec et al., 2013; Zimmerhackl, Scheiring, Pruffer, Taylor, & Loirat, 2007).

Eculizumab is a high-affinity humanized recombinant IgG2/IgG4 monoclonal antibody against the complement component 5 (C5). This medication has recently emerged as a promising agent for the treatment of alternative complement pathway activation disorders. In 2011, the Food and Drug Administration approved eculizumab for use in pediatric patients with aHUS. However, experience using eculizumab in pediatric kidney transplantation remains limited (Barnett et al., 2013; Krid et al., 2012; Nester et al., 2011; Weitz, Amon, Bassler, Koenigsrainer, & Nadalin, 2011; Zuber, Le Quintrec, et al., 2012). Particularly little is known about the preemptive use of this agent in initial living-donor kidney transplantation in pediatric recipients with aHUS.

CASE

At age 5, the patient presented to the emergency department with complaints of fatigue, muscle weakness, pallor, and vomiting without diarrhea. His blood pressure was elevated and laboratory data showed serum creatinine 135.2 $\mu\text{mol/L}$ (1.53 mg/dL), hemoglobin 4.50 g/dL, white blood cell count $15.7 \times 10^9/\text{L}$, platelet count $76 \times 10^9/\text{L}$, and reticulocyte count 15.8%. A peripheral blood smear showed

schistocytes, helmet cells, and reticulocytes. Serum complement C3 level was decreased.

The patient was diagnosed with aHUS, was treated initially with plasma infusions, and was then treated with plasmapheresis. However, the patient's renal function deteriorated, and by age 6 the patient required chronic hemodialysis via an arteriovenous fistula. A kidney biopsy performed at that time showed vascular changes consistent with thrombotic microangiopathy and hypertension. Factor H analyses were performed at the Mario Negri Institute for Pharmacological Research in Bergamo, Italy. Sequencing of short consensus repeat (SCR) 20, a mutation hot-spot region of the factor H gene, revealed no mutations. Other SCRs were then sequenced, and a heterozygous mutation in SCR 15 was found (SCR 15: c.2831T>C, p. Trp920Arg). This mutation has not been previously reported and its pathogenicity has not yet been proven. Serum complement profile at the time of genetic analysis showed normal levels of factor H (512.82 mg/dL, normal range 350–750 mg/dL), C3 (126 mg/dL), and C4 (35 mg/dL). Other major genes associated with aHUS were analyzed, including complement factor I, membrane cofactor protein, complement factor B, and thrombomodulin, and no mutations were found. The ADAMTS13 level was normal at 37%, and no anti-ADAMTS13 antibodies were identified.

The patient remained on chronic hemodialysis in combination with plasma therapy, but he continued to exhibit severe hypertension and had two episodes of seizures and encephalopathy. Although the MRI findings were consistent with posterior reversible encephalopathy syndrome, a thromboembolic etiology of the encephalopathy was not completely excluded. In addition, the patient had an epi-

Table 1 | Parameters of complement system and related laboratory values prior to eculizumab administration. Data shown for the initial seven doses.

	C5 Functional Assay	AH50	CH50	C3	C4	LDH	Hapto-globin	Hemoglobin
Normal range / units	137–37900 U/ml	75–170%	31–60 U/ml	70–245 mg/dL	16–56 mg/dL	120–325 U/L	25–200 mg/dL	10.9–13.3 g/dL
Pre transplant*								
Dose 1 (day -7)	17638	98	44	74	20	245	47	9.5
Dose 2 (day -1)	<10	<10	<10	65	20	140	106	9.1
Post transplant								
day +1	<10	<10	<10	58	12	226	95	7.3
Dose 3 (day +7)	—	<10	<10	109	23	270	—	7.2
Dose 4 (day +14)	<10	<10	<10	—	—	201	194	9.1
Dose 5	—	<10	<10	137	26	213	146	11.7
Dose 6	<10	<10	<10	131	22	—	93	12.1
Dose 7	<10	<10	<10	127	50	—	96	12.5

* Laboratory test samples were drawn before plasma therapy and before eculizumab.

sode of pulmonary edema without signs of fluid overload. The echocardiogram showed left-ventricle dilatation and hypertrophy with diminished systolic function and moderate mitral regurgitation. Of note, the serum troponin level was elevated at 1.85 µg/L (N<0.08 µg/L). The patient was placed on the deceased-donor waiting list for a combined liver-kidney transplant at his home institution. However, no suitable donor became available.

At age 10, the patient was referred to our institution for evaluation for a living-donor kidney transplant. At that time, his height was 126 cm and estimated dry weight was 24.5 kg, both below the 1st percentile for his age (Z-scores -1.81 and -1.85, respectively) despite nutritional support and recombinant growth hormone therapy. The patient was deemed eligible for a nonrelated living-donor kidney transplant with the preemptive use of eculizumab. Prior to transplantation, the patient was fully immunized, including with the meningococcal vaccine.

The University of Iowa protocol (Nester et al., 2011) was fol-

lowed for the administration of eculizumab. On days -7 and -1 prior to the transplantation, the patient received plasmapheresis with 1.5 volumes of fresh frozen plasma. This was followed by eculizumab, 600 mg. (induction dose for body weight between 20 kg and 30 kg), diluted to a concentration of 5 mg/ml, over 35 minutes. The patient tolerated both therapies well. Laboratory assessment of the patient's complement system before and after treatment with eculizumab is shown in Table 1.

Nonrelated living-donor kidney transplantation was performed without perioperative complications. The donor was a 23-year-old male who was T- and B-cell compatible with the recipient. The donor was a 5 antigen mismatch to the recipient. The recipient's panel reactive antibodies were 0% and there were no donor-specific antibodies. Induction immunosuppression consisted of thymoglobulin and methylprednisolone. Triple maintenance immunosuppression included tacrolimus, mycophenolate mofetil, and prednisone. The patient had urine output immediately after the operation and by post-transplant day 2, the serum cre-

atinine was 53.04 $\mu\text{mol/L}$ (0.6 mg/dL). The patient received two weekly doses of eculizumab, and thereafter was placed on an every-other-week maintenance regimen. We observed an initial decrease in the serum complement C3 level after the first dose of eculizumab, which persisted in the immediate post-transplant period but normalized about one month after transplantation (Table 1). Plasma therapies were not used during or after transplantation.

Two months after transplantation, the patient returned to his home institution, where he continues to receive eculizumab infusions every other week. At nine months' follow-up, his renal function remained stable, and there was no clinical or biochemical evidence of aHUS recurrence.

DISCUSSION

Until recently, there were few therapeutic options in the treatment of children with end-stage renal disease (ESRD) secondary to aHUS. In most cases, treatment was limited to chronic dialysis. Isolated kidney transplantation has a high rate of recurrence, and combined liver-kidney transplantation, while potentially curative for the underlying genetic defect, poses a high risk for mortality. Most children with aHUS and ESRD require, in addition to dialysis, chronic plasma therapy to prevent extrarenal manifestations of aHUS. In the case of our patient, his extrarenal complications could have been explained by alternative complement pathway activation. This included two occurrences of encephalopathy and the episode of severe ventricular dysfunction in combination with respiratory insufficiency.

A number of pathogenic mutations in the SCR 15 region of the complement factor H gene have been identified (Bresin et al., 2013). However, to our knowledge, the mutation found in our patient (SCR 15: c.2831T>C) has not been previously reported, and its pathogenicity has not yet been demonstrated. In view of his normal factor H level, it does not appear that the mutation in our patient is associated with a quantitative factor H deficiency, and therefore a functional defect may be expected; however, a functional analysis of factor H has not been performed.

Donor selection is a challenge for children with aHUS and ESRD. Living related donation is usually not an option due to a high level of pathogenic genes encoding alternative complement pathway components carried in the families of these patients. In our case, we did not offer genetic testing to the family members because of financial considerations and because a negative test result cannot exclude the possibility of another causative genetic defect either not yet discovered or not covered by testing. Therefore, genetic testing is not capable of identifying relatives as suitable candidates for kidney donation. Adverse outcomes for both the recipient and the donor after kidney donation by a family member to a child with aHUS have been described (Donne et al., 2002).

Despite promising reports, many questions regarding the preemptive use of eculizumab in renal transplantation

remain unanswered. These include the utility of pretransplant plasmapheresis, optimization of the eculizumab dosage before and after transplantation, treatment regimens for deceased versus nonrelated living-donor transplants, the optimal induction and maintenance of immunosuppression, laboratory criteria for complement blockage under eculizumab, and the length and cost of the treatment with this agent.

In our case, we used preemptive plasmapheresis before eculizumab infusions as per the University of Iowa protocol (Nester et al., 2011). However, other investigators suggest that eculizumab without plasma therapy may be sufficient to prevent aHUS recurrence (Krid et al., 2012; Roman-Ortiz et al., 2014; Weitz et al., 2011). We used eculizumab on days -7 and -1 prior to the transplantation. But even after the first dose of eculizumab, the functional activity of the terminal complement components was fully suppressed (Table 1). This is consistent with data indicating that complement blockade is complete as soon as one hour after the first eculizumab infusion. Effective treatment with a single dose of eculizumab before surgery has been reported (Krid et al., 2012; Roman-Ortiz et al., 2014). Administration of eculizumab within the first 24 hours after surgery is currently recommended due to possible complement activation after kidney reperfusion and surgical trauma. Disease exacerbation in the immediate postoperative period has been documented when eculizumab was not administered within the first day post transplant (Ranch, Crowther, Arar, & Assanasen, 2014). Blockade of the alternative pathway above the C5 step is not expected after eculizumab treatment. Additionally, similar changes in C3 levels observed in our patient after eculizumab treatment have also been reported in other pediatric cases (Nester et al., 2011; Weitz et al., 2011); however, they are not well understood. Finally, we chose thymoglobulin for induction immunosuppression, but successful use of basiliximab in patients with aHUS has also been described (Nester et al., 2011; Roman-Ortiz et al., 2014).

The advantages of eculizumab over previously available standards of care are obvious. The use of this agent reduces central line-related complications associated with plasmapheresis. Additionally, eculizumab improves renal survival, thus reducing kidney transplantation failure due to aHUS recurrence and preventing the need for chronic dialysis. Together, the benefits of eculizumab treatment contribute to improved quality of life and allow parents and children to go about their lives. However, the financial burden associated with maintenance eculizumab therapy is an important issue, especially in resource-limited countries. Depending on the size of the child, the annual cost of standard maintenance treatment may vary from around \$100,000 to more than \$500,000, making eculizumab one of the most expensive lifelong medical treatments (Zuber, Le Quintrec, et al., 2012). This and other concerns prompted some to consider the possibility of discontinuing eculizumab therapy with strict home monitoring for early signs of relapse in patients with aHUS who achieve stable remission (Ardissino et al., 2014).

Eculizumab appears to be an effective agent for preemptive therapy in nonrelated living-donor kidney transplantation in patients with aHUS. However, current protocols for the prophylactic use of eculizumab in renal transplantation are empirical. More observations are required to develop the most effective and cost-efficient approach to the use of this agent. Incorporating cases of this kind into the national registry may help optimize treatment strategies.

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