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Case Report

Early Conversion from Tacrolimus to Belatacept in a Highly Sensitized Renal Allograft Recipient with Calcineurin Inhibitor-Induced de novo Post-Transplant Hemolytic Uremic Syndrome

Vasishta S. Tatapudi[a] Bonnie E. Lonze[b] Ming Wu[c]
Robert A. Montgomery[b]

[a]Department of Medicine, New York University Langone Medical Center, New York, NY, USA; [b]Department of Surgery, New York University Langone Medical Center, New York, NY, USA; [c]Department of Pathology, New York University Langone Medical Center, New York, NY, USA

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Tacrolimus · Belatacept · Hemolytic uremic syndrome

Abstract
Background: Kidney transplantation is the first-line therapy for patients with end-stage renal disease since it offers greater long-term survival and improved quality of life when compared to dialysis. The advent of calcineurin inhibitor (CNI)-based maintenance immunosuppression has led to a clinically significant decline in the rate of acute rejection and better short-term graft survival rates. However, these gains have not translated into improvement in long-term graft survival. CNI-related nephrotoxicity and metabolic side effects are thought to be partly

Vasishta S. Tatapudi
New York University Langone Medical Center
550 1st Avenue
New York, NY 10016 (USA)
E-Mail Vasishta.Tatapudi@nyumc.org

responsible for this. ***Case Presentation:*** Here, we report the conversion of a highly sensitized renal transplant recipient with pretransplant donor-specific antibodies from tacrolimus to belatacept within 1 week of transplantation. This substitution was necessitated by the diagnosis of CNI-induced de novo post-transplant hemolytic uremic syndrome. ***Conclusion:*** Belatacept is a novel costimulation blocker that is devoid of the nephrotoxic properties of CNIs and has been shown to positively impact long-term graft survival and preserve renal allograft function in low-immunologic-risk kidney transplant recipients. Data regarding its use in patients who are broadly sensitized to human leukocyte antigens are scarce, and the increased risk of rejection associated with belatacept has been a deterrent to more widespread use of this immunosuppressive agent. This case serves as an example of a highly sensitized patient that has been successfully converted to a belatacept-based CNI-free regimen.

Introduction

Calcineurin inhibitors (CNIs) suppress T-lymphocyte activation by inhibiting calcineurin phosphatase activity and nuclear factor of activated T cells (NFAT)-regulated gene transcription. However, they have several off-target effects [1]. CNI nephrotoxicity has been linked to chronic allograft nephropathy [2]. CNIs also contribute to hypertension, hyperlipidemia, post-transplant diabetes, and attendant cardiovascular complications [3–5]. The perception that these insalubrious, unintended effects of CNIs hinder long-term graft survival has led to efforts to institute CNI minimization strategies [6]. Borne out of these efforts, the comparative safety and efficacy of belatacept (a costimulation blocker) with respect to cyclosporine (a CNI) was evaluated in 2 phase III trials [7, 8]. Based on the favorable results from these trials, belatacept was approved for use in kidney transplant recipients [6]. Therefore, belatacept has emerged as a viable alternative to cyclosporine and tacrolimus as a maintenance immunosuppressive agent in kidney transplant patients.

De novo post-transplant hemolytic uremic syndrome (HUS) is a serious complication in renal transplant recipients and in cases with systemic manifestations and is associated with graft loss in up to a third of incident cases [9]. An incidence of 4–15% in renal transplant recipients treated with cyclosporine and 1% in those treated with tacrolimus is reported. Endothelial toxicity and prothrombotic and antifibrinolytic actions of CNIs have been implicated in the pathogenesis of thrombotic microangiopathy (TMA) in these cases. mTOR inhibitors have also been reported to cause post-transplant TMA [10]. Belatacept is an attractive alternative to CNIs in such instances. However, the trials that led to Food and Drug Administration (FDA) approval of belatacept included only patients at low immunologic risk [7, 8]. Gupta et al. [11] recently presented their initial experience with conversion from tacrolimus to belatacept in high-immunologic-risk kidney transplant recipients. However, data supporting the use of belatacept in sensitized renal transplant recipients are scarce.

Case Report

We report the case of a 59-year-old female patient of Southeast-Asian descent who underwent deceased donor renal transplantation at our institution in August 2016. At the time of initial referral for transplant evaluation in 2011, she had advanced chronic kidney disease but had not started dialysis. Medical records indicated that she had a slow rise in serum creatinine since 2006 but had never undergone a renal biopsy. No specific etiology had been ascribed to her kidney disease. Due to a history of 5 pregnancies that culminated in 3 live births and 2 miscarriages, she was broadly sensitized to human leukocyte antigens (HLA). Routine screening for anti-HLA antibodies with a Luminex-based solid-phase assay using single-antigen beads detected multiple class I and class II HLA antibodies in April 2016. Based on our institutional policy to denote HLA, to which antibodies of a strength greater than 4,000 mean fluorescence intensity (MFI) units are detected in the transplant candidate serum, as unacceptable, our patient's calculated panel reactive antibody (CPRA) level was 93%.

After an approximate wait-time of 5 years, she received an organ offer from a 46-year-old male deceased donor, who succumbed to a self-inflicted gunshot wound to the head. The deceased donor had a terminal creatinine of 1.2 mg/dL, and the organ offered was assigned a kidney donor profile index of 38%. Pre-implantation biopsy of the transplanted kidney demonstrated glomerulosclerosis in 4 out of 78 sampled glomeruli. Fibrosis affecting up to 10% of the tubule interstitium, mild arteriosclerosis, and patchy areas of acute tubular necrosis were also noted. Donor and recipient were blood type compatible (ABO type A). Complement-dependent cytotoxicity and flow cytometry-based cross-match testing of the current recipient's serum with donor T and B lymphocytes were negative. However, donor-specific antibodies (DSA) to class I antigen-HLA B45 (MFI 3,182) and class II antigen-DQ6 (MFI 3,802) were detected by Luminex-based solid-phase assay in the serum sample from April 2016. We consider antibody strength of MFI 2,000 or greater to be clinically significant. Since this suggested prior sensitization to donor HLA, the risk of early antibody-mediated rejection (AMR) due to a memory B-cell response was predicted to be high. Transplant surgery was uneventful with minimal intra-operative blood loss, and the organ incurred a cold-ischemia time of 15 h.

Immunosuppressive therapy for induction consisted of 6 mg/kg of intravenous (IV) antithymocyte globulin given in divided doses over 4 days; tapering doses of IV methylprednisolone given on postoperative days (PODs) 0–4. In addition, 375 mg/m^2 of rituximab was administered on POD 1 to suppress humoral alloimmune response. For maintenance immunosuppressive therapy, the patient began receiving 1,000 mg of oral mycophenolate mofetil twice daily from POD 0. Excellent urine output of 1.3 L was noted in the first 12 h after transplant, and tacrolimus was initiated on POD 1. Tapering doses of oral prednisone were started on POD 5. The serum creatinine levels declined steadily from 7.9 mg/dL (pre-transplant) to 1.9 mg/dL by POD 5, and the patient did not require dialysis.

However, the hemoglobin trended down to 6.8 g/dL (baseline: 9.8 g/dL), and the platelet count gradually decreased to 61,000/μL (baseline: 302,000/μL) by POD 6. Alarmingly, the patient's creatinine rose to 2.9 mg/dL and then to 3.3 mg/dL in the 24-h period between POD 5 and POD 6. Lactate dehydrogenase was elevated at 1,016 U/L (reference range: 313–618 U/L), and haptoglobin was <10 mg/dL (reference range: 30–200 mg/dL). The corre-

sponding tacrolimus trough level was 5 ng/mL. Renal allograft ultrasound demonstrated mildly heterogeneous echotexture of the transplant kidney, and Doppler evaluation of the intraparenchymal vessels showed resistive indices ranging from 0.80 to 0.83. One unit of apheresis platelets was transfused, and the patient underwent an urgent ultrasound-guided renal allograft biopsy. In the 6 h preceding the biopsy, the patient's recorded urine output was 100 mL. The patient's blood pressure remained stable with a systolic blood pressure of approximately 140 mm Hg throughout the hospitalization leading up to the biopsy.

An adequate biopsy sample consisting of 2 cores of cortical tissue exhibiting 26 glomeruli and 4 interlobular arteries was obtained. No immediate biopsy-related complications occurred. The most prominent finding on light microscopic examination was the demonstration of fibrin thrombi involving 1 arteriole and capillary loops in 2 glomeruli (Fig. 1). Isometric cytoplasmic vacuolization of tubular epithelial cells and arteriolar myocytes was also apparent. There was no evidence of microvascular or tubulointerstitial inflammation. C4d was negative by immunofluorescence microscopy. Electron microscopy revealed diffuse swelling of glomerular capillary endothelial cells and cytoplasmic vacuolization of tubular epithelial cells. Histologic correlates of acute AMR were striking in their absence. DSA that were scored positive in the pretransplant serum sample were not detectable in the serum sample tested on the day of the biopsy (HLA B45: pretransplant MFI 3,182 vs. POD 6 MFI 1,438; DQ6: pretransplant MFI 3,082 vs. POD 6 MFI 640). Histopathologic features noted on the renal allograft biopsy, taken together with clinical and laboratory findings, suggested that CNI-induced de novo post-transplant HUS was the most proximate cause of acute oliguric renal failure in this case (Table 1).

Tacrolimus was discontinued. A reversal of the upward trend in creatinine was immediately apparent after withholding the CNI. Creatinine improved to 2.4, 1.8, and 1 mg/dL in the 3 succeeding days. The patient received a transfusion of 1 unit of packed red blood cells after the kidney biopsy following which hemoglobin improved from 6.8 to 8.6 g/dL and steadily improved to 10.1 g/dL in the following 2 weeks. In the same period, a significant improvement in platelet count occurred (61,000–348,000/μL). Substitution of tacrolimus with another CNI, cyclosporine (CsA), was considered, but we favored the introduction of maintenance immunosuppression with a costimulatory blocker, belatacept, instead, given emerging evidence of its efficacy in highly sensitized renal transplant recipients. The first dose of IV belatacept (5 mg/kg) was administered on POD 9 (3 days after the diagnosis of TMA). The patient received 5 mg/kg of IV belatacept every 2 weeks thereafter for 2 months and was then transitioned to a 5 mg/kg once monthly dosing regimen. Twelve months after transplant, she continues to have excellent renal allograft function with a serum creatinine of 0.7 mg/dL and has had no recurrence of hematologic abnormalities. Her most recent hemoglobin and platelet count were 12.3 g/dL and 271,000/μL, respectively (Fig. 2).

Discussion

End-stage renal disease patients who are sensitized to HLA have a prolonged wait for a transplant and a reduced transplantation rate. Recent evidence suggests that live donor renal transplantation after the depletion of donor-specific anti-HLA antibodies provides significant survival benefit when compared to waiting for a compatible organ [12, 13]. However,

some groups have reported an incidence of early post-transplant AMR as high as 40% in recipients of HLA-incompatible kidney transplants [14]. Currently practiced approaches to desensitization in deceased donor transplant recipients include high-dose IV immunoglobulin (Ig) or plasmapheresis with low-dose IV Ig. However, the rate of AMR is higher and graft survival is poorer with these techniques [15]. Our patient with oliguric acute kidney injury 6 days after transplant was broadly sensitized to HLA and had pre-formed DSA to HLA expressed in her deceased donor's kidney. She represented a kidney transplant recipient at high immunologic risk. Given the patient's high pretransplant CPRA and the detection of DSA prior to transplantation, acute AMR was the leading diagnosis. Laboratory evidence of macroangiopathic hemolytic anemia was also not inconsistent with this diagnosis. However, TMA due to CNI-induced toxicity, thrombotic thrombocytopenic purpura, and viral infections were also considered. Since the etiology of the patient's primary renal disease was unknown, recurrent post-transplant atypical HUS (aHUS) and antiphospholipid syndrome were also considered a possibility. Although thrombotic thrombocytopenic purpura, viral infections, and antiphospholipid syndrome were ruled out with relevant laboratory tests, TMA due to aHUS could not be ruled out since the etiology of the end-stage renal disease in our patient was not established prior to transplantation and we did not perform genetic and serologic testing for complement dysregulatory disorders. These tests are not only expensive, but the results would take several days or weeks to be reported and, therefore, would not have ultimately altered the course of management in this case. In addition, the patient had no known family history of aHUS or chronic kidney disease. We believe that the prompt recovery of allograft function soon after substitution of tacrolimus with belatacept adequately eliminated the possibility that histologic findings of TMA were not due to aHUS but were mediated by CNI.

Belatacept is a fully human fusion protein that is composed of the extracellular domain of human cytotoxic T lymphocyte-associated protein-4 (CTLA-4) and the Fc domain of human IgG1. It is a costimulation blocker that suppresses T-lymphocyte activation by binding to CD80 and CD86 and negatively regulating CD28 signaling [16]. It shows promise in improving long-term renal allograft outcomes that has eluded CNIs [17]. However, first-time transplant recipients with PRA >50% and retransplants with PRA >30% were excluded from the trials that eventually led to the approval of belatacept [7, 8]. Our patient had a pretransplant CPRA of 93%. To the best of our knowledge, no data exist regarding the safety and efficacy of use of belatacept as the backbone of initial maintenance immunosuppressive therapy in such highly sensitized patients. Gupta et al. [11] reported successful conversion of 6 highly sensitized patients with CNI toxicity and/or interstitial fibrosis and tubular atrophy from tacrolimus to belatacept at a median time of 4 months after transplantation. They reported an increase in mean glomerular filtration rate without episodes of clinical or subclinical rejection and no development of new DSA. Le Meur et al. [18] reported favorable results after conversion of 25 patients from CNI to belatacept within the first 6 months after transplantation. However, most patients exhibited low immunologic risk. Only 4 harbored DSA.

A higher incidence of rejection associated with the use of belatacept in comparison with cyclosporine has been reported [17]. Fear of rejection has been one of the impediments to more widespread utilization of belatacept [6]. There are various purported reasons for this increased rejection rate. Blockade of the negative signal that is transduced by the engagement of CTLA-4 may be responsible for the heightened risk of rejection. Resistance of

memory T cells to costimulatory blockade and depletion of certain subsets of T-regulatory cells are also thought to contribute to this [6]. A belatacept-based, steroid-free regimen that utilizes induction with T cell-depleting antithymocyte globulin and substitutes the mTOR inhibitor sirolimus for mycophenolate has been shown to achieve low rejection rates [19]. Optimizing belatacept-based regimens to lower rates of rejection while preserving the ability to favorably impact graft/patient survival and glomerular filtration rate remains an important area of research. Therapeutic agents that are efficacious alternatives to CNIs in highly sensitized patients, such as the one described in this report, will be a valuable addition to the therapeutic tools available to the transplant physician. Abrupt-onset oliguria and acute kidney injury on post-transplant day 6 accompanied by macroangiopathic hemolytic anemia posed a diagnostic challenge in this case. In the context of a highly sensitized transplant recipient with pre-existing DSA, although AMR was the most probable scenario, tacrolimus-induced de novo post-transplant HUS, which is a relatively rare occurrence, was the eventual diagnosis. When rejection afflicts belatacept recipients, it appears almost exclusively in the early post-transplant phase [6]. Emerging evidence from animal models suggests that CTLA-4Ig inhibits memory B-cell responses and promotes allograft survival in sensitized recipients [20]. Underscoring this, another demonstrable benefit of belatacept is the lower incidence of de novo DSA [17]. Our patient, who has been receiving belatacept for over 12 months, has remained free of rejection and without detectable new DSA. She serves as a rare, yet valuable, example of a highly sensitized patient that has been successfully converted to a belatacept-based CNI-free regimen.

Statement of Ethics

Informed consent was obtained from the patient.

Disclosure Statement

The authors have no conflicts of interest to declare.

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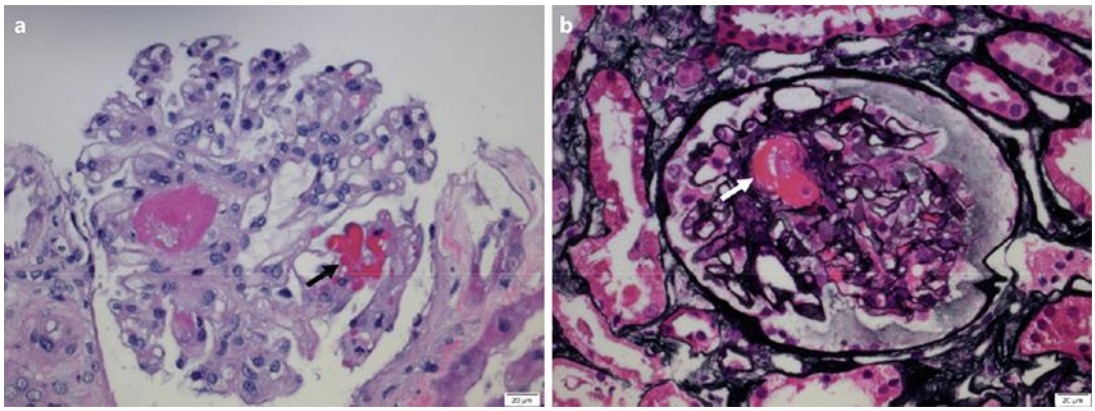
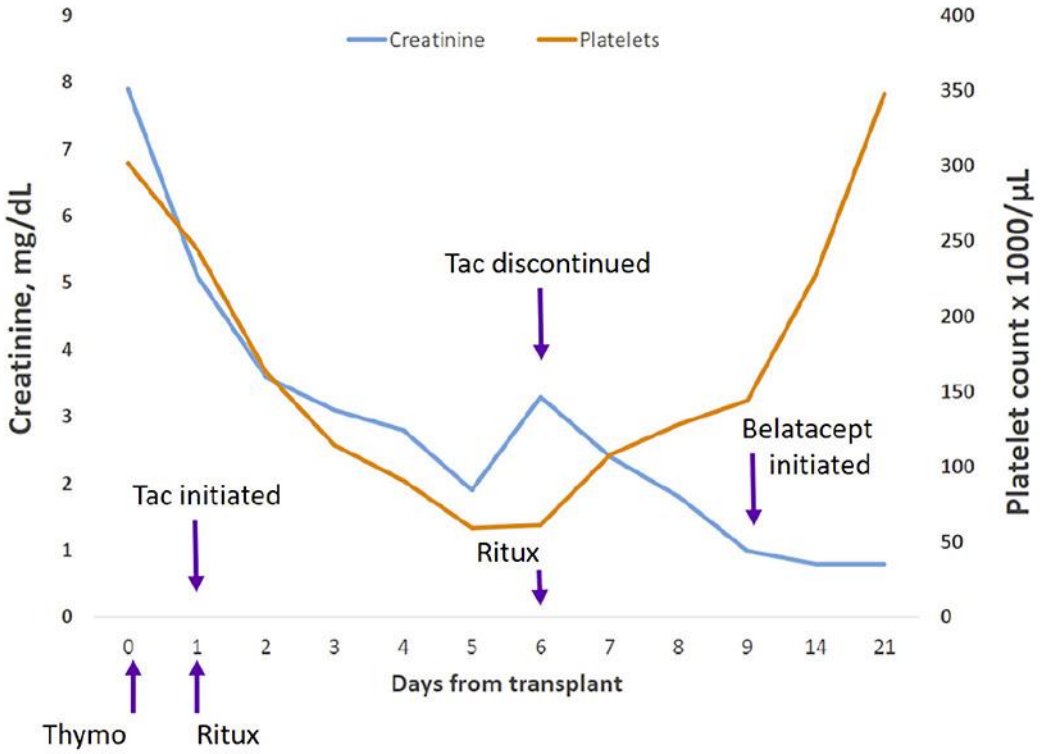


Fig. 1. **a** Hematoxylin and eosin staining of the renal allograft biopsy showing fibrin thrombi in glomerular capillary loops. **b** Jones methenamine silver staining of the renal allograft biopsy showing fibrin thrombi in glomerular capillary loops.



Day	POD 0	POD 1	POD 2	POD 3	POD 4	POD 5	POD 6	POD 7	POD 8	POD 9	POD 14	POD 21
Creatinine	7.9	5.1	3.6	3.2	2.8	1.9	3.3	2.4	1.8	1.0	0.8	0.8
Hemoglobin	9.8	8.2	6.7	8.6	8.2	8.2	6.8	8.6	8.1	8.1	9.3	10.4
Platelets	302	244	163	114	91	59	61	108	128	144	228	348
Tac trough			25.8	8.2	5.7	4.4	5.0	2.5				

Creatinine-mg/dL, Hemoglobin-g/dL, Platelet count- x1000/µL, Tacrolimus trough-ng/ml.

Fig. 2. Graphic and accompanying tabular representation of trends in biochemical, hematologic, and pharmacokinetic parameters and timeline of relevant therapeutic interventions. Tac, tacrolimus; Thymo, antithymocyte globulin; Ritux, rituximab; POD, postoperative day.

Table 1. Laboratory workup for thrombotic microangiopathy

Test	Result
C3, mg/dL[a]	104 (85–165)
C4, mg/dL[a]	32 (14–44)
ADAMTS13, %[a]	66 (>60)
Anticardiolipin Ab (IgG and IgM)[a]	negative
Anti-β2 glycoprotein 1 Ab (IgG and IgM)[a]	negative
ANA[a]	1:40
Anti-dsDNA, IU/mL[a]	1 (<5)
HIV PCR[a]	not detected
BK virus PCR[b]	not detected
CMV PCR[b]	not detected

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; Ab, antibody; ANA, antinuclear antibody; dsDNA, double-stranded DNA; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; CMV, cytomegalovirus. [a] Tests done on the day of renal allograft biopsy. [b] Tests done 2 months after biopsy.