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Blood group-specific apheresis in combination with daratumumab as a rescue therapy of acute antibody-mediated rejection in a case of ABO- and human leukocyte antigen-incompatible kidney transplantation

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Abstract

We report a case of antibody-mediated rejection treated with the human CD38 monoclonal antibody daratumumab in a 58-year-old female patient with end-stage kidney disease due to autosomal dominant polycystic kidney disease who received an ABO- and human leukocyte antigen antibody-incompatible living donor kidney transplant. The patient experienced an episode of severe antibody-mediated rejection within the first week of transplantation. Blood-group-antibody selective immunoadsorption in combination with administration of four doses of daratumumab (each 1800 mg s.c.) led to a persistent decrease of ABO- and more interestingly donor-specific human leukocyte antigen antibody reactivity and resulted in clinical and histopathological remission with full recovery of graft function, which has remained stable until post-transplant day 212. This case illustrates the potential of targeting CD38 in antibody-mediated rejection.

Keywords

Case report, daratumumab, antibody-mediated rejection, kidney transplantation, living-donor transplantation, HLA incompatibility, blood-group incompatibility, rejection therapy

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Introduction

The human monoclonal antibody daratumumab targets CD38, a transmembrane glycoprotein expressed at high levels on normal or malignant plasma cells (PCs) and natural killer cells (NK cells).[1,2] Use of daratumumab for eradication of antibody-producing PCs is well established in the therapy of multiple myeloma (MM) and has more recently been proposed as a promising approach in the treatment of antibody-mediated autoimmune diseases such as red-cell aplasia, autoimmune hemolytic anemia, and refractory systemic lupus erythematosus.[3–5]

Antibody-mediated rejection (ABMR) is a major cause of renal allograft failure. Current treatment options for ABMR include immunoadsorption (IA), plasmapheresis (PPH), corticoid-pulse therapy, intravenous application of

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Table 1. HLA typing of donor and recipient.

Recipient	Donor
A*32, A*68	**A*24**, A*68
B*44, B*58	**B*35**, B*44
C*05, C*07	**C*04**, C*07
DRB1*07:01, DRB1*13:01	**DRB1*01:01**, DRB1*07:01
DQB1*02:02, DQB1*06:03	DQB1*02:02, DQB1***05:01**

PCR-SSP Olerup method was used for HLA typing. HLA-A, -B, -DRB1, and -DQB1 mismatches are indicated by bold marking.

immunoglobulins, anti-T-lymphocyte globulin, anti-CD20 antibody rituximab, and anti-complement factor 5 antibody eculizumab. Additional agents, such as bortezomib and tocilizumab, are also being investigated. However, there are only few systematic randomized controlled trials, most of which have revealed disappointing results.[6–10] Therefore, our knowledge is mainly based on the results of observational studies and case series. Here, we report a case of daratumumab as an auxiliary therapy for acute ABMR in a patient who received an ABO- as well as HLA-incompatible living donor kidney transplant.

Case report

A 58-year-old female with end-stage kidney disease due to autosomal dominant polycystic kidney disease received a living donor kidney transplant from her 58-year-old husband.

In addition to five human leukocyte antigen (HLA)-A, -B, -C, -DRB1, and -DQB1 mismatches (Table 1), a major ABO blood group incompatibility (A donor, O recipient; initial isoagglutinin titer measured before desensitization; anti-blood group A IgM titer 1:128 and IgG titer 1:1024) and an HLA-incompatibility due to donor-specific antibodies (DSAs) against HLA-DRB*01:01 with a mean fluorescence intensity (MFI) of 1562 were present (institutional acceptable DSA threshold before transplantation 1000 MFI). Known immunizing events included two pregnancies with the organ donor being the father of her children. Complement-dependent cytotoxicity crossmatches were negative.

The recipient presented preoperatively with grade-III obesity (body mass index [BMI] of 32.8 kg/m^2) and was treated with peritoneal dialysis for 11 months resulting in a high risk for burst abdomen. Therefore, an abdominoplasty was performed 4 months before transplantation. Baseline immunosuppressive therapy with tacrolimus, mycophenolate mofetil, and prednisolone was started 2 weeks before transplantation.

Due to the high-risk immune constellation with HLA- and ABO-incompatibility, an extended desensitization protocol with five IA (Immusorba™) and four PPH sessions (Plasmaflo™) was performed preoperatively (Figure 1(a)). The isoagglutinin titer measured on the day before transplantation were decreased under the institutions' acceptable limit (anti-blood group A IgM titer not detectable and IgG titer $<$1:8).

On the day of transplantation, induction therapy with basiliximab, prednisolone (250 mg) and on post-transplant day 1, rituximab (375 mg/m^2) was administered to reduce antigen presentation by B cells. Two additional PPH treatments followed on days 1 and 2 post-transplant.

Initially, renal function improved gradually; however, on day 5 after transplantation, a rapid increase of Serum-creatinine (S-creatinine) from 1.8 mg/dL on day 4 to 3.4 mg/dL was observed (Figure 1(a)). The graft biopsy performed on the same day indicated severe C4d-positive and hemorrhagic ABMR associated with inflammation and intimal arteritis (Figure 1(b)). Initial rejection therapy consisted of high-dose prednisolone-therapy (250 mg) for 3 days beginning on day 5 after transplantation and three additional PPH on days 6, 7, and 8. S-creatinine levels kept increasing until day 8 post-transplant (4.8 mg/dL), indicating a limited response to standard rejection therapy and PPH. The rise in S-creatinine was accompanied by a marked rebound of anti-blood group A antibody levels (peak IgM titer 1:8 and IgG titer 1:32) despite PPH and adequate tacrolimus trough levels of 13.4 µg/L on day 6 and 10.2 µg/L on day 8 (Figure 2(a)). For this reason, we considered rescue treatment with daratumumab. On post-transplant day 9, a first dose of 1800 mg was administered subcutaneously. In addition, a switch to a more specific IA using the blood group A antibody-specific SECORIM ABO-A Column (VitroSorb™) was initiated. A total of four IA treatments on post-transplant days 9, 10, 11, and 12 were applied.

S-creatinine levels as well as anti-A IgM and IgG titers decreased continuously after the first application of daratumumab and use of anti-A selective IA to 2.6 mg/dL on day 14 (anti-blood group A IgM titer 1:2 and IgG titer 1:8 after the last IA on day 12), where a second graft-biopsy was performed (Figure 1(b)). In the subsequent course, three further doses of daratumumab were administered on days 15, 23, and 30. An abdominal wound dehiscence after laparotomy occurred on day 30 requiring operative revision.

On day 49, the preformed DSA against HLA-DRB*01:01 were decreased below 500 MFI and the additionally present non-DSA HLA class II antibodies had become close to undetectable. The third graft biopsy conducted on day 62 showed further improvement of ABMR-related changes (Figure 1(b)). S-creatinine levels remained stable at 1.4 mg/dL until day 212 after transplantation and anti-A levels determined on day 132 were close to the low levels observed immediately after the last anti-A selective IA (anti-blood group A IgM titer 1:1 and IgG titer 1:16).

Discussion

Kidney transplantation of patients with preformed DSA and blood group-incompatibility is challenging due to high rates of ABMR with consecutive early graft loss.[10] Bearing in mind the non-satisfactory results with previously described therapeutics for ABMR, daratumumab could provide a

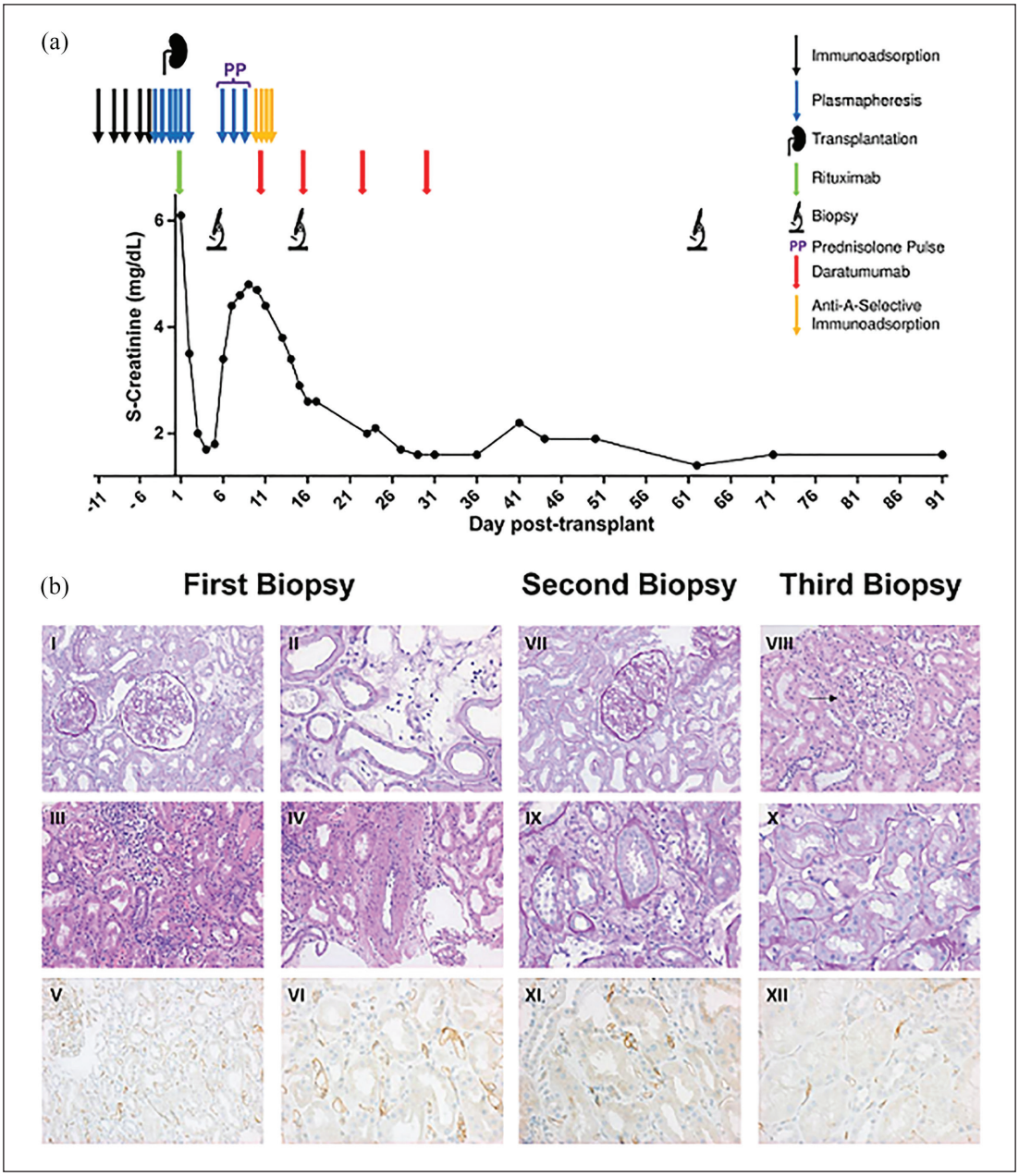


Figure 1. Clinical course before and after application of daratumumab. (a) Summary of events and therapy before and after transplantation including five IA and four PPH sessions for desensitization, rituximab (375 mg/m^2), biopsies, ABMR therapy with prednisolone pulse (250 mg/kg body weight), post-transplant PPH, ABO-A antibody-selective IA and application of daratumumab (each 1800 mg s.c.). Serum-Creatinine levels after transplantation. (b) Histopathological images of the transplant biopsies performed on day 5, 14, and 62 after transplantation (I–XII). First biopsy (I–VI) on post-transplant day 5 with morphological features of C4d-positive active ABMR (BANFF 2019 classification: g2 i1 ti2 i-IFTA2 t1 t-IFTA1 v1 ptc2 aah2 cg1 ci1 ct1 cv2 mm0). I: transplant glomerulitis (g2). PAS × 20. II: peritubular capillaritis (ptc2). PAS × 40. III: Focal interstitial inflammation and hemorrhage. HE × 20. IV: Mild endothelialitis. HE × 40. V, VI: Strong diffuse C4d-positivity of peritubular capillaries (C4d3, V: × 20, VI: × 40). Second biopsy (VII, IX, XI) on post-transplant day 14 (BANFF 2019 classification: g1 i1 ti1 i-IFTA0 t-IFTA0 t0 v0 ptc2 aah0 cg0 ci0 ct0 cv1 mm0) and third biopsy (VIII, X, XII) on post-transplant day 62 with markedly improved morphology (BANFF 2019 classification: g1 ptc0 v0 t0 i0 ti0 t-IFTA0 iIFTA0 cg1 cv0 ct1 ci1 aah0 mm1). VII: Mild focal transplant glomerulitis (g1). PAS x 20; VIII: Focal-segmental glomerular thrombotic microangiopathy (→) and mild transplant glomerulitis (g1). HE × 20. IX: Focal mild peritubular capillaritis (ptc1). PAS × 40. X: No peritubular capillaritis (ptc0). HE × 40. XI: Diffuse C4d-positivity of peritubular capillaries (C4d3, XI: × 40). XII: Weaker diffuse C4d-positivity of peritubular capillaries (C4d2, XII: × 40).

aah: arteriolar hyalinosis; ABMR: antibody-mediated rejection; cg: chronic glomerulopathy (transplant glomerulopathy); ci: interstitial fibrosis in cortex; ct: tubular atrophy in cortex; g: glomerulitis; i: inflammation in non-scarred cortex; IA: immunoadsorption; i-IFTA: inflammation in areas of the cortex with interstitial fibrosis and tubular atrophy; mm: mesangial matrix expansion; PPH: plasmapheresis; ptc: peritubular capillaritis; t: tubulitis in cortical tubules within non-scarred cortex; t-IFTA: tubulitis in areas of the cortex with interstitial fibrosis and tubular atrophy; v: endarteritis (intimal arteritis).

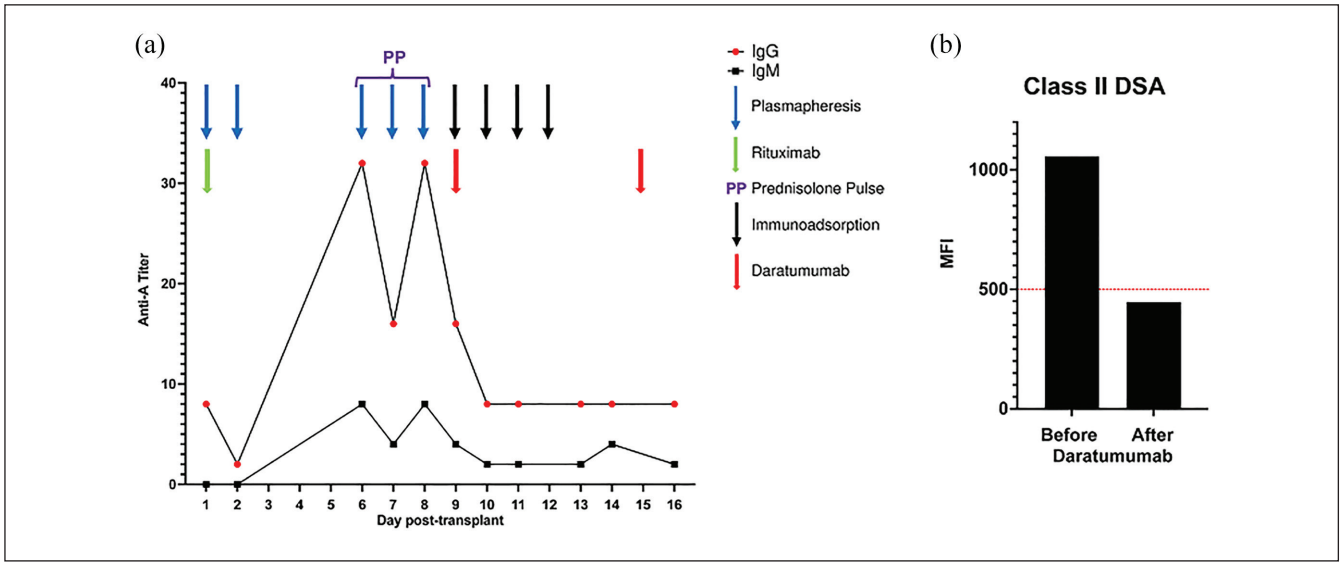


Figure 2. Antibody measurements. (a) Anti-A IgG- and IgM blood group antibody titers post-transplant. (b) Donor-specific antibody (DSA) level against HLA-DRB1*01:01 in mean fluorescence intensity (MFI) measured on post-transplant day 5 (before application of daratumumab) and on post-transplant day 49 (after application of daratumumab). Cut-off for post-transplant DSA positivity is shown by dotted red line.

promising approach targeting not only PCs but also NK cells that may critically contribute to ABMR through Fc-receptor interaction.[10,11]

To date, there is only limited clinical experience with daratumumab beyond its broad use in MM. While several studies reported its use in the treatment of HLA-related ABMR after kidney transplantation, the literature concerning ABO incompatible ABMR is scarce. Chapuy et al. reported effectiveness of daratumumab in a case of a 72-year-old who had developed red-cell aplasia after allogeneic stem-cell transplantation (allo-SCT) with major ABO blood-group incompatibility.[3] Schuetz et al. demonstrated successful daratumumab-treatment of refractory post-transplant autoimmune hemolytic anemia after allo-SCT in three patients.[12] Our uniquely ABO- as well as HLA antibody-incompatible case adds to the previously described reports of daratumumab use for ABMR therapy in kidney transplantation by Spica et al. (ABO-incompatible), Kwun et al., and Doberer et al. (both HLA-incompatible).[13–15]

We administered a regimen of only four doses of daratumumab subcutaneously instead of intravenously and decided to stop treatment based on the observed histopathological and clinical remission of ABMR. Application-associated toxicities or infections were not observed. Therefore, we argue that a shortened less intensive regimen can be feasible, while improving the safety of rejection therapy with daratumumab. Preliminary data suggests that subcutaneous delivery as performed in our case report is associated with fewer administration-related reactions at a comparable response rate.[16]

We found that in our case additional antibodies (Table 1) were present before desensitization and on the day of rejection against B*73:01 (MFI 3072 and 4701, respectively) which shared the same epitope as the mismatch B*35 (HLAMatchmaker eplet 80N) and against A*01:01, A*29:01, A*29:02 and A*80:01, which shared the same epitopes as the mismatch A*24 (HLAMatchmaker eplets 144KR + 166DG) on the day of rejection (MFI 1176, 935, 1051 and 1146, respectively). Therefore, it is possible that the severity of ABMR could have been a result of cross-reactivity as described by Rodey et al., who defined HLA class I serologically cross-reactive groups (CREGs).[17]

We cannot prove a definite causality between daratumumab and the observed reduction of anti-A titers and DSA levels albeit it is highly suggestive by the time course and limited response to PPH that initially resulted in a rebound of anti-A titers. Short half-life of IgM antibodies, an allograft tolerance for blood group antibodies, and a doubtful association of ABO-antibody titers with graft dysfunction and early active ABMR may also have contributed to the favorable clinical course, as also discussed by Spica et al.[13]

However, we observed a lasting reduction of DSA and non-DSA HLA antibodies after daratumumab application, which cannot be explained by anti-A-immunoglobulin-selective IA (Figure 2(b) and Table 2). However, other therapeutic regimens, such as more intense PPH treatment, could have been similarly effective cannot be excluded.

As recently reported by Scalzo et al. in a case of a patient who received daratumumab for maintenance of MM before a low immunologic risk living donor kidney transplantation, concerns of an increased risk of acute T-cell-mediated rejection (TCMR) due to expansion of both CD4+ and CD8+ populations need to be considered in patients treated with daratumumab.[18] Daratumumab has been described to deplete CD38+ regulatory T-cell subsets in MM promoting

Table 2. Serum HLA class I and class II antibody measurements.

Day of measurement	Detected antibodies							
	A*01:01	A*29:01	A*29:02	A*80:01	B*73:01	DRB1*01:01	DRB1*01:02	DRB1*01:03
–34 pre-transplant before desensitization	0	0	0	211	3072	1562	1473	723
5 post-transplant on day of rejection diagnosis	1176	935	1051	1146	4701	1056	1069	856
49 post-transplant after rejection therapy	0	0	0	316	714	447	403	288

A*24; B*35; C*04; DRB1*01:01; DQB1*05:01 were the donor HLA mismatches. The patient had donor-specific antibodies against DRB1*01:01. However, there were additional antibodies before desensitization and on the day of rejection against B*73:01 (MFI 3072 and 4701, respectively) which shared the same epitope as the mismatch B*35 (HLAMatchmaker eplet 80N) and against A*01:01, A*29:01, A*29:02, and A*80:01, which shared the same epitopes as the mismatch A*24 (HLAMatchmaker eplets 144KR + 166DG) on the day of rejection (MFI 1176, 935, 1051, and 1146, respectively).

expansion of T-helper and cytotoxic T cells.[19] Since we introduced standard immunosuppressive therapy with tacrolimus, mycophenolate mofetil and basiliximab and furthermore initialized prednisolone pulse therapy prior to application of daratumumab, it can be rationalized that the risk of TCMR had been lowered significantly in our case. However, we strongly advise to evaluate and monitor the likelihood of TCMR when applying CD38 antibodies in kidney transplantation.

Conclusion

In conclusion, a patient who displayed severe treatment-resistant clinical and histopathological ABMR, predominately caused by an initially high anti-A antibody titer and possibly epitope sharing of CREG HLA class I non-DSA, was successfully treated with blood group-specific IA and daratumumab. Furthermore, a wound dehiscence unlikely associated with daratumumab therapy, no adverse events or infections occurred. Although follow-up biopsy on day 62 showed minimal ABMR activity, anti-A antibody and especially DSA as well as non-DSA levels remained low. Our case suggests that daratumumab is effective in interfering with ABMR pathogenesis by inhibiting alloantibody production. Daratumumab should therefore be investigated and considered in therapy of ABMR and possibly also for desensitization of ABO- and HLA-incompatible kidney transplantation, whereas risk–benefit evaluation is highly warranted.

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All authors approved the final version of the manuscript.

Author contribution

C.C.S. analyzed and interpreted the data and wrote the paper with support from V.S., G.B., and C.S.. G.B., C.S., L.K., A.S., and V.S. helped with conceptualization of the paper. CC.S, G.B., C.S., and V.S. designed the research and contributed to the interpretation of the results. K.A. provided pathology images and helped with interpretation. A.E. performed antibody measurements and helped with analysis and interpretation. All authors provided critical feedback and helped shape the research, analysis and manuscript.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

Declaration of conflicting interests

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Written informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Consent for publication statement

The authors certifies the accuracy of content given to the journal, in particular, the names of coauthors present and correctly spelt, and that addresses and affiliations are up to date. The corresponding author ensures that all the co-authors have agreed to all of the contents and will notify all the authors when the manuscript is accepted. The corresponding author is answerable to all the inquiries on behalf of all the co-authors. The corresponding author ensures that

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Supplemental material

Supplemental material for this article is available online.

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