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BRIEF COMMUNICATION

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# Upfront use of eculizumab to treat early acute antibody-mediated rejection after kidney allotransplantation and relevance for xenotransplantation

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## Abstract

Acute antibody-mediated rejection (AMR) early after transplant remains a challenge, both in allotransplantation and in xenotransplantation. We report the case of an early and severe acute AMR episode in a kidney transplant recipient that was successfully treated with upfront eculizumab. A 58-year-old woman had been on dialysis since 2014. She underwent a first kidney transplant in 2018 with primary non-function and received several blood transfusions. Postoperatively, she developed anti-HLA antibodies. One year later, she received a second allograft from a deceased donor. At day 0, there was only one preformed low-level donor-specific antibody (DSA) anti-DQ7. After initial excellent allograft function, serum creatinine increased on days 7-9, and this was associated with oligo-anuria. On day 7, there was an increase in her DSA anti-DQ7 and 4 de novo DSA had developed at high MFI values. Allograft biopsy showed severe active AMR with diffuse C4d deposits in peritubular capillaries. The early acute AMR episode was treated with upfront eculizumab administration (2 doses) with efficient CH50 blockade (< 10% CH50). Rituximab was also administered on day 12, and intravenous immunoglobulin (IVIG) was given over the following days. There was an excellent clinical response to eculizumab administration. Eculizumab administration rapidly reversed the acute AMR episode without the need for plasmapheresis. Rituximab and IVIG were also used as B-cell immunomodulators to decrease DSA. Blocking efficiently the terminal complement pathway may become a useful strategy to treat acute AMR in sensitized recipients of allografts, and possibly in recipients of discordant xenografts.

KEYWORDS

antibody-mediated rejection, eculizumab, kidney allotransplantation, xenotransplantation

**Abbreviations:** AMR, antibody-mediated rejection; ARDS, acute respiratory distress syndrome; BMI, body mass index; DSA, donor-specific antibodies; HLA, human leukocyte antigen; IVIG, intravenous immunoglobulins; SOC, standard of care.

## 1 | INTRODUCTION

Similar to the early acute humoral rejections occurring in discordant xenotransplantation (eg, due to anti-pig antibodies in monkey recipients), early acute antibody-mediated rejection (AMR) in highly sensitized recipients after kidney allotransplantation currently remains an important immunological and therapeutic challenge.[1,2] Complement activation and its associated tissue injury plays an important pathogenic role in most early (less than 30 days post-transplant) acute AMR episodes, and therefore, complement inhibition may be beneficial in that setting.[2] Eculizumab is a humanized monoclonal antibody that binds to the human C5 complement protein, resulting in terminal complement blockade. Recently, the safety and efficacy of eculizumab to prevent early acute AMR has been studied prospectively in sensitized deceased-donor and living-donor kidney allotransplant recipients, suggesting a potential benefit for eculizumab, which was overall well tolerated.[3-5] However, little is known about the upfront use of eculizumab to treat early and severe acute AMR in allotransplantation, because most reports to date using eculizumab in that setting (mainly as "rescue therapy") have also included other treatments to remove circulating donor-specific alloantibodies (DSA), such as plasmapheresis[6] or immunoadsorption and/or administration of intravenous immunoglobulins (IVIG).[2,6-11] As a result, the precise contribution of upfront complement inhibition to treat early acute AMR has remained difficult to assess. Interestingly, in a recent retrospective analysis from the Mayo Clinic, 15 kidney allotransplant recipients were identified with early acute AMR within the first 30 days post-transplant, all having an abrupt increase in donor-specific antibodies (DSA) with rapid allograft dysfunction. Prompt eculizumab treatment, together with plasmapheresis in most cases, was found safe and effective for this type of early acute and active AMR, indicating that targeting C5 with immediate blockade of the terminal pathway of complement may be useful to prevent graft loss.[12]

Here, we describe the case of an early acute AMR episode in a sensitized kidney transplant recipient who was successfully treated with upfront eculizumab, without the need of plasmapheresis or extracorporeal antibody removal. We suggest that upfront eculizumab to block the terminal complement pathway may become a useful strategy to treat acute AMR in sensitized recipients of kidney allografts, and possibly of discordant kidney xenografts in the near future.

## 2 | CASE REPORT

The patient is a 58-year-old obese woman (BMI 32 kg/m$^2$) who suffered from terminal kidney failure due to reflux nephropathy and was on dialysis since 2014. She underwent a first kidney transplant that had to be explanted on the day of transplant because of arterial complications with thrombosis. She received several blood transfusions, and postoperatively, she developed anti-HLA antibodies (class I and class II). One year later, she received a second kidney allograft from a deceased donor. At day 0, there was only one preformed donor-specific antibody (DSA) anti-DQ7 with an MFI value of 1316 (ie, a low-level DSA at transplant) and a negative cytotoxic crossmatch (T&B). Induction immunosuppression with thymoglobulin had to be discontinued after the first dose (1 mg/kg) because of an acute respiratory distress syndrome (ARDS). Basiliximab induction therapy was thus administered (two doses). After initial excellent kidney allograft function, her serum creatinine increased rapidly on days 7-9, and this was associated with oligo-anuria (Figure 1). Repeated anti-HLA antibody measurements on day 7 revealed a significant increase in her anti-DQ7 DSA and 4 "de novo" DSA (present below 1000 MFI pre-transplantation). DSA were now present at high MFI values: DSA class I: anti-A33 (10922 MFI), anti-A11 (4808 MFI); DSA class II: anti-DR11 (20508 MFI), anti-DQ7 (18847 MFI), anti-DP2 (17698 MFI). Allograft biopsy showed active AMR with glomerulitis,

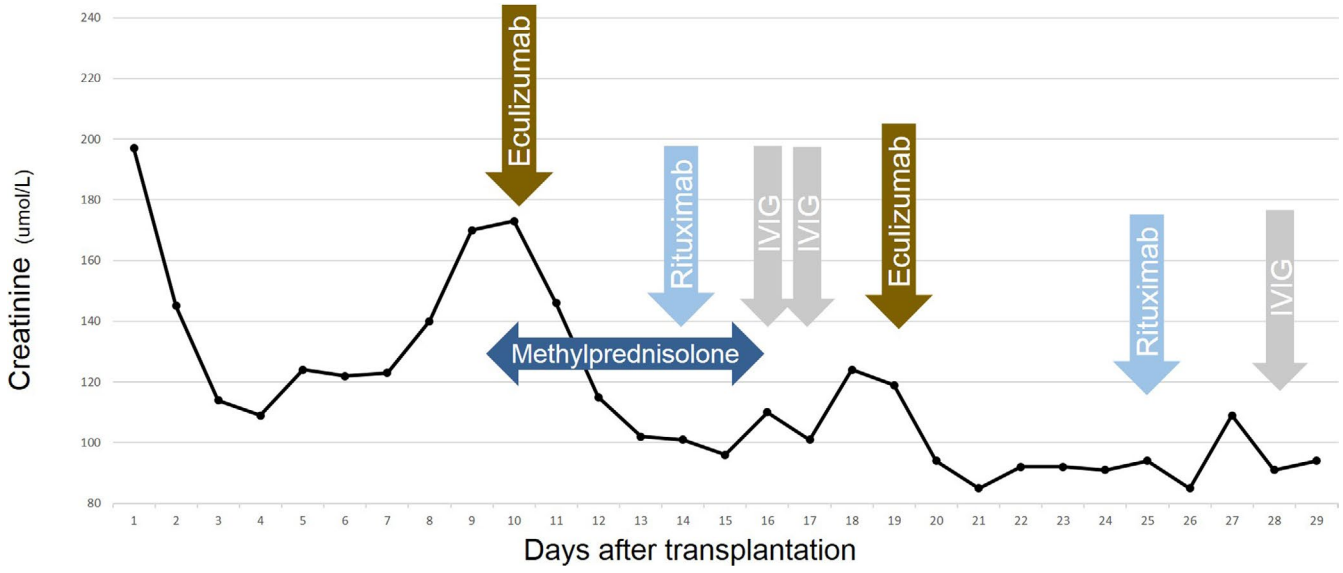


**FIGURE 1** Treatment of early acute antibody-mediated rejection

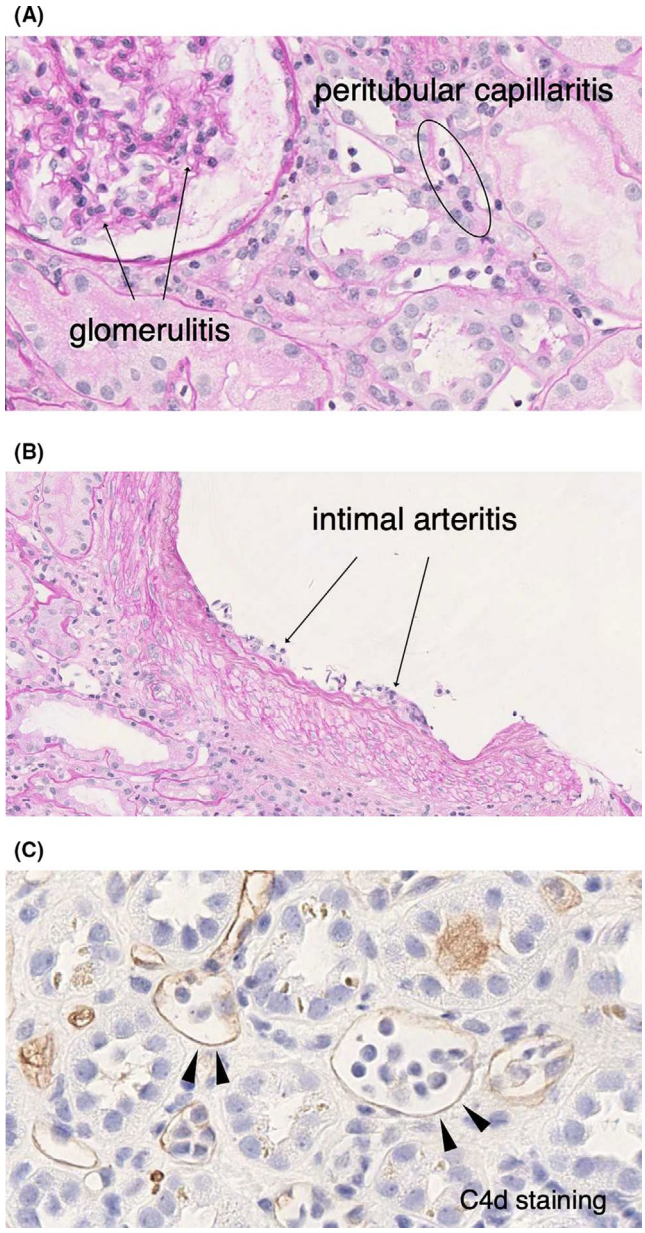


**FIGURE 2** Allograft biopsy showing active AMR with glomerulitis, peritubular capillaritis, and diffuse complement C4d deposits in peritubular capillaries. Banff score: t1-i0-ti0-ptc3-v2-cv0-g1-cg0-mm1-ci1-ct1-ah1-aah0-C4d3-pv0-iIFTA1

peritubular capillaritis, and diffuse C4d deposits in peritubular capillaries, without T-cell infiltrate (Figure 2). Banff score was t1-i0-ti0-ptc3-v2-cv0-g1-cg0-mm1-ci1-ct1-ah1-aah0-C4d3-pv0-iIFTA1. The severe acute AMR episode was treated with upfront eculizumab (900 mg iv) and daily methylprednisolone boluses. A second dose of eculizumab was repeated 8 days later (900 mg iv), with an excellent CH50 blockade (<10% CH50). Rituximab (375 mg/m$^2$) was also administered on day 12, and IVIG (total dose 2 g/Kg) was given over the following days. There was a striking immediate clinical response to eculizumab administration, as her urine output and kidney function improved rapidly. No plasmapheresis was used, and no anti–T-cell depletion agents were administered. Follow-up anti-HLA

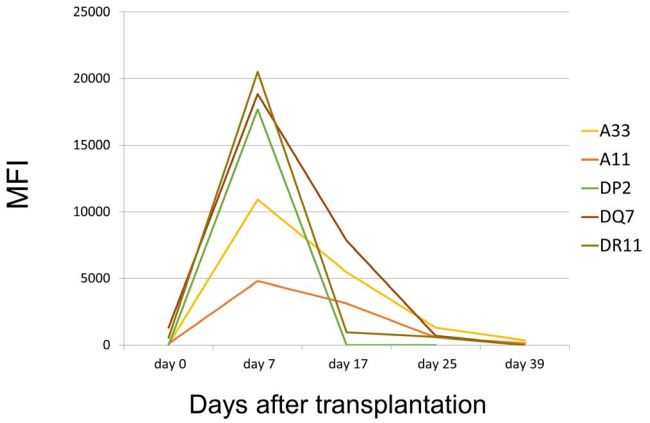


**FIGURE 3** DSA time course and MFI values after kidney transplantation

measurements showed progressive lowering of DSA MFI values over 2-3 weeks (Figure 3), and eculizumab was thus discontinued after 2 doses. Complement function was inhibited with the CH50 suppressed to <10% during a total of 20 days. Kidney function recovered to baseline with the eGFR estimated by CKD-EPI at 52 mL/min, and it was at 55 mL/min 3 months after kidney transplantation. Currently, 9 months after transplantation, the allograft function continues to be good, with serum creatinine levels of 100-120 μmol/L without proteinuria. All circulating DSA remain undetectable.

## 3 | DISCUSSION

In xenotransplantation, the key role of complement in mediating tissue injury, for example, in pig to primate hyperacute or acute humoral rejection (acute AMR), has been known for many years, and various approaches to help protecting recipients against the complement cascade have been progressively developed to improve results.[1] Similarly, early acute and active AMR after kidney allotransplantation in humans is a rare but potentially dramatic complication, if not rapidly diagnosed and adequately treated.[2] Diagnosis is based on clinical and pathological features that are characterized by rapid allograft dysfunction, histologic evidence of active tissue injury with microvascular inflammation, evidence of antibody interaction with vascular endothelium, C4d deposition in peritubular capillaries, and the presence of circulating donor-specific anti-HLA alloantibodies (DSA), that is, serologic evidence of DSA.[2] Early acute AMR after desensitization or in previously sensitized patients is caused by an anamnestic memory B-cell activation and is complement-dependent in most cases.[8] Acute AMR typically occurs early after transplantation (less than 30 days) with an overall incidence of 1-10% in kidney allotransplantation, and is generally related to preformed DSA or previous exposure to HLA antigens. Late acute AMR, associated de novo DSA, can also occur in non-adherent patients, or in cases of excessive intentional immunosuppression lowering. Importantly, in highly sensitized recipients with preformed circulating DSA, acute AMR can occur in

up to 30%-50% of cases.[13] Its rapid diagnosis is crucial in order to initiate immediately adequate treatment as acute AMR carries a high risk of early allograft loss, or of long-term allograft dysfunction due to chronic allograft rejection.

Up to now, treatment strategies for acute AMR in kidney allotransplantation have been based on antibody removal (using plasmapheresis or immunoadsorption) and administration of high-dose IVIG and T-cell–depleting agents.[2,7,9,14] In most centers, plasmapheresis (or immunoadsorption) with high-dose IVIG administration has become the standard of care to treat acute AMR.[14] These therapeutic approaches aim to remove and suppress the production of anti-HLA antibodies; however, their use is not based on best evidence derived from randomized clinical trials. Despite these limitations, due in part to the low incidence of acute AMR, plasmapheresis has remained a common treatment for acute AMR in many centers worldwide. High-dose IVIG are also often used for their various immunomodulatory effects on T and B cells and on complement activation, and are used both for desensitization and treatment of acute AMR.[14,15] B-cell depletion (anti-CD20 rituximab) is also often used in the treatment of acute AMR, even though clinical trials showed conflicting results.[2] At last, "rescue splenectomy" has also been described as salvage therapy in very rare cases.[16] Overall, despite this recent progress, it is important to emphasize that good quality evidence is still lacking to guide and optimize clinical practice for the treatment options of acute AMR in kidney allotransplantation.[14] The same is true in the rapidly evolving research field of discordant xenotransplantation, particularly in the pre-clinical pig kidney xenotransplant models, which are currently under investigation; that is, more data are needed to efficiently prevent and treat acute AMR, even if the nature and characteristics of the anti-graft antibodies may be different.

Interestingly, complement blockade has recently emerged as an interesting therapeutic option for acute AMR in kidney allotransplantation.[17] Eculizumab is a humanized monoclonal antibody that binds to the human C5 complement protein, resulting in terminal pathway complement inhibition and blockade of C5a, a crucial anaphylatoxin that promotes neutrophil attraction and acute inflammation. Based on its mechanisms and data in pre-sensitized animal models,[18] the first documented clinical episode of acute AMR treated by eculizumab was reported by Locke et al in 2009.[6] Since then, various case reports have been published in patients on "salvage" or "rescue" treatments for acute AMR.[11,14] However, there are only rare cases where acute AMR was treated without plasmapheresis. We have previously reported favorable outcomes with eculizumab in the treatment of early acute AMR in lung and pediatric kidney allotransplantation, but only in one case (a lung transplant recipient) without plasmapheresis.[11,19] Overall, a more selective and consistent treatment strategy of early acute AMR is needed, given the potential adverse events related to plasmapheresis or immunoadsorption (eg, infectious complications, line placements, costs), which can also be cumbersome and associated with significant morbidity.

Until now, most reports on complement inhibition in acute AMR had focused on preventive protocols in highly sensitized recipients, with strategies that combined thymoglobulin induction and plasmapheresis (or immunoadsorption), intravenous IVIG, or rituximab. In particular, much was initially learned from the series of Stegall et al in 2011[3] where 26 highly sensitized patients with positive crossmatches (by flow cytometry) were transplanted with an eculizumab-based induction protocol. Compared with a historical control group, they found that the incidence of acute AMR was reduced in the eculizumab group (7.7% vs 41.2%).[3,12,20] All patient had thymoglobulin induction, and the majority of patients (69%) had pre-transplant plasmapheresis. Interestingly, only 12% of patients needed post-transplant plasmapheresis in the eculizumab group, compared with 76% in controls. These important initial findings were the basis for two recent clinical trials, both reported in 2019, on eculizumab-based induction to prevent early acute AMR in highly sensitized patients with preformed DSA.[4,5] In the single-arm study of Glotz et al,[5] 80 patients transplanted with C5 blockade during the first 9 weeks were compared with pooled analysis of acute AMR data derived from published data and similar results to the Stegall et al series[4] were found (an 8.8% incidence of acute AMR, that is, lower than the 40% expected rate for standard care (SOC) in such high immunological risk recipients). No plasmapheresis or IVIG was used in the eculizumab group, and both groups had thymoglobulin induction. The only randomized controlled trial on eculizumab induction to prevent acute AMR in highly sensitized living-donor kidney recipients was conducted by Marks et al[4] In a phase 2 study, a total of 102 patients were randomized to SOC versus eculizumab. The treatment failure rate was 9.8% (eculizumab) and 13.7% (SOC group) in the first 9 weeks post-transplant. Even though this difference was not statistically significant, post hoc analysis revealed significant difference in treatment failure (eculizumab 11.8% and SOC 29.4%, $P = .048$) when grade I acute AMR was taken into account and if diagnosis was based on clinical and pathological criteria. Thus, C5 and terminal complement inhibition with eculizumab appears to provide an interesting clinical strategy in recipients at high immunological risk of developing early acute AMR post-transplant in kidney allotransplantation.

In summary, we report here the first detailed description of successful plasmapheresis-free treatment with upfront eculizumab in a kidney transplant recipient to treat severe early acute AMR. This case adds more experience on the safe and efficient use of C5 and terminal pathway complement blockade in early acute AMR in kidney allotransplantation. In view of the recent reports on eculizumab in the prevention or treatment of early acute AMR in kidney transplantation, we suggest that a properly controlled prospective clinical trial, for example, comparing upfront eculizumab to plasmapheresis, should be conducted to determine the optimal treatment of early acute AMR in kidney allotransplantation. Finally, the accumulating recent experience on the prevention and treatment with eculizumab of acute AMR in kidney allotransplantation may also be very relevant to the field of discordant xenotransplantation, particularly if clinical attempts of discordant solid organ xenotransplantation in human patients are planned in the near future.

## CONFLICT OF INTEREST

None.

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