Belatacept conversion in African American kidney transplant recipients with severe renal dysfunction

Heather S Snyder1,2, Benjamin T Duhart, Jr1,2, Amy G Krauss1,2 and Vinaya Rao3

Abstract
Objectives: Conversion from calcineurin inhibitor–based maintenance immunosuppression to belatacept in kidney transplant recipients has been demonstrated to improve renal function while maintaining efficacy against rejection. However, conversion studies to date have excluded patients with an estimated glomerular filtration rate < 35 mL/min/1.73 m².
Methods: We describe two patients with an estimated glomerular filtration rate < 30 mL/min/1.73 m² who underwent conversion from maintenance calcineurin inhibitor to belatacept.
Results: Both patients experienced improvement in renal function following conversion.
Conclusions: These results suggest that patients with more severe degrees of allograft impairment may benefit from conversion of maintenance calcineurin inhibitor to belatacept-based immunosuppression. Larger, randomized studies are warranted to evaluate the impact of such an approach.

Keywords
Belatacept, calcineurin inhibitor nephrotoxicity, kidney transplantation

Introduction
Over the past three decades, implementation of calcineurin inhibitor (CNI)-based maintenance immunosuppression protocols has achieved considerable success in reducing the incidence of acute rejection and increasing 1-year graft survival outcomes following kidney transplantation.¹,² However, proportional improvements in long-term outcomes have not been realized. Renal and cardiovascular toxicity associated with CNI may negatively influence long-term graft and patient survival. Unfortunately, previous CNI withdrawal strategies have resulted in increased rejection rates.³

Belatacept, a costimulation blockade biologic agent, is approved for de novo use in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids for prophylaxis of rejection in low to moderate risk adult kidney transplant recipients.⁴ Due to superior estimated glomerular filtration rates (eGFR) observed with belatacept-based immunosuppression versus cyclosporine in the BENEFIT trials, Rostaing et al. pursued a CNI conversion strategy to maintain efficacy against rejection while avoiding CNI-induced nephrotoxicity. In this randomized trial, stable renal transplant patients with a baseline eGFR ≥ 35 mL/min/1.73 m² were either switched to belatacept or remained on a CNI-based regimen. At 1 and 2 years, the mean change in eGFR from baseline was +7.0 and +8.8 mL/min/1.73 m² in the belatacept group and +2.1 and +0.3 mL/min/1.73 m² in the cyclosporine group.⁵,⁶

Below, we describe the outcomes of CNI conversion to belatacept in two patients with an eGFR < 30 mL/min/1.73 m².

Case presentations
Two African American males (aged 50 and 53 years) with end-stage renal disease (ESRD) secondary to hypertension each received an expanded criteria donor kidney transplant.

1Department of Pharmacy, Methodist University Hospital, Memphis, TN, USA
2College of Pharmacy, University of Tennessee Health Science Center, Memphis, TN, USA
3Methodist University Hospital Transplant Institute and University of Tennessee Health Science Center, Memphis, TN, USA

Corresponding Author:
Heather S Snyder, Department of Pharmacy, Methodist University Hospital, 1265 Union Avenue, Memphis, TN 38104, USA.
Email: Heather.Snyder@MLH.ORG
Both received induction therapy with rabbit antithymocyte globulin (4.5 mg/kg) and methylprednisolone, then were maintained on tacrolimus, mycophenolic acid, and prednisone (tapered to 5 mg/day) following transplant. Both patients had immediate allograft function post-transplant and were noted to be Epstein–Barr virus (EBV) seropositive at the time of transplant.

Patient 1 renal function had peaked approximately 1 month post-transplant with eGFR of 65.8 mL/min/1.73 m² (modification of diet in renal disease (MDRD) equation), then declined over the following 7 months. A biopsy performed at 8 months post-transplant showed mild interstitial fibrosis, tubular atrophy, and arterioles with adventitial hyaline thickening, suggesting CNI toxicity. All prior biopsies were unremarkable. By post-transplant month 13, the patient’s eGFR had stabilized at 26.5 mL/min/1.73 m² which was maintained at 10 months post-transplant.

Table 1. Tacrolimus doses and levels for patient 1.

| Day | Dose                   | Level a |
|-----|------------------------|---------|
| 0   | 10 mg every morning and 9 mg every evening | 6.2     |
| 14  | 10 mg every morning and 9 mg every evening | 8.3     |
| 28  | 9 mg twice daily        | 6.6     |
| 42  | 9 mg twice daily        | 5.9     |
| 56  | 9 mg twice daily        | 5.8     |
| 84  | 7 mg twice daily        | 3.7     |
| 98  | Discontinue            | N/A     |

aTacrolimus level measured in ng/mL.

Patient 2 experienced acute rejection, infections with BK virus, cytomegalovirus (CMV), or EBV nor signs and symptoms of post-transplant lymphoproliferative disorder (PTLD).

Discussion

We described two African American patients up to 13 months from kidney transplant with an eGFR < 30 mL/min/1.73 m² who experienced improvements in renal function following conversion from a tacrolimus-based regimen to belatacept. Study subjects in Rostaing et al.’s 5 trial with a baseline eGFR between 35 and 45, 45 and 60, and >60 mL/min/1.73 m² experienced a mean change in eGFR at 12 months of 3.7, 10, and 5.7 mL/min/1.73 m², respectively. In comparison, our first patient’s eGFR nearly doubled to 47.6 mL/min/1.73 m² at 12 months post-conversion (Δ21.1 mL/min/1.73 m²). The increased physiological change in renal function noted for this patient may have also been related to the resolution of biopsy-proven CNI-induced nephrotoxicity. Unfortunately, a repeat biopsy was not available to confirm this histological resolution.

Table 2. Tacrolimus doses and levels for patient 2.

| Day | Dose                   | Level a |
|-----|------------------------|---------|
| 0   | 9 mg twice daily        | 6.6     |
| 14  | 9 mg twice daily        | 6.6     |
| 28  | 9 mg twice daily        | 6.1     |
| 42  | 5 mg twice daily        | 6.5     |
| 56  | Discontinue            | 4.4     |

aTacrolimus level measured in ng/mL.

Paz et al. 7 utilized belatacept conversion for patients with renal dysfunction and achieved renal recovery, but distinct differences exist. In contrast to our study, there were differences in the patient population, reasons for converting to belatacept, initial dose, and duration of the tacrolimus taper to discontinuation. Sirolimus was also utilized in conjunction with belatacept for maintenance immunosuppression in one case. Gupta et al. 9 reported the renal recovery after belatacept conversion in high-immunologic risk patients with allograft dysfunction. Even though multiple patients were switched to belatacept for complications from delayed graft function and antibody mediated rejection, one patient was diagnosed with...
biopsy-proven CNI toxicity, and belatacept conversion was initiated 9 months post-transplant. This patient also displayed significant renal recovery similar to our results reported for patient 1. In contrast to this study, belatacept conversion occurred approximately 13 months post-transplant and a slower tacrolimus taper was utilized with discontinuation occurring on day 98 and 56, respectively. Previous studies reported discontinuation of tacrolimus within 28–42 days after conversion to belatacept.7–9 Due to our conservative nature, the duration of the tacrolimus taper was elongated in patient 1. Furthermore, many previously reported cases did not achieve a peak eGFR until after belatacept conversion, whereas the cases reported in our study achieved a peak eGFR with a subsequent decline due to CNI-induced nephrotoxicity as confirmed by biopsy results.

Belatacept blocks the B7/CD28 co-stimulatory pathway and inhibits T-cell activation which allows for CNI withdrawal. Conversion from a CNI-based regimen to belatacept may provide long-term benefits in kidney transplant recipients by preserving allograft function.5,6 CNI have been associated with increased expression of proteins such as p16INK4α related to cellular senescence and chronic allograft nephropathy. In contrast, this biomarker was shown not to increase after 12 months of belatacept treatment which has been suggested as a possible mechanism of graft function preservation.10

CNI may also exacerbate cardiac risk factors such as hypertension, hyperlipidemia, and diabetes that contribute to cardiovascular death with a functioning graft, a major cause of long-term patient and graft loss.11,12 In a 5-year follow-up study, kidney transplant patients receiving belatacept were shown to have a more favorable cardiovascular risk profile compared to patients receiving cyclosporine.13 Therefore, improving preservation of renal function may indirectly benefit overall cardiovascular risk and long-term outcomes in kidney transplant recipients.

The results of our case report suggest that African American patients with an eGFR less than 30 mL/min/1.73 m² may benefit from conversion to belatacept. It is unclear whether the renal recovery in kidney recipients after belatacept conversion is dependent upon the indication, time of initiation post-transplant, or the duration of the tacrolimus taper. However, larger, randomized, long-term studies are necessary to further evaluate the potential benefits of belatacept conversion and to further identify which patients could most benefit from such an approach.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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

References
1. Hariharan S, Johnson CP, Bresnahan BA, et al. Improved graft survival after renal transplantation in the United States, 1988 to 1996. N Engl J Med 2000; 342: 605–612.
2. Meier-Kriesche HU, Schold JD, Srinivas TR, et al. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. Am J Transplant 2004; 4: 378–383.
3. Budde K, Becker T, Arns W, et al. Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomized, controlled trial. Lancet 2011; 377: 837–847.
4. Bristol-Myers Squibb Co. Nujolix® (belatacept) (package insert). Princeton, NJ: Bristol-Myers Squibb Co., 2013.
5. Rostaing L, Vincenti F, Grinyó J, et al. Long-term belatacept exposure maintains efficacy and safety at 5 years: results of a phase III study in kidney transplant recipients with allograft dysfunction. Am J Transplant 2015; 15: 2726–2731.
6. Furuzawa-Carballeda J, Lima G, Alberú J, et al. Infiltrating cellular pattern in kidney graft biopsies translates into forkhead box protein 3 up-regulation and p16INK4α senescence protein down-regulation in patients treated with belatacept compared to cyclosporin A. Clin Exp Immunol 2014; 167: 330–337.
7. Miller LW. Cardiovascular toxicities of immunosuppressive agents. Am J Transplant 2002; 2: 807–818.
8. Meier-Kriesche HU, Baliga R and Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. Transplantation 2003; 75: 1291–1295.
9. Rostaing L, Vincenti F, Grinyó J, et al. Long-term belatacept exposure maintains efficacy and safety at 5 years: results from the long-term extension of the BENEFIT study. Am J Transplant 2013; 13: 2875–2883.