Eculizumab to Treat Antibody-Mediated Rejection in a 7-Year-Old Kidney Transplant Recipient

Hassib Chehade, MD; Samuel Rotman, MD; Maurice Matter, MD; Eric Girardin, MD; Vincent Aubert, MD; Manuel Pascual, MD

We report on successful early eculizumab administration to treat acute antibody-mediated rejection (ABMR) in a highly sensitized kidney transplant recipient. The recipient is a 7-year-old boy who received, 6 months after a desensitization protocol with monthly intravenous immunoglobulin infusion, a second kidney transplant in the presence of low donor-specific antibodies (DSAs). Both pretransplant lymphocytotoxic and flow cytometric crossmatch were negative. Allograft function recovered promptly, with excellent initial function. On postoperative day (POD) 4, the child developed significant proteinuria with an acute rise in serum creatinine. Allograft biopsy showed severe acute ABMR. Intravenous eculizumab (600 mg), preceded by a single session of plasmapheresis, was administered on POD 5 and 12 along with a 4-day thymoglobulin course. After the first dose of eculizumab, a strikingly rapid normalization of allograft function with a decrease in proteinuria occurred. However, because circulating DSA levels remained elevated, the child received 3 doses of intravenous immunoglobulin (POD 15, 16, and 17), with a significant subsequent decrease in DSA levels. At 9 months after transplant, the child continues to maintain excellent allograft function with undetectable circulating DSA levels. This unique case highlights the potential efficacy of using early eculizumab to rapidly reverse severe ABMR in pediatric transplantation, and therefore it suggests a novel therapeutic approach to treat acute ABMR.

Humoral sensitization to HLA antigens as a result of a previous transplant, pregnancy, or blood transfusions has emerged in recent years as one of the most challenging clinical problems in kidney transplantation. Approximately 30% of patients active in the United Network for Organ Sharing waiting list are sensitized.1–3 Pretransplant sensitization is indeed a major risk factor for acute antibody-mediated rejection (ABMR) after transplant, with an increased risk of allograft loss.1–4 Despite its recognition for >20 years as a defined clinicopathologic entity,4–7 treatment strategies for acute biopsy-proven ABMR are still not standardized. In general, therapeutic strategies have been based on the removal of antidonor alloantibodies (eg, by plasmapheresis or immunoadsorption sessions), associated with attempts to suppress antidonor humoral responses (eg, by using intravenous immunoglobulin [IVIg] or the anti-CD20 monoclonal antibody rituximab). Activation of the complement cascade in acute ABMR rejection has been identified as a major pathophysiological mechanism leading to allograft damage and dysfunction.1,2,8–10 As a consequence, it has been proposed that specific inhibition of the recipient’s complement system of limited duration may be useful to prevent acute ABMR.1,2 We hereby report the first case of successful upfront early
eculizumab administration to treat ABMR in a child after solid organ transplant.

CASE REPORT

A 7-year-old boy with end-stage kidney failure secondary to nephronophthisis received a deceased donor kidney transplant a year before, which was removed on postoperative day (POD) 2 because of allograft infarction. He was listed for a second kidney transplant. Ten circulating anti-HLA antibodies against major histocompatibility complex class I antigens with mean fluorescence index (MFI) levels between 2000 and 10 000 and 15 anti-HLA antibodies against major histocompatibility complex class II antigens (9 with MFI levels between 2000 and 10 000 and 6 with MFI levels >10 000) were determined by solid phase single-antigen-based testing Luminex assay.11

A desensitization protocol with monthly IVIg infusions (2 g/kg) had been initiated 6 months earlier, with a progressive decrease in the MFI levels of his circulating anti-HLA class I and II alloantibodies. A second deceased donor kidney transplant was performed on October 24, 2013 in the presence of very low levels of donor-specific antibodies (DSAs) (MFI levels were 100, 232, 523, and 1367, respectively, against mismatched donor antigens DR1, DQ6, DR13, and B62[15]). The second transplant shared 2 HLA antigens (DR13 and DQ6) with the patient’s previous transplant. Both pretransplant T- and B-cell flow cytometric crossmatch (FCXM) and antihuman globulin–enhanced complement-dependent cytotoxic crossmatch were negative. Basiliximab induction was used at a dose of 20 mg, before transplant and on POD 4. Initial maintenance immunosuppressive therapy consisted of tacrolimus (aiming for levels of 8–10 ng/mL), steroids (intravenous methylprednisolone 440 mg on day 0, followed by a progressive steroid taper to 5 mg/day per os on month 3), and mycophenolate mofetil (350 mg per os twice daily).

The initial clinical course was excellent, with a normalizing serum creatinine (62 µmol/L) over the first 48 hours. On POD 4, the child developed significant proteinuria (10 g per 24 hours) with an increase in serum creatinine to 110 µmol/L (Fig 1). Subsequently, he developed marked allograft dysfunction with oliguria, and his serum creatinine level increased to 160 µmol/L.

Allograft biopsy showed the presence of severe acute ABMR (Banff score t1-i0-ptc3-v1-cv0-g2-cg0-mm0-ci0-ct0-ah0-aah0-c4d2-pv0), with intense glomerulitis and capillaritis, intimal arteritis, acute tubular injury, and linear C4d staining in the peritubular capillaries, associated with a borderline cellular rejection. Abundant staining for C5b-9 deposits was also demonstrated by immunofluorescence in glomerular and peritubular capillaries (Fig 2). There were no immunoglobulin deposits by immunofluorescence.

In view of the biopsy findings and the severe allograft dysfunction, early administration of intravenous eculizumab (600 mg) preceded by a single session of plasmapheresis was selected, with the informed consent of the family. The potential risks of complement inhibition of short duration were explained to the parents. Antibiotic prophylaxis with penicillin G was administered. Four daily doses of thymoglobulin treatment (3 doses at 0.75 mg/kg and 1 dose at 1 mg/kg) were administered right after eculizumab therapy. The treatment response after the first dose of eculizumab was dramatic, and allograft function recovered within 24 to 48 hours (Fig 1). In view of this excellent treatment response, a second infusion of eculizumab (600 mg), preceded by a session of plasmapheresis, was given 7 days later on POD 12.

At the time of acute ABMR diagnosis, immunologic monitoring revealed a positive B- and T-cell FCXM because of an increase in the DSAs against the donor’s HLA B62(15), DR13, and DQ6, with MFI levels >2000 on the
In the days that followed, because of persistently detectable DSAs in serum, despite normal allograft function, the child received 3 doses of IVIg on POD 15, 16, and 17 (total dose of IVIg received: 2.2 g/kg), which were associated with a subsequent decrease in all DSA MFI levels (<500) by the Luminex assay. A second kidney allograft biopsy performed 2 months after transplant showed normal histologic features with complete resolution of the ABMR. No deposits of C4d or C5b-9 were present. After a follow-up of 9 months, the allograft function is excellent, with an inulin clearance of 75 mL/min×1.73 m² and normal serum creatinine levels of 50 to 65 µmol/L, without proteinuria, and the circulating DSA levels remain undetectable.

**DISCUSSION**

The case reported herein indicates that eculizumab administration, with its associated blockade of the terminal complement pathway, was associated with a striking improvement in allograft kidney function in a child with acute severe ABMR. Despite the great efficacy of eculizumab in neutralizing ABMR, as expected, eculizumab treatment did not have any impact on the circulating levels of DSA. A treatment with IVIg was later added to the overall antirejection therapy to reduce the DSA levels with a favorable eventual response, which was durable.

It is well known that the presence of preexisting anti-HLA DSA antibodies predicts acute ABMR. Moreover, Burns et al found that in acute ABMR with positive pretransplant B-cell FCXM, complement activation within the allograft, as indicated by C4d deposition in peritubular capillaries, was related to DSA levels. These data confirm that the main pathophysiological mechanism of acute ABMR occurring early after transplant is related to the presence of high levels of DSAs, which result in the local activation of the classic complement pathway.

Eculizumab has recently been used successfully by Stegall et al to prevent acute ABMR in high-risk recipients. They showed that the incidence of biopsy-proven acute ABMR in the first 3 months was 7.7% in eculizumab-treated group, compared with 41.2% in a control group. Interestingly, all patients with persistently high DSA values after...
transplant in the control group had ABMR, whereas only 2 patients (15%) in the eculizumab group with high DSA showed ABMR. As expected, eculizumab did not prevent activation of the complement classic pathway, as all allograft biopsies of patients with high posttransplant DSA showed the presence of C4d deposits in peritubular capillaries. Overall, these data highlight the critical role of terminal complement activation in the development of ABMR, possibly because of the production of various mediators such as C5a (a potent anaphylatoxin and chemoattractant) and of C5b-9 during the rejection process.

Eculizumab was also used by Locke et al as salvage treatment in severe and refractory ABMR not responding to plasmapheresis, anti-CD20 monoclonal antibody, and IVIg treatment. A limitation of this observation was that multiple therapeutic agents were given before or simultaneously with eculizumab treatment, making it difficult to draw solid conclusions about the efficacy of eculizumab in ABMR improvement. Additionally, plasmapheresis and eculizumab were successfully used to treat ABMR and thrombotic microangiopathy in an adolescent kidney transplant recipient with complement factor H deficiency. It should be noted that eculizumab has also been used successfully in children, including transplant recipients, to treat atypical hemolytic uremic syndrome.

In our case, complement levels of CH50, C3, C4, factor H, and factor I were normal, and no anti–factor H autoantibody was present. Genetic analysis of complement regulatory genes was also negative for mutations on complement factor H, factor I, MCP/CD46, and complement factor H–related protein 5 and for hybrid complement gene.

To our knowledge, this is the first case describing early successful eculizumab use to treat severe acute ABMR in a young solid organ transplant recipient. The observed renal function improvement within 24 to 48 hours indicated that complement blockade played the predominant role in rapidly reversing C4d- and C5b-9 positive ABMR. It should be noted that thymoglobulin administration may have partly contributed to the rejection reversal in our patient because the graft biopsy indicated a borderline cellular rejection associated with the ABMR. Moreover, anti-T cell therapy can also be beneficial in this setting by decreasing T help to the antidonor B cell response.

Regarding cost-effectiveness, it is known that to treat acute ABMR of a kidney allograft, several sessions of plasmapheresis (5–10 sessions) are generally needed. In addition, plasmapheresis can be cumbersome, and it can be associated with several complications. The use of a short course of eculizumab (eg, only 2 doses of 600 mg each) could be considered cost-effective for the treatment of this type of early severe ABMR, particularly if eculizumab administration can rapidly reverse the rejection episode and thus avoid acute dialysis or even potential allograft loss with return to chronic dialysis. However, the precise cost-effectiveness of such short-duration eculizumab treatment in kidney transplants should be determined in future studies. In conclusion, we suggest that in the setting of early acute and severe ABMR, the prompt and upfront administration of eculizumab has the potential to rapidly reverse the ongoing pathophysiological process of ABMR. This may obviate alloantibody removal by plasmapheresis or immunoadsorption, but this response should be confirmed prospectively in a series of recipients with ABMR, with appropriate controls, to unequivocally demonstrate the efficacy of eculizumab. Finally, our observation of a rapid ABMR treatment response with eculizumab may be relevant for ABMR in other solid organ transplant recipients, was as recently reported in lung transplants.

FIGURE 3
Trends in donor-specific anti-HLA class I and II antibody (DSA) levels. The time relative to transplant operation is represented on the x-axis. The MFI level of DSA was determined by using Luminex solid phase single antigen assays and is represented on the y-axis.

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