

# The use of eculizumab as a bridge to retransplantation for chronic antibody-mediated rejection in a heart transplant recipient: a case report

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## Background

Antibody-mediated rejection (AMR) remains a major management challenge in heart transplantation given the complexity of pathological diagnosis and dearth of evidence for effective management. Eculizumab, an anti-C5 monoclonal antibody which inhibits terminal complement activation, has been reported to decrease early AMR in sensitized renal transplant recipients.

## Case summary

We report a case of a 29-year-old gentleman with chronic AMR 8 years after heart transplantation, manifesting as significant graft dysfunction. Donor-specific antibodies to DQ7 were found to be causative. Antibody-mediated rejection was managed with quadruple oral immunosuppressive therapy (mycophenolate, prednisolone, everolimus, and tacrolimus) as well as a sequence of broad-spectrum immunological therapies; intravenous (IV) methylprednisolone, plasmapheresis, IV immunoglobulin, rituximab, bortezomib, tocilizumab, and splenic irradiation. No treatment had a sustained impact on donor-specific anti-HLA antibodies (DSAs) or graft function. After testing showed the DQ7 antibodies were complement-binding, a trial of eculizumab was started. This improved DSAs somewhat, and improved graft function and New York Heart Association functional class substantially. The patient was relisted for heart transplantation and successfully retransplanted in March 2018. Specifically, the new organ and recipient were matched at DQ7. After discontinuation of eculizumab, the patient has remained healthy and well, with normal graft function 28 months after retransplantation.

## Discussion

To the best of our knowledge, this is the first case of chronic AMR in a heart transplant patient, successfully stabilized with eculizumab and bridged to retransplantation.

## Keywords

Cardiac transplantation • Antibody-mediated rejection • Immunomodulation • Case report

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## Learning points

- Antibody-mediated rejection (AMR) in cardiac transplantation is difficult to diagnose.
- Treatments for AMR are broad spectrum in approach.
- Clinical response guides therapy better than donor-specific antibodies.

## Introduction

Antibody-mediated rejection (AMR) remains a major management challenge in heart transplantation given the complexity of pathological diagnosis and dearth of evidence for effective management strategies. Eculizumab, an anti-C5 monoclonal antibody which inhibits terminal complement activation, has been reported to decrease early AMR in sensitized renal transplant recipients<sup>1</sup> although it failed to prevent chronic AMR in renal transplant recipients with persistently high levels of donor-specific anti-HLA antibodies (DSAs).<sup>2</sup>

## Timeline

November 2009	Left ventricular assist device as bridge to transplantation for dilated cardiomyopathy
October 2010	Orthotopic heart transplantation
October 2011	First episode late cellular rejection, treated with intravenous (IV) methylprednisolone
December 2011	Second episode cellular rejection, treated with PO prednisolone pulse
January 2012	Third episode cellular rejection, treated with PO prednisolone pulse
May 2013	First episode antibody-mediated rejection (AMR), presenting with graft dysfunction and AV block, treated with apheresis, IV immunoglobulin (IVIG), IV methylprednisolone, and bortezomib
December 2016	Second episode AMR, treated with apheresis, IVIG, IV methylprednisolone, and rituximab
May 2017	Third episode AMR, treated with apheresis, IVIG, splenic irradiation, and rituximab
August 2017	Fourth presentation with AMR, treated with apheresis, IVIG, and tocilizumab without clinical improvement, followed by second round of apheresis and IVIG with initiation of eculizumab
November 2017	Listed for re-do heart transplantation
March 2018	Retransplanted, with specific matching at DQ7, concomitant thymectomy
April 2018–July 2020	Normal graft function, no episodes of rejection

## Case presentation

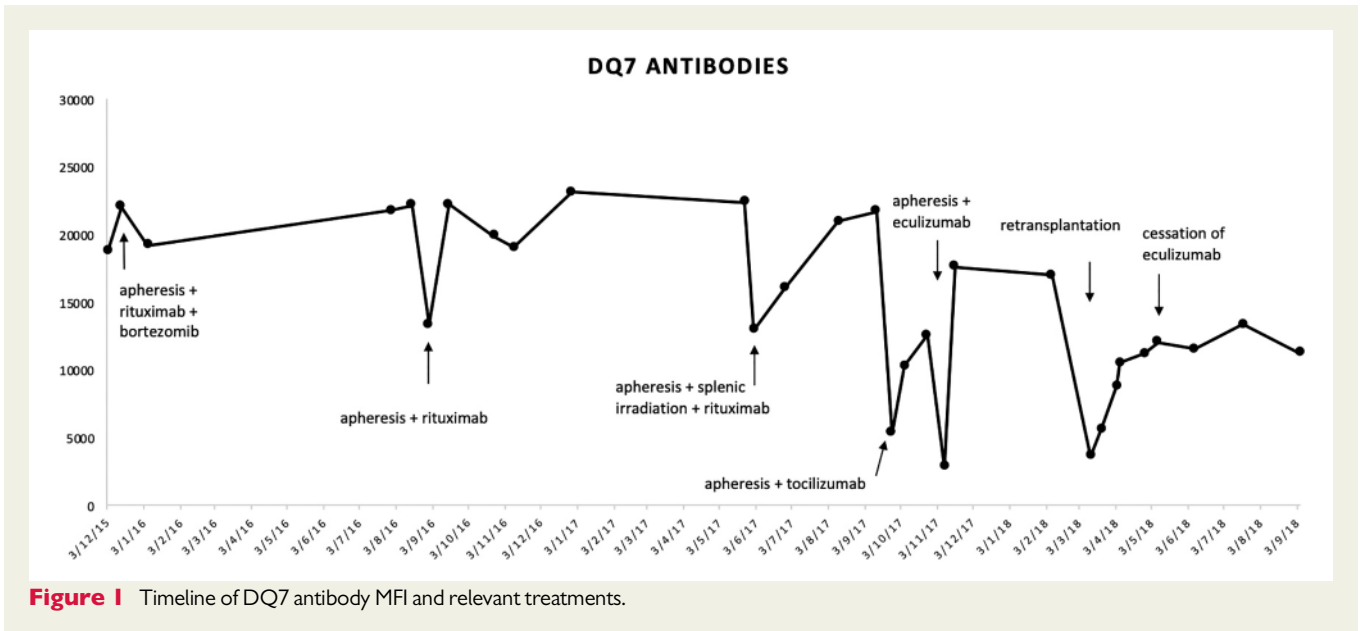
We report a case of a 29-year-old male, who underwent heart transplantation for dilated cardiomyopathy, bridged to transplant with left ventricular assist device (LVAD) and transplanted semi-urgently due to LVAD-related sepsis. At the time of transplantation, T-cell crossmatch was negative, but B-cell crossmatch was weakly positive. Low titre human leukocyte antigen (HLA) antibodies were detected including DQ7 (MFI 628). Induction immunosuppression included basiliximab at Day 0 and Day 4 and three doses of 125 mg intravenous (IV) methylprednisolone. This was followed by 1 mg/kg per day oral prednisolone in divided doses weaning by 5 mg/day. Additionally, the patient received cyclosporin and mycophenolate from Day 1 post-transplant.

His post-transplant course was complicated by presentation with recurrent exertional dyspnoea, with clinical findings consistent with

heart failure. This was diagnosed as multiple episodes of acute cellular and humoral rejection with graft dysfunction. Graft dysfunction with severely impaired left ventricular systolic function (estimated ejection fraction 30–35%) was first noted in at 2.5 years post-transplant, with concomitant moderate right ventricular dysfunction. Three episodes of acute cellular rejection (Grade 3A/2R) requiring treatment occurred, starting at 12 months post-transplant, and four episodes of AMR (pAMR Grade 2) started at 2.5 years post-transplant. Multiple Classes I and II DSAs were detected, including to complement-binding DQ7 with mean fluorescence intensity (MFI) when first measured 2.5 years after transplantation. Maintenance therapy was quadruple oral immunosuppressive therapy (mycophenolate, prednisolone, everolimus, and tacrolimus) from 12 months onwards. Treatment for

AMR included multiple cycles of methylprednisolone, plasmapheresis, and IV immunoglobulin (IVIG), with adjuvant rituximab (375 mg/m<sup>2</sup> via IV infusion), bortezomib (3 mg subcutaneously), splenic irradiation (350 Gy in twice weekly 50 Gy fractions) in combination with further rituximab and tocilizumab (800 mg via IV infusion monthly) in order of escalation, none of which produced a sustained response. *Figure 1* details the timeline and treatment course. There was persistent moderate left ventricular systolic dysfunction (ejection fraction 35–40%), elevated filling pressures, and cardiac index of 2.0 L/min/m<sup>2</sup> coinciding with functional class (FC) III–IV heart failure symptoms. Coronary angiography was performed at 5 and 6 years after transplantation, showed allograft vasculopathy with a chronically occluded right coronary artery and minor irregularities of the left coronary system, not amenable to revascularization.

Donor-specific anti-HLA antibodies to DQ7 were persistently elevated with strongly positive C1q testing. It was decided to treat with



**Figure 1** Timeline of DQ7 antibody MFI and relevant treatments.

a loading regimen of eculizumab (1200 mg on Day 1, 900 mg on Day 2, and 900 mg on Weeks 2, 3, and 4), after five further plasma exchanges, and fortnightly 1200 mg eculizumab thereafter. Given the extensive immunosuppression regimen, prophylaxis with itraconazole, valganciclovir, and amoxicillin was used for fungal, cytomegalovirus, and encapsulated bacteria prophylaxis, respectively. Prophylactic treatment was effective in protecting against infection, and this patient suffered no infective complications of the aggressive immunosuppressive strategy undertaken.

After initiation of eculizumab, ejection fraction improved to 45% and heart failure symptoms reduced to FC II. The MFI for DQ7 initially dropped to <10 000 but slowly trended upward. Despite this, he experienced the first sustained improvement in heart failure symptoms and graft function in over 3 years. However, persistent diastolic dysfunction and restrictive physiology were noted at echocardiography.

The decision for relisting was taken after clinical stabilization. Given that ongoing diastolic dysfunction and restrictive physiology led to ongoing New York Heart Association functional Class II symptoms and advanced coronary allograft vasculopathy, felt unlikely to respond to immunosuppressive therapy, as well as his young age and potential infective implications of long-term eculizumab, the patient was relisted for transplantation, and successfully transplanted 8 years following initial transplantation and 5 months after commencing eculizumab. Concomitant thymectomy was performed at retransplantation. Both T and B cell crossmatch were negative, but he had persistent strong DSAs. Notably, the recipient and organ were matched at DQ7.

He underwent pre-emptive plasmapheresis at the time of transplantation and maintained on fortnightly 1200 mg eculizumab empirically for 3 months post-retransplantation, as well as usual post-transplant quadruple immunosuppressive regimen including prednisolone, tacrolimus, mycophenolate, and everolimus. Now, almost 3 years after transplant, there have not been any episodes of rejection

and graft function is normal. As part of routine protocol, we continued to monitor DSAs following the second allograft transplant coinciding with endomyocardial biopsy. We surveilled DSAs up to 1 year after transplantation, at weekly for the first month and then fortnightly from months 2–3, monthly at months 4–6, and then at 9 and 12 months. Because DQ7 testing is part of routine Luminex monitoring after transplant, continued monitoring has been performed but given matched transplant, weight has not been placed on these results.

Explanted heart showed accelerated coronary and intramyocardial vasculopathy, leading to diffuse multifocal ischaemic cardiomyopathy with subsequent myopathic features.

## Discussion

This is the first report of utilization of eculizumab for chronic AMR as bridge to retransplantation in a heart transplant patient.

Antibody-mediated rejection is both a diagnostic and management challenge in heart transplantation. Commonly, patients present with graft dysfunction, elevated DSAs, accelerated coronary artery vasculopathy, and endomyocardial biopsies showing an absence of severe cellular rejection.<sup>3</sup> Management strategies are based on aggressive immunosuppression with IVIG, plasmapheresis, and high-dose corticosteroids, as well as second-line therapy including rituximab and bortezomib. Tocilizumab, an anti-interleukin-6 receptor antibody, has been shown to reduce complement components C3 and C4, and may have some utility in AMR. Eculizumab, specifically binding to terminal complement C5, acting at a late stage in the complement cascade and preserving the proximal components of the complement system.

Targeting of complement-binding antibodies was key to managing AMR in this patient. This guided the use of eculizumab which targets complement despite elevated DQ7 levels as the case highlights.

Eculizumab has been demonstrated as a successful treatment for AMR in renal transplantation<sup>4,5</sup> but this case represents, to the best of our knowledge, the first use for the management of chronic AMR. Despite not having complete resolution of DSA titres, but in context of definite clinical response, identification and quantification of complement-binding DSAs has a significant role in both diagnosis and management of AMR. The use of eculizumab as treatment is reasonable short to medium term to prevent the need for retransplantation in patients without concurrent allograft vasculopathy or diastolic dysfunction. Whether, if used prior to onset of significant allograft vasculopathy eculizumab could be considered as a treatment, rather than just a bridge to transplantation, is yet to be explored. In this case, concern about ongoing diastolic dysfunction, significant coronary allograft vasculopathy and the implications of long-term heavy immunosuppressive therapy for a young patient prompted relisting for transplantation, with an excellent response to retransplantation.

This case demonstrates the importance of DQ7 matching; however, the broader implications for transplanting patients mismatched at DQ7 are not clear. Our experience demonstrates this should be taken with caution, only when absolutely necessary, and consideration to de-sensitisation therapies prior with follow-in IVIG and plasmapheresis following initial transplantation should be given if the recipient has imminent risk of death.

In eligible patients with chronic AMR, retransplantation is the only cure but stabilization to permit relisting is critical. For this patient, eculizumab stabilized graft function and functional class, allowing time on the list for a suitable match to be found.

## Lead author biography



Katherine Kearney is a cardiologist with an interest in advanced heart failure, pulmonary hypertension, and congenital heart disease.

## Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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