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

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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 m^2.

Methods: We describe two patients with an estimated glomerular filtration rate < 30 mL/min/1.73 m^2 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

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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 verses 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 m^2 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 m^2 in the belatacept group and +2.1 and +0.3 mL/min/1.73 m^2 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 m^2.

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.

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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

[a]Tacrolimus level measured in ng/mL.

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

[a]Tacrolimus level measured in ng/mL.

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 m^2 (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 m^2 and he was converted to belatacept 5 mg/kg on days 1, 15, 29, 43, and 57, and then every 28 days thereafter. Tacrolimus dosing was maintained to achieve a goal trough of 6–8 ng/mL for 4 weeks and was tapered off by week 14 (Table 1). The patient continued on mycophenolic acid and prednisone throughout the conversion period and thereafter. His renal function began to improve within 6 weeks of conversion. His eGFR increased to 47.6 mL/min/1.73 m^2 at 12 months post-conversion. It further improved to 54.6 mL/min/1.73 m^2 and was maintained by 15 months post-conversion.

Renal function of patient 2 improved over 3 months following transplant to an eGFR of 33.4 mL/min/1.73 m^2; but his renal function started to decline over the following 7 months. The biopsy from post-transplant month 7 showed interstitial fibrosis, tubular atrophy, and small artery intimal fibrosis with moderate arteriolar hyalinosis. All prior biopsies were unremarkable. By post-transplant month 10, the patient's renal function had stabilized with an eGFR of approximately 28 mL/min/1.73 m^2 and he was converted to belatacept. The same belatacept, tacrolimus taper, mycophenolate, and prednisone dosing protocol was followed as in the previous patient (Table 2). The patient's renal function started to improve within 6 weeks of conversion and then stabilized at eGFR of 36.4 mL/min/1.73 m^2 which was maintained at 10 months post-transplant.

Although no specific infectious prophylaxis was reinstated, viral surveillance was conducted. Neither patient 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 m^2 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 m^2 experienced a mean change in eGFR at 12 months of 3.7, 10, and 5.7 mL/min/1.73 m^2, respectively. In comparison, our first patient's eGFR nearly doubled to 47.6 mL/min/1.73 m^2 at 12 months post-conversion (Δ21.1 mL/min/1.73 m^2). 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. The eGFR of patient 2 also improved to 36.4/mL/min/1.73 m^2 at 156 days post-conversion (Δ8.4mL/min). Decreased renal benefit in the second patient may have been due to the presence of greater interstitial fibrosis on initial biopsy prior to belatacept conversion. Previous reports also included patients who were converted from CNI due to suspected CNI-induced nephrotoxicity or the presence of fibrosis on the initial biopsy; however, most conversions to belatacept occurred within 30 days post-transplant and were initiated for prolonged delayed graft function.[7,8] When belatacept conversion is utilized in kidney recipients for delayed graft function, it may be difficult to ascertain the effect of the conversion versus the natural resolution of the allograft dysfunction.

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 p16INK$^{4\alpha}$ 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 m^2 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.

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