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Research Article

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Side Effect Driven Conversion to Belatacept for Kidney Transplant Recipients in a Clinical Setting

Elizabeth Cohen[1], Richard N Formica[2], and Ramesh K Batra[3]*

[1]*Transplant Data Administrator, Yale New Haven Transplant Center, New Haven, CT USA*

[2]*Professor of Medicine and Surgery, Yale University School of Medicine, New Haven, CT, USA*

[3]*Assistant Professor of Surgery, Yale University School of Medicine, New Haven, CT, USA*

***Corresponding author:**
Ramesh K Batra Assistant Professor of Surgery, Yale University School of Medicine, Yale New Haven Hospital, New Haven, CT – 06520, USA, E-mail: drrkbatra@gmail.com

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Abstract

Maintenance immunosuppression after kidney transplantation is critical to graft and patient survival. However, the optimal immunosuppressive medication may differ for patients based on adverse effects. Here we report one-year outcomes of 73 kidney transplant patients converted from tacrolimus to belatacept because of adverse effects at least 90 days after transplant.

Keywords: Kidney transplant, Tacrolimus, Rejection, Immunosuppression, Chronic Allograft Nephropathy, Neurotoxicity

Introduction

The early success of kidney transplantation relied on overcoming, a. the technical challenge of successful engraftment and b. the immunologic barrier by avoiding early rejection. However, the level of immunosuppression had to be balanced with toxic side effects of medication. Thus it was recognized that ideal immunosuppression for kidney transplant recipients was based on a balance between preventing rejection and avoidance of infections, malignancies and other immunosuppressive medication related side effects.

Over time, graft loss decreased in part due to the discovery and FDA approval of calcineurin inhibitors (CNIs), cyclosporine A (CsA) and tacrolimus (TAC) in 1983 and 1997 respectively. Since then, CNIs formed the backbone for immunosuppressive regimens amongst most kidney transplant programs in USA [1]. Despite these advancements with immunosuppression in kidney transplantation, CNIs only benefitted short-term outcomes, as their associated chronic nephrotoxicity formed the Achilles' heel to further prolonging graft and patient survival after a kidney transplant [2].

Chronic allograft nephropathy, a term defining late graft failure due to many factors is largely attributed to CNI related nephrotoxicity [3]. Hence, the toxic effects of CNIs have to be closely monitored to balance graft and patient survival. Amongst CNIs, TAC based regimens are more popular than CsA due to lesser nephrotoxicity and greater potency [4]. But TAC in turn is associated with more neurotoxic and gastrointestinal side effects and new onset diabetes for the patients than CsA [5]. Furthermore, there are several direct and indirect metabolic side effects of TAC, affecting patient survival due to cardiac events, a risk far greater than the risk of graft failure due to chronic allograft nephropathy.

Besides minimizing CNI exposure, selective and careful avoidance of CNI after kidney transplant helps in the management and prevention of chronic allograft nephropathy, by either switching from CNI to another alternative due to toxic side effects, or a using a de novo agent to avoid CNI altogether. Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression (BENEFIT) and Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial-Extended criteria donors (BENEFIT-EXT), the two 3 year phase III studies, found lesser nephrotoxicity with belatacept over cyclosporine and also demonstrated improvement in the metabolic and cardiovascular profiles of recipients of a living donor, Standard Criteria Donor (SCD) and Extended Criteria Donor (ECD) derived kidney allografts [5-7]. These studies have relatively long follow-up in transplant literature and offer a ray of hope for longer patient survival after kidney transplant.

TAC based immunosuppression has been the standard choice after kidney transplants at our center following the national trend. However, when our kidney transplant patients have encountered toxic effects of CNIs, we have elected to switch certain subset of those patients to belatacept, following a need-based approach. As our experience with belatacept grows to include more patients over time, we performed this retrospective study at our center to illustrate the non-renal indications for conversion to belatacept over TAC in kidney transplant patients and potential neurologic and metabolic benefits.

Methods

A retrospective chart review was performed of kidney transplant recipients at our center who converted from TAC to belatacept for

any reason with at least one year of follow-up from the date of conversion. Patients were included if they were over the age of 18 and converted to belatacept at least 90 days post kidney transplant as patients converted earlier followed a different conversion protocol and tacrolimus taper. Exclusions included 1. Patients who received no belatacept 2. Patients who received belatacept as de novo immunosuppression 3. Patients who received belatacept within 90 days of transplant 4. Patients included in other study protocols 5. Patients who converted from other immunosuppression besides TAC to belatacept. The primary outcome measure was the indication for conversion to belatacept. Secondary outcomes included change in metabolic parameters including serum magnesium, sodium, cholesterol, triglycerides, hemoglobin A1C, reason for discontinuation of belatacept, and documented improvement in the indication for belatacept conversion.

Charts were reviewed at baseline, one month, and then quarterly post-conversion to belatacept. Transplant demographics, indication for conversion, serum creatinine, magnesium, glucose, hemoglobin A1C, blood pressure, cholesterol, weight, infection, cancer, and adverse effects were collected. Missing data points were treated as no value. Descriptive statistics were used for demographics. Rates were reported as medians with the range. Student's paired t-test was used for continuous data including serum-magnesium, sodium, cholesterol, triglycerides, and hemoglobin A1C.

Results

Our program's belatacept dosing strategy for conversion is 5mg/kg every two weeks for the first six doses, then every four weeks thereafter. At the same time, the patient's TAC dose is halved at two weeks post conversion and discontinued at four weeks after conversion. TAC levels are not monitored during the conversion time period.

At the time of analysis, 113 patients were converted to belatacept who had at least one year of follow-up. Of these, 40 patients were excluded, leaving 73 patients reported here (Figure 1). Baseline demographics are reported in (Table 1). The median time from transplant to conversion was 22.2 months (range 3 – 192 months). Primary and secondary indications for conversion are demonstrated in (Figure 2) with the most common reason being neurotoxicity, manifested as tremors or short-term memory loss as reported by transplant nephrologist; many patients had more than one reason for conversion.

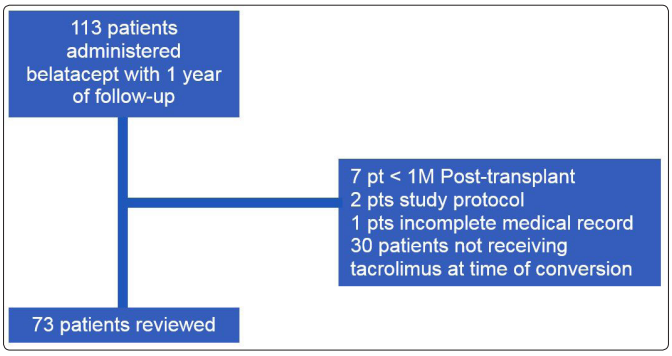

Figure 1: Patient Inclusion

Demographics	
	Total (N = 73)
Age (median, range)	55 (23 - 78)
Male (n,%)	36 (49.3%)
Median time post-transplant to conversion (months, range)	22.2 (3 - 192)
No. of Patients < 1 year post-transplant	21 (28.8%)
Type of transplant (n,%)	
LUKT	28 (38.4%)
LRKT	16 (21.9%)
DDKT	29 (39.7%)
Immunosuppression	
MMF + pred	58 (79.5%)
MMF	7 (9.6%)
pred	2 (2.7%)
Aza + pred	6 (8.2%)

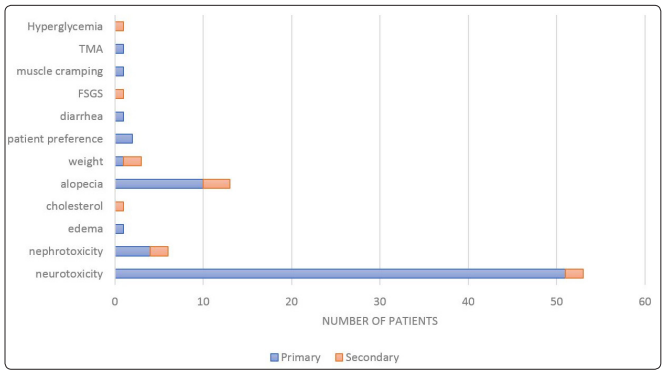

Figure 2: Indication for Conversion to Belatacept Primary and Secondary

Average serum magnesium at the time of conversion was 1.7mg/dL and increased to 2.0mg/dL ($p < 0.05$) one year post-conversion (Figure 3). Other metabolic markers were not significantly changed after conversion (Table 2).

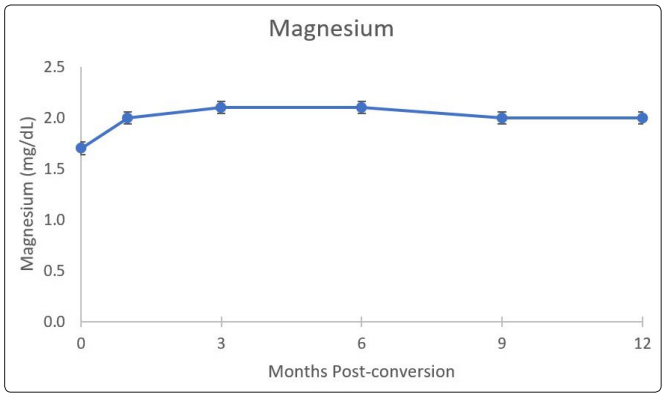

Figure 3: Magnesium changes after belatacept conversion

Table 2: Metabolic Changes

	Prior to conversion	> 3 months after conversion
Magnesium (mg/dL)*	1.7	2
Sodium (mmol/L)	140	140
Total Cholesterol (mg/dL)	185	187
Triglycerides (mg/dL)	127	140
Hemoglobin A1c (%)	6.1	6.2
Creatinine Clearance (mL/min)	52.5	56
Creatinine (mg/dL)	1.4	1.2

*$p < 0.05$

Seven patients (9.6%) failed conversion-requiring return to their original immunosuppressant or an alternative agent (Table 3). This was primarily related to adverse effects (5.5%) including infusion related reactions. Only one (1.4%) patient required switch to an alternative immunosuppressant due to acute cellular rejection, which resolved upon switch to CNI. Of the 66 patients who remained on belatacept, 58 (88%) had improvement in symptoms following the switch to belatacept.

Table 3: Belatacept Conversion Failures

Indication	n (%)
Adverse Drug Effect	4 (5.5%)
Deceased	2 (2.7%)
Rejection	1 (1.4%)

There were two deaths (2.7%) due to cardiac arrest in patients with known cardiac disease, one patient aged 74 and one-aged 58, both with a magnesium level of 1.9 mg/dL, thought to be unrelated to immunosuppression or transplant. We had no cases of post-transplant lymphoproliferative disorder (PTLD) within one year of conversion.

Discussion

In this manuscript, we report positive outcomes converting patients to belatacept from TAC in an active clinical setting. Most of our patients were converted for reasons other than nephrotoxicity due to CNI and to our knowledge; we are the first group to report large numbers on conversion to belatacept for a non-renal indication. As belatacept is not FDA approved for conversion, there is no approved conversion dosing protocol. Although our dosing strategy differs from others published in the literature, we have had no reason to alter this dosing and have not had issues in obtaining insurance coverage for belatacept [8-11].

Neurotoxicity is commonest amongst the early complications of immunosuppression following organ transplant. Neurotoxicity due to CNIs is as high as 20-40%, with TAC being more neurotoxic than CsA [5, 12]. CNI related neurotoxic features are increased in the presence of multiple factors including i).steroids, ii). Low cholesterol-, which increases free drug concentrations of CNIs, damaging the blood-brain barrier by higher expression on the LDL receptor of astrocyte cell membrane, and iii). Hypomagnesemia, amongst others. The neurologic complications are therefore unsurprisingly more pronounced in the early post-transplant phase due to higher dose of corticosteroids. However, once steroids are tapered down, the disabling neurologic complications are solely attributed to the CNIs. The neurotoxic effects could be central or peripheral in distribution. More common manifestations are tremors, headache, insomnia, memory loss and less commonly, but more severly, seizures. These symptoms may compromise the quality of life after organ transplant, and are reversible by either discontinuing or changing the CNI.

In our patient cohort, neurologic complications due to their disabling nature was the most common reason for the switch from TAC to belatacept. The most common central neurotoxic feature was memory loss, which occurred in 36 patients (49%) who were converted to belatacept, of which 97%, i.e. 35 patients had complete resolution of symptoms. 26 (36%) patients reported tremors as their neurologic complication, with all patients reporting improvement after converting to belatacept. All of these reports were subjective reporting by the transplant nephrologist and patient report, without specific testing evaluating neurocognitive effects or tremors. We acknowledge that a limitation to our study is that it is retrospective, without a control arm. Thus, we cannot conclude that the improvement in symptoms was due to conversion to belatacept. Further prospective studies with a tacrolimus arm would be helpful to draw further conclusions.

Although 88% of patients saw improvement in their indication for conversion to belatacept, with the most common indication being neurotoxicity, patients potentially saw additional metabolic benefits that were not the original reason for conversion. As more data is available for belatacept and non-renal indications for conversion, providers should also consider the metabolic benefits as an indication for conversion.

Cardiovascular disease is the leading cause of death in 40-55% of patients following a kidney transplant, more so than the general population [13, 14]. Although the increased cardiovascular morbidity and mortality could be attributed to the duration of dialysis pre-transplant or the natural history of the cause of renal failure prior to transplant i.e. diabetes or hypertension. Immunosuppressant medications further add to the cardiovascular risk and increases the incidence of cardiovascular disease through hyperlipidemia, new onset diabetes, hypertension and coronary vessel remodeling [15]. Therefore, patient death accounts for 40% of kidney allograft loss, i.e. death with a functioning graft, in long-term follow-up studies [16].

TAC aids in the development of metabolic syndrome and new onset diabetes by impairing glucose tolerance [17]. TAC also independently and significantly increases plasma triglyceride concentration whilst also reducing the lipoprotein lipase concentration [18]. Belatacept in BENEFIT and BENEFIT-EXT trials only had a slight improvement in the dyslipidemia at baseline when compared to CsA [19]. Although, our results are with conversion to belatacept from TAC, unlike the BENEFIT or BENEFIT-EXT trial of de novo belatacept use, we also did not see any benefits to the lipid profile when patients were switched from TAC to belatacept. However, due to the retrospective nature of our study, we have missing data points weakening our conclusions regarding belatacept and lipid profile.

Magnesium, directly or indirectly affects all the listed criteria of metabolic syndrome, causing vascular atherogenesis from the impairment of both glucose and lipid metabolism which explains the high cardiovascular risk associated with magnesium deficiency.

A recent systematic review and meta-analysis have observed similar results, whereby, with an increment of 0.2mmol/L of circulating magnesium ions, there was a 30% lowered risk of cardiovascular death [20]. In the patients described here, we saw the average magnesium increase by 0.3mg/DL, potentially conferring benefits with regard to cardiovascular death, but the one-year follow-up may be too short a duration to see the potential cardiovascular benefits.

CsA and TAC both lead to hypomagnesemia due to renal magnesium losses [21, 22]. This impact is pronounced when TAC levels are high and much reduced when the dose is lowered or entirely resolved when changed to another alternative like a mTOR inhibitor, sirolimus [22-24]. In our experience, belatacept positively and significantly impacted on the magnesium levels after patients were switched over from TAC. We believe that although our median time to switch was 22 months, the impact could have been even larger, if the switch to belatacept was performed in the earlier post-transplant period whereby TAC levels are kept much higher. It is also noteworthy, that no change in magnesium supplementation was done during the one year following the conversion.

PTLD was a concern in both BENEFIT and BENEFIT-EXT trial. Although in BENEFIT trial, PTLD developed in high-risk patients i.e. EBV negative patients or patient who received T-cell depleting therapy, but such was not the case in BENEFIT-EXT trial [11, 12]. However, a Cochrane systematic review after reviewing 4 studies showed no change in the risk of PTLD with belatacept vs CNI treated patients in both EBV seronegative or seropositive states [25]. In our patient cohort also, with the switch to belatacept from CNI, there was no incidence of PTLD for 12 months following conversion.

There were 4 patients who had infusion related reactions leading to discontinuation of belatacept. This is a higher rate than that was reported in BENEFIT or BENEFIT-EXT and they did not report discontinuations [6, 7]. As our experience with belatacept has continued, our center has not continued to see this rate of adverse effects related to the infusion.

We conclude that the safety profile of belatacept, without the added infection or PTLD risks, is vitally important for long-term patient survival by minimizing the metabolic and cardiovascular risk factor of renal transplant patients who are at an inherently higher risk of cardiovascular deaths due to the natural history of their renal disease.

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