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Case Report

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Successful Desensitization with Imlifidase and Daratumumab in a Highly Immunized, Crossmatch Positive, Blood Group-Incompatible Living-Donor Re-Transplant Recipient with Systemic Lupus Erythematosus and Antiphospholipid Syndrome

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Keywords
Daratumumab · Imlifidase · Kidney transplant

Abstract

Introduction: The transplantation of highly sensitized patients remains a major obstacle. Immunized patients wait longer for a transplant if not prioritized, and if transplanted, their transplant outcome is worse. ***Case Presentation:*** We report a successful AB0- and HLA-incompatible living donor kidney transplantation in a 35-year-old female patient with systemic lupus erythematosus (SLE) and antiphospholipid syndrome. The patient had a positive T- and B-cell complement-dependent cytotoxicity (CDC) crossmatch and previous graft loss due to renal vein thrombosis. We treated the patient with intravenous immunoglobulins, rituximab, horse anti-thymocyte globulin, daratumumab, and imlifidase, besides standard immunosuppression. All IgG antibodies were sensitive to imlifidase treatment. Besides donor-specific HLA antibodies, anti-dsDNA antibodies and antiphospholipid antibodies were cleaved. The patient initially had delayed graft function. Two kidney biopsies (day 7 and day 14) revealed acute tubular necrosis without signs of HLA antibody-mediated rejection. On posttransplant day 30, hemodialysis was stopped, and creatinine levels declined over the next weeks to a baseline creatinine of about 1.7 mg/dL after 12 months. ***Conclusion:*** In this case, a novel multimodal treatment strategy including daratumumab and imlifidase enabled successful kidney transplantation for a highly immunized patient with antiphospholipid antibodies.

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Introduction

Highly sensitized patients wait longer for a transplant and have inferior outcomes after transplantation [1]. In Europe, imlifidase is approved for desensitization of highly immunized adult kidney transplant patients with a positive crossmatch (XM) against available deceased donors [2]. Imlifidase is a cysteine protease that generates single-cleaved immunoglobulin G (IgG) in a rapid first reaction and subsequently 2 F(ab')2 fragments and a fully separated Fc fragment in a longer second reaction [3]. In order to achieve a negative XM, a single dose is given within 24 h before transplantation [4]. Three years after transplantation, highly sensitized patients with imlifidase graft survival is 84%, but the rate of antibody-mediated rejection (ABMR) is 38%, indicating the need for better rejection prophylaxis [2]. Recently, anti-CD38 monotherapy with isatuximab was used to deplete plasma cells for desensitization in highly sensitized patients awaiting kidney transplants [5]. Here we report a case where we used combined therapy of imlifidase and anti-CD38 therapy to successfully transplant a patient with high levels of allo- and autoantibodies.

Detailed Case Presentation

We present a case of a 35-year-old Caucasian female patient who presented at the age of 11 years with diffuse membrano-proliferative sclerosing glomerulonephritis with endomembranous immune complex deposits, positive for IgG, C3, and C4, while negative for IgA and C1q. At the age of 23, she started on peritoneal dialysis, and after 2 years, she received a high-urgency deceased donor kidney transplant in another center due to failure of peritoneal dialysis and recurrent fistula thrombosis. In 2015, the patient had a pregnancy without complications. The patient lost her first transplant in 2017 due to a thrombosis in the allograft vein. At this time, she did not receive anticoagulants, despite numerous thrombotic events in the past. During the workup, a triple positive antiphospholipid syndrome (APS) was diagnosed with high-positive anti-beta2-glycoprotein and anti-cardiolipin IgG autoantibodies (IgM negative) together with positive lupus anticoagulant. Further, elevated antinuclear antibodies (ANA) and anti-dsDNA antibodies were detected, and current EULAR/ACR criteria allowed the diagnosis of systemic lupus erythematosus (SLE) without other signs of SLE. After graft loss, the patient restarted peritoneal dialysis, and oral phenprocoumon was initiated for APS. When she presented at our center for transplant reevaluation, she was highly immunized (cPRA of 99% for HLA classes I and II and mean fluorescence intensity (MFI) > 25,000 in the Luminex Single Antigen Bead (SAB) assay). Almost all HLA antibodies showed complement binding activity (PRA of 99% in complement-dependent cytotoxicity [CDC]) and a calculated donor frequency of 0.03%. The patient was accepted for the Eurotransplant acceptable mismatch (AM) program but did not receive any organ offers. Three living donors were evaluated, while the mother was the only one eligible for donation. One year prior to transplantation, a first attempt at desensitization with rituximab (1 g) and 6 cycles of immunoadsorption were performed, but donor-specific HLA antibodies (DSA) against the mother remained almost unchanged (stable cPRA of 99% with only slightly decreased MFI values in SAB assay). In May 2021, peritoneal dialysis had to be switched to hemodialysis with brachial basilic fistula. The fistula clotted after 2 months, necessitating complex surgery. At this time point, a life-threatening situation became apparent, and the health insurance agreed to pay for the off-label use of imlifidase for the proposed living transplantation. Anti-B isoagglutinin titers (donor blood group AB, recipient blood group A) were 1:4 for IgM and 1:8 for IgG. Against four of the six total mismatches, HLA-B*07:02 (B7), -C*07:02 (Cw7), -DRB1*11:04 (DR11), and -DRB3*02:02 (DR52) antibodies with MFI values of 26,000, 16,000, 17,000, and 12,000, respectively, were detected by SAB assay. Antibodies against HLA-B7, -Cw7, and -DR11 were proven to be complement-binding in the C1q assay and CDC. CDC-XM on T and B cells without and with DTT was highly positive. Immunosuppressive treatment was started 5 days before transplantation with tacrolimus (0.17 mg/kg/day, target level: 10 ng/mL), 1,440 mg/d mycophenolic acid, and 5 mg methylprednisone. Anticoagulation was switched to heparin (target doubling of PTT). Two days before transplantation, the patient received one dose of 1,800 mg daratumumab (anti-CD38), targeting plasma cells, activated T and B cells, NK cells, and able to modulate pDCs. One day before transplantation, horse anti-thymocyte globulin (not cleaved by imlifidase) was started and given daily for 5 days (each 15 mg/kg). Sixteen h before transplantation, she received 20 mg of imlifidase and 500 mg of methylprednisone (500 mg day 1, 250 mg day 2, 125 mg day 3, 80 mg day 3–7, further tapered until 4 mg on day 42). Transplant-related interventions are summarized in Figure 1a. XM on T and B cells without and with DTT before imlifidase was repeatedly strong positive and was converted to negative within 2 h following imlifidase administration, together with MFI values of DSA in the SAB and C1q assays. After uncomplicated surgery, diuresis started (1.5 L on day 1). After removal of the inguinal arterial catheter for invasive blood pressure, monitoring severe bleeding and hypotension

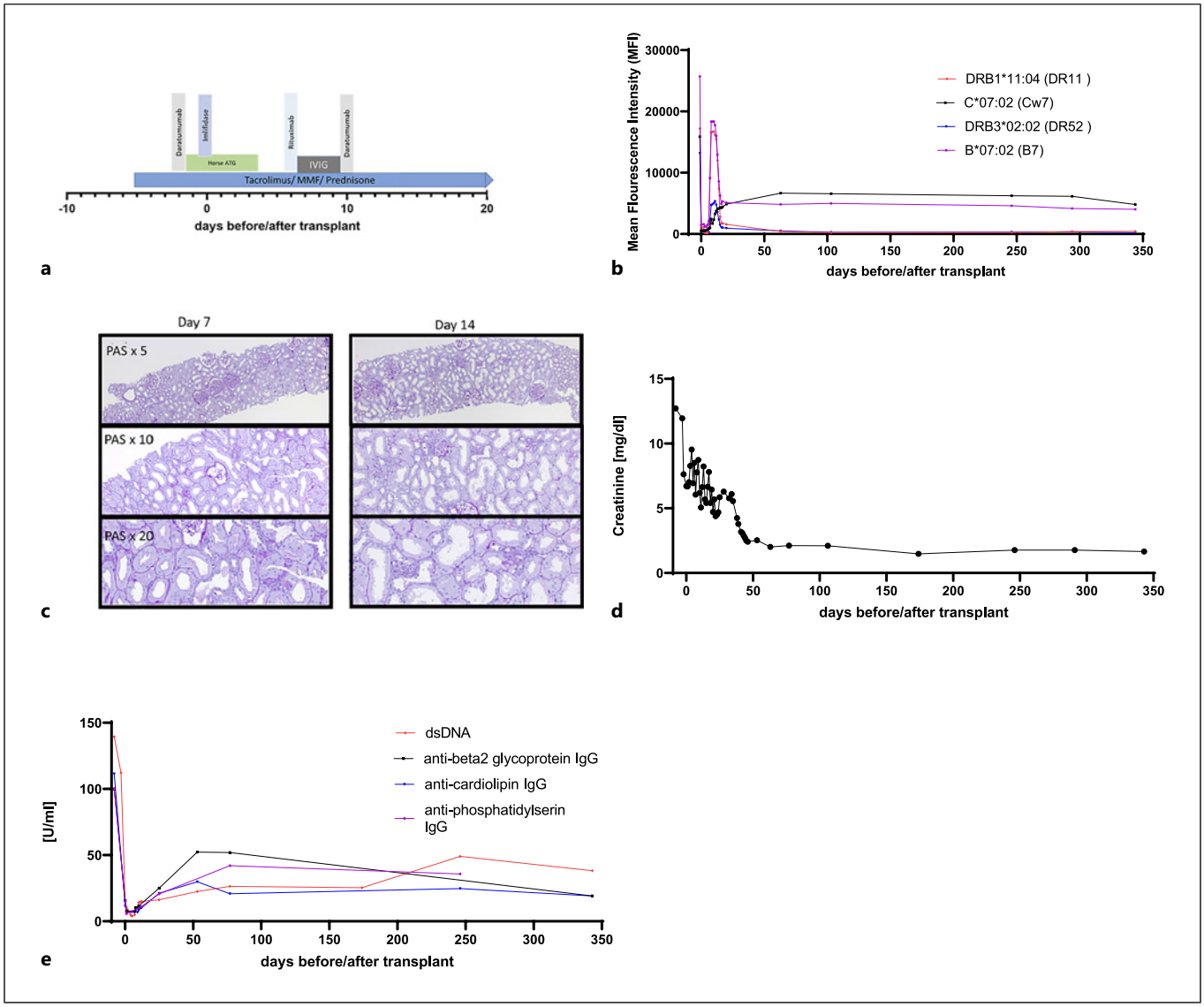

Fig. 1. a Sequence of drugs administered. **b** Mean fluorescence intensities (MFIs) of donor-specific antibodies. **c** Representative histology of the kidney allograft on day 7 and day 14 after transplantation stained with periodic acid-Schiff reaction in different magnifications. Course of serum creatinine (**d**) and autoantibodies (**e**) over time.

occurred, and a perfused pseudoaneurysm was treated with an ultrasound-guided thrombin injection. Diuresis stopped after this event, and hemodialysis was reinitiated on day 3. HLA antibody testing showed rising donor-specific and non-donor-specific antibodies (Fig. 1b) suspicious for humoral rejection. The patients received an additional dose of rituximab (1 g), 3 doses of intravenous immunoglobulins (IVIGs) (35 g each), as well as an additional dose of 1,800 mg daratumumab. A kidney biopsy 7 days after transplant revealed severe acute tubular necrosis (Fig. 1c) without signs of rejection. Moderate acute tubular necrosis was still present in a repeat biopsy on day 14, which caused another bleeding episode. C4d was positive after AB0i transplantation. Diuresis started on day 28, and on day 30, hemodialysis was stopped. Serum creatinine slowly declined over the next weeks to 1.7 mg/dL (Fig. 1d). The course of autoantibodies against dsDNA, beta2 glycoprotein, cardiolipin, and phosphatidylserine is shown in Figure 1e. Anti-CD38 treatment affected mainly peripheral NK cell numbers, while T cells recovered fast after anti-thymocyte globulin treatment. The patient was still able to generate peripheral plasmablasts despite anti-CD20 and anti-CD38 treatment without measurable peripheral B cells (Fig. 2a, b).

Before transplantation, the patient had received 3 COVID vaccinations (1xChAdOx1-S, 2xBNT162b2). On day 35, she developed symptomatic SARS-CoV-2 infection with nasal congestion and cough. Remdesivir (200 mg day 1, 100 mg day 2, 3) and tixagevimab 300 mg/

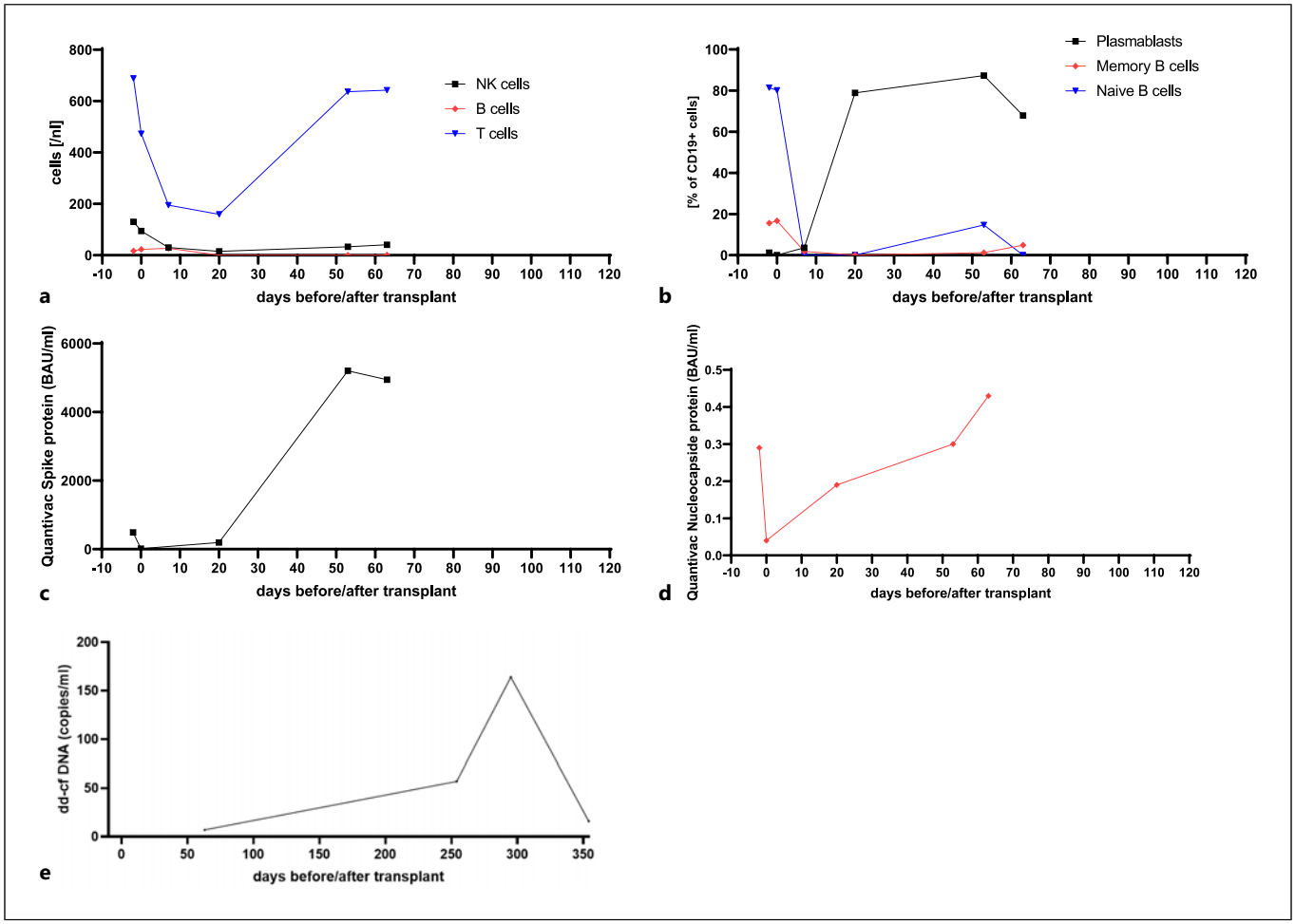

Fig. 2. **a** Course of B, T, and NK cells. **b** B cells subsets. **c** SARS-CoV-2 spike protein. **d** SARS-CoV-2 nucleocapside protein. **e** Course of donor-derived cell-free DNA.

cilgavimab 300 mg were administered, and the infection resolved without further sequelae. The course of anti-spike antibodies and nucleocapsid protein is shown in Figure 2 c and d. Interestingly, the patient was able to mount a weak immune response against the nucleocapsid protein despite heavy immunosuppressive treatment. Anti-spike antibodies were influenced by the application of tixagevimab/cilgavimab.

The patient was discharged from the hospital on day 47 after transplantation. The out-patient follow-up visits remained uneventful, and graft function and proteinuria remained stable 12 months post-transplantation. Ten months after transplantation, a mild increase in donor-derived cell-free DNA was observed (Fig. 2e), and a repeat biopsy was performed, showing peritubular capillaritis (ptc2) but absence of glomerulitis (g0). C4d was positive but cannot be used in the case of AB0i transplantation. Therefore, the biopsy result was suspicious for ABMR but formally did not fulfill the criteria according to Banff 2019. Donor-derived cell-free DNA normalized again after 1800 mg of daratumumab (Fig. 2e).

Discussion

Here, we report the complicated second-living donor AB0i transplantation against a positive CDC XM in a highly sensitized patient with APS. Together with imlifidase for cleavage of HLA and AB0i alloantibodies together with APS autoantibodies, we administered the anti-CD38 antibody daratumumab in order to deplete plasma cells in the bone marrow as well as NK cells [6], which are involved as potent effector cells in the pathogenesis of ABMR.

Daratumumab is cleaved by imflidase, why a false-positive XM under daratumumab was not problematic in our case [7]. The half-live of daratumumab is approximately 9 days, why an earlier administration should have been considered in our case, and the full effect might have been diminished by the short time between daratumumab and imlifidase administration [8]. An immediate cell depletion can be assumed to be mediated by antibody-dependent cellular cytotoxicity or

complement-dependent cellular cytotoxicity. Whether imlifidase is also able to cleave cell-bound antibodies is unknown. Imlifidase converted the XM to negative within 2 h after administration, but despite heavy pretreatment, HLA antibodies and DSA increased again after transplantation. For prophylaxis of ABMR rituximab, IVIGs and a second dose of daratumumab were administered. Unfortunately, severe bleeding under anticoagulation complicated the case, but a biopsy did not show signs of ABMR 7 and 14 days after transplant, eventually due to the depletion of NK cells, which are thought to be potent effector cells in ABMR [9]. A strong NK cell depletion has previously been described in the peripheral blood as well as in the kidney allograft of a patient treated with daratumumab for ABMR [10]. After redosing rituximab, daratumumab, and IVIG, DSA declined and remained low. Interestingly the rapid and transient increase was only observed in anti-HLA antibodies but not in autoantibodies such as anti-dsDNA or antiphospholipid autoantibodies. HLA antibodies in HLA-A, -B, and -C increased gradually to almost the initial level, while antibodies in HLA-DR only increased gradually.

Several case reports highlighted the potential benefit of daratumumab treatment in ABMR by reducing levels of DSA and inducing histopathological as well as molecular remission [10–14]. While these results are promising, it is important to consider the potential risk of T cell-mediated rejection (TCMR) following daratumumab use. Scalzo et al. recently reported a case where a patient who had received daratumumab as maintenance therapy for multiple myeloma prior to kidney transplantation experienced grade IIB TCMR 4 days after the transplant [15]. Additionally, Doberer et al. [10] reported a case of concurrent multiple myeloma and ABMR in which daratumumab therapy resulted in regression of both myeloma and AMR; however, a protocol biopsy conducted 3 months after daratumumab initiation revealed subclinical tubulointerstitial infiltrates, which decreased following steroid pulse therapy. In our patient, no TCMR episode was observed.

Imlifidase has been used in ANCA-associated vasculitis in single cases [16]. Catastrophic APS is a rare and life-threatening antibody-mediated disease [17] which is so far mainly treated with plasma exchange, especially in this indication, imlifidase could be a new promising approach. The concept of targeting plasma cells with daratumumab has already been described in several other indications such as SLE [18], ANCA-associated vasculitis [19], and autoantibody-driven neurological autoimmune diseases [20], while larger studies and studies on long-term effects are still missing. Here we report the combination of imlifidase and daratumumab in a multimodal treatment regimen for a patient with APS, demonstrating the profound effect of this combination on APS and SLE autoantibodies. Despite the promising approach, the described treatment protocol is extremely costly, particularly regarding imlifidase, which holds orphan drug status and costs several hundred thousand euros in Europe. Furthermore, it is only approved in the setting of deceased donor transplantation. Besides the off-label use of imlifidase in the context of living donation, Eurotransplant has offered desensitization with imlifidase within the AM program since 2023. However, this program was not available for our patients in 2022.

In summary, we report as the case of a successful second AB0- and HLA-incompatible living kidney transplantation in a highly sensitized patient with SLE and APS with multiple thrombosis and limited vascular access treated with imlifidase, rituximab, and daratumumab, providing a new treatment strategy for highly immunized patients.

Statement of Ethics

Written informed consent was obtained from participants for publication of the details of their medical case and any accompanying images. No ethics approval was obtained for the case presentation. All presented data were part of routine clinical care.

Conflict of Interest Statement

K.B. declares honoraria or travel support from Aicuris, Astellas, Astra, CareDx, Carealytics Digital Health, Chiesi, MSD, Neovii, Natera, Paladin, Stada, Takeda, Veloxis, and Vifor. F.H. declares honoraria or travel support from MSD, Hansa, Chiesi, and Novartis. E.S. declares honoraria from Novartis, Astra Zeneca, and Medupdate. The other authors declare no conflicts of interest with the current study.

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Author Contributions

E.S. and F.H. wrote the manuscript. E.S. did laboratory analysis for B, T, and NK cells as well as SARS-CoV-2 antibodies. K.A. performed the histological analysis and provided the pictures. N.L. performed HLA antibody testing. B.O. performed donor-derived, cell-free DNA testing. M.C., B.G., T.D., A.L., A.S., K.B., K.-U.E., R.Ö., and F.H. treated the patient and made all clinical decisions. All authors read and approved the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Mamode N, Bestard O, Claas F, Furian L, Griffin S, Legendre C, et al. European guideline for the management of kidney transplant patients with HLA antibodies: by the European society for organ transplantation working group. Transpl Int. 2022;35:10511. https://doi.org/10.3389/ti.2022.10511.

2 Kjellman C, Maldonado AQ, Sjoholm K, Lonze BE, Montgomery RA, Runstrom A, et al. Outcomes at 3 years posttransplant in imlifidase-desensitized kidney transplant patients. Am J Transpl. 2021;21(12):3907–18. https://doi.org/10.1111/ajt.16754.

3 Vindebro R, Spoerry C, von Pawel-Rammingen U. Rapid IgG heavy chain cleavage by the streptococcal IgG endopeptidase IdeS is mediated by IdeS monomers and is not due to enzyme dimerization. FEBS Lett. 2013;587(12):1818–22. https://doi.org/10.1016/j.febslet.2013.04.039.

4 Jordan SC, Legendre C, Desai NM, Lorant T, Bengtsson M, Lonze BE, et al. Imlifidase desensitization in crossmatch-positive, highly sensitized kidney transplant recipients: results of an international phase 2 trial (highdes). Transplantation. 2021;105(8):1808–17. https://doi.org/10.1097/TP.0000000000003496.

5 Vincenti F, Bestard O, Brar A, Cruzado JM, Seron D, Gaber AO, et al. Isatuximab monotherapy for desensitization in highly sensitized patients awaiting kidney transplant. J Am Soc Nephrol. 2024;35(3):347–60. https://doi.org/10.1681/ASN.0000000000000287.

6 Kwun J, Matignon M, Manook M, Guendouz S, Audard V, Kheav D, et al. Daratumumab in sensitized kidney transplantation: potentials and limitations of experimental and clinical use. J Am Soc Nephrol. 2019;30(7):1206–19. https://doi.org/10.1681/ASN.2018121254.

7 Ho CS, Putnam KR, Peiter CR, Herczyk WF, Gerlach JA, Lu Y, et al. Daratumumab interferes with allogeneic crossmatch impacting immunological assessment in solid organ transplantation. J Clin Med. 2022;11(20):6059. https://doi.org/10.3390/jcm11206059.

8 Kim K, Phelps MA. Clinical pharmacokinetics and pharmacodynamics of daratumumab. Clin Pharmacokinet. 2023;62(6):789–806. https://doi.org/10.1007/s40262-023-01240-8.

9 Yazdani S, Callemeyn J, Gazut S, Lerut E, de Loor H, Wevers M, et al. Natural killer cell infiltration is discriminative for antibody-mediated rejection and predicts outcome after kidney transplantation. Kidney Int. 2019;95(1):188–98. https://doi.org/10.1016/j.kint.2018.08.027.

10 Doberer K, Klager J, Gualdoni GA, Mayer KA, Eskandary F, Farkash EA, et al. CD38 antibody daratumumab for the treatment of chronic active antibody-mediated kidney allograft rejection. Transplantation. 2021;105(2):451–7. https://doi.org/10.1097/TP.0000000000003247.

11 Spica D, Junker T, Dickenmann M, Schaub S, Steiger J, Rufli T, et al. Daratumumab for treatment of antibody-mediated rejection after ABO-incompatible kidney transplantation. Case Rep Nephrol Dial. 2019 Sep-Dec;9(3):149–57. https://doi.org/10.1159/000503951.

12 Zhu L, Guo Z, Zhao D, Sa R, Zhao G, Guo H, et al. Case report: Daratumumab for treatment of refractory late or chronic active antibody-mediated rejection in renal allograft recipients with high levels of de novo donor-specific antibodies. Front Immunol. 2022;13:1087597. https://doi.org/10.3389/fimmu.2022.1087597.

13 de Nattes T, Kaveri R, Farce F, Francois A, Guerrot D, Hanoy M, et al. Daratumumab for antibody-mediated rejection: is it time to target the real culprit? Am J Transpl. 2023;23(12):1990–4. https://doi.org/10.1016/j.ajt.2023.06.018.

14 Susal CC, Kraft L, Ender A, Susal C, Schwenger A, Amann K, et al. 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. SAGE Open Med Case Rep. 2023. Vol. 11; p. 2050313X231211050. https://doi.org/10.1177/2050313X231211050.

15 Scalzo RE, Sanoff SL, Rege AS, Kwun J, Knechtle SJ, Barisoni L, et al. Daratumumab use prior to kidney transplant and T cell-mediated rejection: a case report. Am J Kidney Dis. 2023;81(5):616–20. https://doi.org/10.1053/j.ajkd.2022.11.010.

16 Enghard P, Zickler D, Sonnemann J, Schneider W, Lurje G, Elezkurtaj S, et al. Imlifidase as novel treatment strategy in anti-neutrophil cytoplasmic antibody-induced pulmonary-renal syndrome. Kidney Int. 2021;100(6):1344–5. https://doi.org/10.1016/j.kint.2021.09.020.

17 Hubben A, McCrae KR. Emerging therapies in antiphospholipid syndrome. Transfus Med Rev. 2022;36(4):195–203. https://doi.org/10.1016/j.tmrv.2022.09.002.

18 Ostendorf L, Burns M, Durek P, Heinz GA, Heinrich F, Garantziotis P, et al. Targeting CD38 with daratumumab in refractory systemic lupus erythematosus. N Engl J Med. 2020;383(12):1149–55. https://doi.org/10.1056/NEJMoa2023325.

19 Ostendorf L, Burns M, Wagner DL, Enghard P, Amann K, Mei H, et al. Daratumumab for the treatment of refractory ANCA-associated vasculitis. RMD Open. 2023;9(1):e002742. https://doi.org/10.1136/rmdopen-2022-002742.

20 Scheibe F, Ostendorf L, Pruss H, Radbruch H, Aschman T, Hoffmann S, et al. Daratumumab for treatment-refractory antibody-mediated diseases in neurology. Eur J Neurol. 2022;29(6):1847–54. https://doi.org/10.1111/ene.15266.