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LETTER TO THE EDITORS

Living-donor kidney transplantation for atypical haemolytic uremic syndrome with pre-emptive eculizumab use

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Dear Sirs,

Atypical haemolytic uremic syndrome (aHUS) is an ultra-rare disease with a poor long-term prognosis and high recurrence after kidney transplantation (KT). Among others, a mutation in the complement regulatory protein complement factor H (CFH) is associated with the highest recurrence rate ranging between 70% and 85% [1]. Eculizumab, a monoclonal antibody that inhibits cleavage of complement protein C5 and subsequent membrane attack complex formation, has been proofed to be effective in the prevention or treatment of recurrent aHUS after kidney transplantation from a deceased donor [2,3]. Living-donor kidney transplantation (LDKT) has not been recommended so far. We herein report a case of successful LDKT from the unrelated donor after eculizumab pretransplant therapy in patient with end-stage renal failure due to factor H mutation and ongoing aHUS overactivity, with just partial responsiveness to plasma therapy.

A 43-year-old man presented with clinical features of aHUS, confirmed by biopsy and genetic analysis (heterozygous mutation in the SCR8 region of CFH - C1352G, Ser451Stop) progressed to end-stage kidney disease and became dialysis-dependent despite 34 plasma exchanges and supportive therapy. The exacerbations manifested frequently by haemolysis, resistant malignant hypertension and encephalopathy.

Living-donor kidney transplantation from his wife was planned under eculizumab-driven control of aHUS activity. Before eculizumab treatment, the patient was immunized against meningococcal infection. Eculizumab

treatment was initiated after 26 months of haemodialysis, 2 months before scheduled surgery (900 mg initial dose, 900 mg weekly for 4 weeks and 1200 mg every 2 weeks thereafter), at the time of the last recurrence of disease activity. Eculizumab therapy was associated with a marked improvement in the patient's mental status (cessation of cephalea, confusion) and improved blood pressure (BP) control.

There was no human leucocyte antigen (HLA) match, the panel reactive antibodies (PRA) were 46%, and no donor-specific antibodies (DSAs) were detected at transplantation. Hand-assisted retroperitoneoscopic live-donor nephrectomy and subsequent kidney transplantation were uneventful.

On the day of surgery, 1200 mg of eculizumab was given before reperfusion, followed by 900 mg eculizumab 24 h post-transplant. Immunosuppression consisted of basiliximab induction, tacrolimus, mycophenolate sodium and prednisone. Cotrimoxazole and valganciclovir were administered in appropriate doses for infection prophylaxis.

The kidney graft had immediate function, and the patient's serum creatinine levels rapidly fell from 10.6 to 1.9 mg/dl on the fourth postoperative day (POD). On POD 5, graft biopsy was performed that showed borderline changes (Banff 07 classification) with no signs of thrombotic microangiopathy nor C4d deposition. Methylprednisolone (1.5 g) was administered with the effect on creatinine level.

At POD 14, creatinine decreased to 1.4 mg /dl. The patient's serum lactate dehydrogenase levels increased to 5.7 μkat/l, and schistocytes appeared in peripheral blood samples. Systemic hypertension (an increase in the mean BP by 30 mmHg and BP repeatedly exceeded 160/100 mmHg) returned, despite stable graft function. Tacrolimus trough level was 11ug/l. Peripheral blood samples were obtained to assess eculizumab levels and efficacy. The eculizumab serum concentration was 293 μg/ml (reference range: >99 μg/l), that is sufficient to block C5 in case of non-transplant setting. Anti-eculizumab antibodies were not detected. It was considered that aHUS activity may be exacerbated, and repeated induction doses of eculizumab were administered (900 mg weekly for 4 weeks, then 1200 mg every 2 weeks) (Fig. 1).

Serum creatinine was 1.6 mg/dl at 3 months, and protocol biopsy revealed polyoma BK virus nephropathy (BKVN). Polyoma BK virus (BKV) load was 8.01×10^3 copies per ml. There were neither C4d deposition nor signs of thrombotic microangiopathy in the biopsy. Therefore, tacrolimus (trough levels 9.9 ± 2.4 μg/l) was replaced by cyclosporine, and the mycophenolate sodium reduced from 720 to 360 mg twice daily along with ciprofloxacin administration.

BK viremia (2.7×10^4 copies per ml) and creatinine (2.1 mg/dl) increased in the next 2 weeks; another graft biopsy was performed and confirmed BKVN without rejection. Therefore, immunosuppression was further reduced (mycophenolate sodium was eliminated and reduced doses of cyclosporine were administered) and cidofovir treatment (25 mg) commenced. After 4 days of this protocol, graft failure manifested with urea 103 mg/dl and creatinine 7.3 mg/dl with graft enlargement. Immunosuppression was reintroduced and antirejection therapy with 2 g of intravenous methylprednisolone initiated. Within 7 days, serum creatinine levels decreased to 2.2 mg/dl. In total, five doses (5×25 mg) cidofovir was given 2 weeks, and creatinine decreased further to 1.8 mg/dl at the end of cidofovir therapy.

Six months post-LDKT, the patient's BKV DNA viremia was below the detection limit, the serum creatinine level was 1.9 mg/dl, and analysis of the urinary sediment was completely negative. The patient is free of aHUS activity 18 months post-LDKT, plasma creatinine level remains stable at 1.7 mg/dl and has normal platelet counts; there is no evidence of haemolysis, and blood pressure is maintained ≤135/80 mmHg.

The eculizumab pretreatment in LDKT in aHUS patients appears to be clearly advantageous as complement activation during ischaemia-reperfusion injury, and early post-transplant is efficiently controlled [4]. However, several points need to be addressed. In our case, 14 days after transplantation, increased complement activation was noted, as indicated by the presence of serum haemolytic markers. As the target trough levels of eculizumab based on pharmacodynamics-pharmacokinetic correlations were set in aHUS involving native kidneys, conventional eculizumab doses might not be sufficient in early post-transplant course. For safety reasons, higher eculizumab doses were reintroduced. Similar observations have not been described in the recent literature. Therefore, we advise caution in similar cases in the future. Despite the use of a standard immunosuppression protocol, polyoma BKV replication and nephropathy were observed at 3 months. Cidofovir therapy and immunosuppression reduction allowed the patient's immune system to eliminate the BKV despite maintenance therapy with eculizumab. Therefore, the role of complement in the CD8(+) T-cell antiviral response seems to be less important, as previously suggested [5].

Moreover, steroid-sensitive acute rejection, which presented as graft failure, occurred after 4 days of reduced immunosuppression due to persistent polyoma BKVN, despite therapeutic levels of eculizumab. As eculizumab inhibits activation of the complement membrane attack complex, the observed graft failure could not be associated with complement activation. To conclude, pre-emptive eculizumab therapy allows aHUS remission before kidney

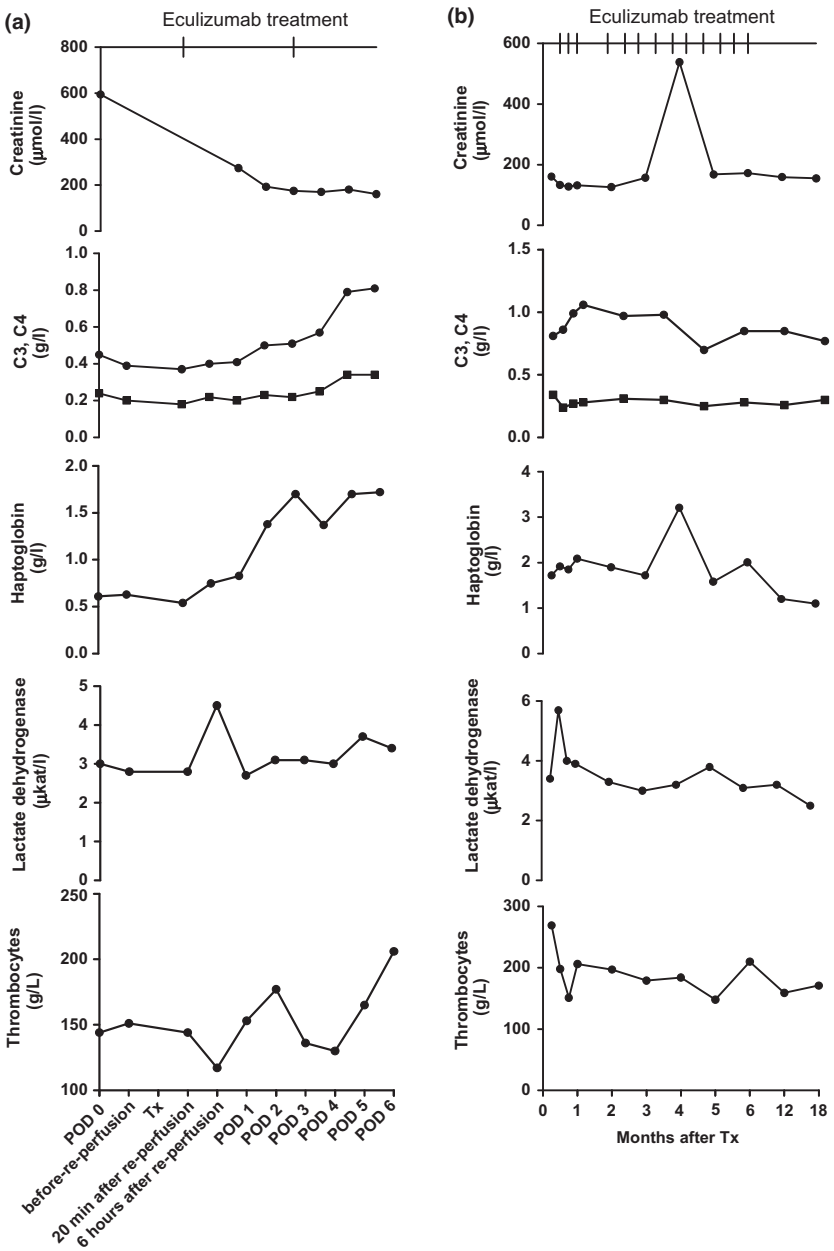

Figure 1 (a) Time course of laboratory parameters on the day of transplantation and consecutive days in a patient with aHUS. In the peri-operative period, 1200 mg of eculizumab was given before reperfusion on the day of surgery, followed by a dose of 900 mg 24 h post-transplantation. POD, postoperative day. Vertical lines on the top of the figure represent single doses of eculizumab. (b) Renal function and haemolytic markers during a 18-month follow-up period. As it was considered that aHUS activity was exacerbated, repeated induction doses of eculizumab were given 2 weeks after the transplant instead of the planned maintenance therapy. Weekly doses of 900 mg eculizumab were administered for 4 weeks. Thereafter, a maintenance therapy of 1200 mg every 2 weeks was commenced. Vertical lines on the top of the figure represent single doses of eculizumab. After 6 months, anti-C5 every 2 weeks is administered.

transplantation. However, transient clinical features of aHUS of unclear significance may occur post-transplantation. Based on our experience, we recommend the immunosuppression reduction in eculizumab-treated patients with caution.

Authorship

AP: data analysis, writing the paper. JF: contribution by important suggestions. OV: involved in the writing of the paper, data analysis.

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