



## ORIGINAL ARTICLE

# Conversion from tacrolimus to belatacept improves renal function in kidney transplant patients with chronic vascular lesions in allograft biopsy

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## ABSTRACT

**Background.** Conversion from tacrolimus to belatacept has been shown to be beneficial for an increasing number of kidney transplant (KT) patients. Predicting factors for favorable outcomes are still unknown. We aimed to investigate whether histological vascular lesions at the time of conversion might correlate with greater improvement in renal function post-conversion.

**Methods.** The study was conducted on a retrospective cohort of 34 KT patients converted from tacrolimus to belatacept. All patients underwent an allograft biopsy prior to conversion. We analyzed the evolution of the estimated glomerular filtration rate (eGFR) at 3 and 12 months after conversion.

**Results.** Median time to conversion was 6 (2–37.2) months post-transplant. About 52.9% of patients had moderate-to-severe chronic vascular lesions (cv2–3). We observed an increase in eGFR in the whole cohort from 35.4 to 41 mL/min/1.73 m<sup>2</sup> at 3 months (P = 0.032) and 43.7 at 12 months (P = 0.013). Nine patients experienced acute rejection post-conversion, with one graft loss observed beyond the first year after conversion. Patients with cv2–3 had significant improvement in eGFR at 12 months (+8.6 mL/min/1.73 m<sup>2</sup>; 31.6 to 40.2 mL/min/1.73 m<sup>2</sup>; P = 0.047) compared with those without these lesions (+6.8 mL/min/1.73 m<sup>2</sup>; 40.9 to 47.7 mL/min/1.73 m<sup>2</sup>; P = 0.148).

**Conclusions.** Conversion from tacrolimus to belatacept has a beneficial effect in terms of renal function in KT patients. This benefit might be more significant in patients with cv in the biopsy.

**Keywords:** creatinine clearance, immunosuppression, kidney transplantation, renal biopsy, tacrolimus

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## INTRODUCTION

Although calcineurin inhibitors (CNIs) represent the cornerstone of therapy for kidney transplant (KT) recipients, they are associated with significant adverse events, including nephrotoxicity [1]. The dose-dependent vasoconstriction of afferent arterioles is the primary mechanism responsible for acute reduction in glomerular filtration rate (GFR) by both tacrolimus and cyclosporine, whereas interstitial fibrosis and arterial hyalinosis are thought to be related to chronic CNI nephrotoxicity [2, 3]. Histological data from surveillance renal allograft biopsies have demonstrated the presence of lesions compatible with CNI-induced nephrotoxicity in 50% of KT recipients at 2 years and 100% at 10 years after transplantation [4]. CNI nephrotoxicity is potentially enhanced in patients who receive kidneys from elderly donors with preexisting intrarenal vascular lesions [1]. Given the lack of improvement in long-term KT outcomes and the roles of CNIs in some forms of chronic allograft nephropathy [3], efforts have been targeted to new immunosuppression (IS) regimens with CNI avoidance. *De novo* belatacept has shown a benefit in renal function both with standard criteria donors [5] and expanded criteria donors [6]. As belatacept is not associated with nephrotoxicity and has several other advantages compared with CNIs, such as fewer metabolic complications, it has also emerged as a rescue therapy in cases where CNI withdrawal may be considered beneficial. Late conversion (>6 months after KT) from CNI to belatacept has shown a gain in estimated GFR (eGFR) [7] that persists in medium-term follow-up [8]; some reports with early conversion [9–12] point to the same benefit. However, improvement in renal function is not universal for all patients and factors related to a better response after belatacept conversion are still unknown [13, 14]. As CNI nephrotoxicity seems to be more prominent in allografts with previous vascular lesions, we aimed to compare patients whose biopsies presented with moderate-to-severe vascular lesions with those who did not have these lesions, to clarify the potential benefit after belatacept conversion with a subsequent CNI withdrawal.

## MATERIALS AND METHODS

### Study design and patients

We conducted a retrospective study that analyzed all KT recipients who were converted from tacrolimus to belatacept in our center between January 2014 and November 2017. All patients who had received belatacept were consecutively identified through electronic medical record-based information. Patients without an allograft biopsy prior to conversion ( $n=2$ ) were excluded. Demographics, lab tests and clinical data were collected, as well as histological information according to Banff 2013 criteria [15]. Patients were divided into two groups according to their findings of chronic vascular lesions (cv) in the biopsy: (i) patients with absence or mild cv0–1 and (ii) patients with moderate–severe cv2–3. Patients with clinically suspected acute allograft rejection underwent a kidney biopsy and were treated per protocol at our center.

### Outcomes

Our primary outcome was the change in eGFR estimated by the Modification of Diet in Renal Disease-4 from time of conversion to 3 and 12 months post-conversion. Secondary outcomes were acute rejection after conversion, proteinuria, blood pressure and glycemic control. Safety outcomes as infections or *de novo*

neoplasm, as well graft and patient survival, were recorded. The median time of follow-up in the whole cohort was 26.5 [interquartile range (IQR): 18–36.5] months. Two patients were lost to follow-up (one per group) before the 12-month time-point.

### Conversion protocol

Belatacept (5 mg/kg) was administered intravenously on Days 1, 15, 29, 43 and 57, and then every 28 days thereafter. Tacrolimus dose was reduced by 25% weekly and was off by Day 29 and thereafter. Any adjunctive immunosuppressive or corticosteroid treatments that patients were receiving before conversion were maintained unless modification was medically necessary.

### Statistical analyses

Statistical analyses were performed using Stata<sup>®</sup>13 software (StataCorp LP, College Station, TX, USA). The tests were two-sided, with a Type I error set at  $\alpha=0.05$ . The baseline characteristics are presented as mean ( $\pm$  SD) or median (IQR) values according to the statistical distribution for continuous data and percentages for categorical parameters. Comparisons of patient characteristics between independent groups were conducted using the Chi-squared test for categorical variables and Student's t-test or the Mann–Whitney U test for quantitative parameters (homoscedasticity verified using Fisher–Snedecor test). Paired t-test or Wilcoxon test was done for comparisons between same patients before and after conversion, according to variable distribution.

## RESULTS

We identified a total of 34 patients who met predefined inclusion criteria: 16 patients had cv0–1 and 18 patients had cv2–3 pre-conversion. In the whole cohort of patients that converted to belatacept, the mean age was 49.6 years and 61.8% of patients were male. Kidney allografts were received from standard criteria donors in 32.4% cases, expanded criteria in 11.8%, donors after cardiac death in 11.8% and living donors in 44.1%. Re-transplants accounted for 29.4% of the patients; 20.6% had a calculated panel reactive antibody (cPRA) (Class I and/or II) over 30%; and 17.6% had positive donor-specific antibodies (DSAs) at the time of transplantation. The incidence of acute rejection prior to conversion was 14.7%. Median time to conversion was 6 (2–37.2) months post-transplantation, and mean eGFR at the time of conversion was 35.4 mL/min/1.73 m<sup>2</sup>. The reason for conversion was graft-biopsy-based in >80% of patients: 26.5% had acute tubular necrosis; 14.7% glomerular hypoperfusion; 35.3% cv; and 5.9% thrombotic microangiopathy. Moderate-to-severe cv2–3 was present in 52.9% of the patients' renal biopsies prior to conversion. Patients with vascular lesions were older, received a kidney from an older donor and a higher percentage of patients received basiliximab induction therapy. No other differences were noticed between these patients and those without vascular lesions in the graft biopsy. Baseline characteristics of both patient groups and the whole cohort are shown in Table 1.

We observed a significant increase in eGFR in the whole cohort at 3 and 12 months. At 3 months, the eGFR improved from 35.4 to 41 mL/min/1.73 m<sup>2</sup> ( $P=0.032$ ). Data were available for 32 patients at 12 months and the eGFR improved from 36 to 43.7 mL/min/1.73 m<sup>2</sup> ( $P=0.013$ ). Patients with cv2–3 prior to conversion had a substantial increase in eGFR (31–38.7 mL/min/1.73 m<sup>2</sup> at 3 months in 18 patients,  $P=0.034$  and 31.6–40.2 mL/

Table 1. Baseline and demographic characteristics

	All patients (n = 34)	Absence of cv0-1 (n = 16)	Presence of cv2-3 (n = 18)	P-value <sup>a</sup>
<b>Recipient characteristics</b>				
Age, mean (SD) (years)	49.5 (16.2)	40.7 (12.5)	57.3 (15.4)	0.002
Gender (female, %)	38.2	31.3	44.4	0.332
BMI [mean (SD)]	29.5 (6)	29.5 (5.9)	29.6 (6.3)	0.946
<b>Race (%)</b>				
Caucasian	55.9	56.3	55.6	0.935
African-American	29.4	31.3	27.8	
Hispanic	14.7	12.5	16.7	
Diabetes mellitus (%)	17.6	6.3	27.8	0.116
<b>Cause of ESRD (%)</b>				
Vascular	2.9	0	5.6	
Diabetic nephropathy	11.8	6.3	16.7	0.597
Glomerulonephritis	50	62.5	38.9	
Interstitial	23.5	25	22.2	
PKD	5.9	0	11.1	
Unknown	5.9	6.3	5.6	
<b>Donor characteristics</b>				
Age, mean (SD) (years)	44.5 (14.9)	34.8 (14.8)	52.2 (9.8)	0.001
<b>Type of donor (%)</b>				
Standard criteria donor	32.4	37.5	27.7	0.791
Expanded criteria donor (KDPI >85%)	11.8	6.3	16.6	
Donor after cardiac death	11.8	12.5	11.1	
Living donor	44.1	43.8	44.4	
<b>Transplant characteristics</b>				
Patients with a previous KT (%)	29.4	37.5	22.2	0.275
Patients with a cPRA (Class I or II) > 30% (%)	20.6	12.5	27.8	0.357
Patients with pretransplant DSA (%)	17.6	12.5	23.5	0.358
Cold ischemia time, mean (range) (h)	8.9 (0.3-25)	7.7 (0.3-25)	9.9 (0.8-20)	0.295
<b>Induction IS (%)</b>				
Basiliximab	37.5	18.8	50	0.03
Thymoglobulin	62.5	81.3	50	
<b>Maintenance IS (%)</b>				
Tacrolimus	100	100	100	0.652
Steroids	88.2	87.5	88.2	0.591
Mofetil mycophenolate	91.2	87.5	94.1	
Delayed graft function	32.4	25	38.8	0.314
<b>Rejection pre-conversion (%)</b>				
ACR	0	0	0	0.559
cABMR	14.7	12.5	16.7	
Post-transplant diabetes mellitus (%)	14.7	12.5	16.7	0.559
<b>Conversion post-transplant</b>				
Time of conversion, median (IQR) (months)	6 (2-37.2)	5 (2-20.5)	11 (2.7-42)	0.403
eGFR at the time of conversion, mean (SD) (mL/min/1.73 m <sup>2</sup> )	35.5 (20.2)	40.4 (22.8)	31 (17.1)	0.181
<b>Reason for conversion (%)</b>				
<b>Biopsy-related</b>				
Acute tubular injury	26.5	37.5	16.7	
Glomerular hypoperfusion	14.7	25	5.6	0.260
Chronic vascular damage	35.3	18.8	50	
Thrombotic microangiopathy	5.9	0	11.1	
<b>Patient-related</b>				
Lack of adherence to tacrolimus	5.9	6.3	5.6	
Clinical side effect of tacrolimus	5.9	6.3	5.6	
Tacrolimus trough at the time of conversion, mean (SD) (ng/mL)	5.9 (2.9)	6 (3.6)	5.7 (2.3)	0.742
<b>Maintenance IS (%)</b>				
Steroids	91.2	87.5	94.1	0.591
Mofetil mycophenolate	91.2	87.5	94.1	0.591
Acute rejection post-conversion (%)	26.5	25	27.7	0.311
<b>Follow-up</b>				
Time of follow-up, median (IQR) (months)	26.5 (18-36.5)	31 (18-37.5)	25 (21-35.7)	0.851

<sup>a</sup>Analysis between patients with and without cv.

BMI, body mass index; ESRD, end-stage renal disease; PKD, polycystic kidney disease; KDPI, kidney donor profile index; cABMR, chronic antibody mediated rejection.

min/1.73 m<sup>2</sup> at 12 months in 17 patients,  $P=0.047$ ) compared with those who did not have these lesions (40.4–43.6 mL/min/1.73 m<sup>2</sup> at 3 months in 16 patients,  $P=0.408$  and 40.9–47.7 mL/min/1.73 m<sup>2</sup> at 12 months in 15 patients,  $P=0.148$ ) (Table 2). This benefit was more significant early after the conversion, with an increase in eGFR that plateaued after 3 months.

When we analyzed other clinical outcomes, we did not find any difference in glycemic or blood pressure control among patients converted to belatacept. We did not find any significant change in proteinuria after conversion (Table 3). Nine patients suffered from acute rejection after the conversion: eight were acute cellular rejection (ACR) (five Grade IA–B; two Grade IIA; and one Grade IIB) and treated with steroids (plus antithymocyte globulin in the IIB case), and one patient had antibody-mediated rejection. Mean time to rejection was  $6.2 \pm 4.4$  months post-conversion. All patients kept receiving belatacept despite the acute rejection although two patients restarted low-dose tacrolimus. One patient returned to dialysis >1 year after conversion. He was from the group without severe vascular lesions on biopsy but had a history of rejections and DSA development prior to conversion due to noncompliance. No biopsy was performed prior to graft failure. Three patients had infections after the conversion: one cytomegalovirus (CMV) viremia, one BK viremia and one patient developed multiple episodes of urinary tract infection. No organ solid cancer or lymphoproliferative disorder or patient death was observed during the follow-up period.

## DISCUSSION

CNI nephrotoxicity can be more severe in kidneys from elderly donors and preexisting vascular lesions. Knowing the factors that might predict potential responders to belatacept conversion would allow practitioners to better individualize IS. In this study, we show how patients with moderate-to-severe cv in their allografts have a greater benefit in kidney function after

belatacept conversion and tacrolimus withdrawal than those without these lesions.

We use the term 'CNI nephrotoxicity' to define a broad spectrum of histological lesions caused by two different but linked mechanisms: acute and chronic nephrotoxicity. While acute CNI nephrotoxicity is responsible for a reduced GFR and tubular dysfunction in a CNI dose-dependent and reversible manner [16], chronic nephrotoxicity is thought to be associated with interstitial fibrosis and arterial hyalinosis [2, 3]. Multiple factors contribute to the variable intensity of CNI nephrotoxicity, including donor age, preexisting vascular lesions, cold ischemia time, ischemia–reperfusion injuries, CNI dose, and the genetic backgrounds of the donor and the recipient [1, 17, 18]. In animal studies, older animals with preexisting age-related renal dysfunction developed significantly worse nephrotoxicity than younger animals [19]. In humans, CNIs appear to induce greater irreversible kidney damage if the kidney comes from an older donor versus a younger one [20]. In our cohort, we observed that patients with moderate-to-severe cv who were converted from tacrolimus to belatacept were older and received kidneys from older donors. Therefore, many of these lesions were likely preexisting in the donor. When we compared the evolution of kidney function after conversion, we noticed that these patients with cv2–3 started from lower eGFR than those with cv0–1, but achieved greater gain after 3 months of conversion (7.7 versus 3.2 mL/min/1.73 m<sup>2</sup>). This improvement in eGFR seems to plateau after 3 months, with a slight increase between 3 and 12 months.

Other authors have investigated the role of belatacept conversion in grafts with suboptimal kidney function and/or cv. The German experience has been reported in two different studies [13, 14]. In the first report, patients were converted to belatacept late post-transplant (mean 69 months after KT), and those with lower eGFR (<25 mL/min/1.73 m<sup>2</sup>) gained 10 mL/min/1.73 m<sup>2</sup> at 12 months after conversion, whereas those with eGFR >25 mL/min/1.73 m<sup>2</sup> gained 4 mL/min/1.73 m<sup>2</sup>. About half of these patients were on cyclosporine before conversion, which limits the applicability of the study to the current practice since cyclosporine is now rarely used in clinical practice [13]. In the second study, lower proteinuria at the time of conversion was a significant predictor of better outcomes after conversion. They also compared chronic lesions in those who had a graft biopsy <6 months before conversion, without finding any difference between responders and nonresponders [14]. Le Meur et al. [9] described a cohort of KT patients from expanded criteria donors who were converted early (median 71 days) from CNI to belatacept. They found an increase in eGFR about 15 mL/min/1.73 m<sup>2</sup> at 6 months of conversion that stabilized thereafter. About half of the patients presented with moderate-to-severe cv in their biopsies prior to conversion, but the authors did not assess potential differences in evolution for this subgroup. More recently, another French group reported the results comparing patients

Table 2. Evolution of eGFR between patients with and without cv converted to belatacept

	eGFR, mean (SD) (mL/min/1.73 m <sup>2</sup> )		
	Baseline	3 months	12 months
All patients (n = 34)	35.4 (20.2)	41 (19)*	
cv0–1 (n = 16)	40.4 (22.7)	43.6 (19.8)	
cv2–3 (n=18)	31 (17)	38.7 (18.7)*	
Patients at 12 months (n = 32)	36 (20.7)		43.7 (17.4)*
cv0–1 (n = 15)	40.9 (23.4)		47.7 (14.7)
cv2–3 (n = 17)	31.6 (17.4)		40.2 (19.1)*

Two patients were lost to follow-up between 3 and 12 months after conversion.  
\* $P < 0.05$ .

Table 3. Clinical outcomes after belatacept conversion

	Pre-conversion	Post-conversion	P-value
UPCR, median (IQR) (g/g)	0.6 (0.2–1.4)	0.4 (0.2–0.6)	0.455
Non-fasting blood glucose, mean (SD) (mg/dL)	118.5 (35.9)	120.9 (50.3)	0.772
SBP, mean (SD)	135 (13.8)	133.3 (17.5)	0.671
DBP, mean (SD)	78 (10.5)	75.6 (9.6)	0.315
No. of antihypertensive drugs, median (IQR)	1 (1–3)	2 (0.75–3)	0.417

UPCR, urine protein/creatinine ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure, No., number.



with cv that were converted to belatacept late (average 51.5 months) after KT as 'rescue therapy' in patients with poor kidney function versus a historical cohort that continued on CNIs. They showed a benefit in those who were converted, with an increase in eGFR of 7 mL/min/1.73 m<sup>2</sup> after 6 months [21]. In this cohort, 47% of patients were on cyclosporine in the conversion group, and 28% in the group that continued on CNIs. The European experience has been joined in a very recent communication where the authors reaffirm the benefit in eGFR gain after conversion. They also found that interstitial fibrosis and tubular atrophy were predictors of eGFR gain at 3 months after conversion, but the median vascular lesions score in this cohort was 0 [22]. Finally, Abdelwahab et al. [12] reported the results of a case-control study with 30 patients with low eGFR converted early post-transplant (median 107 days) from tacrolimus to belatacept or continued on tacrolimus. They reported that almost 60% of patients had cv >0 before conversion but without specifying the grade. Although they found an increase in eGFR at 4 months in the belatacept group (11 versus 5 mL/min/1.73 m<sup>2</sup>), after controlling for the slope during the 4-month pre-conversion period, the slope of the inverse creatinine for 12 months post-conversion was not significantly higher in the belatacept conversion group. The authors conclude that this modest benefit in the belatacept group should be interpreted carefully.

To our knowledge, we present the first study that compares outcomes from KT patients converted to belatacept at a median of 6 months after KT with and without cv in their biopsies. Our cohort is homogeneous both in terms of IS (all patients received tacrolimus before conversion) and histological findings (they were grouped into cv0-1 versus cv2-3), which better supports the conclusions.

Although belatacept conversion and CNI withdrawal are an option, it has been shown to increase the risk of acute rejection (7% versus 0%) compared with CNI group in low immunologic risk KT recipients [7, 8]. About 25% of our patients suffered from acute rejection after conversion. This rate is higher than previously reported and probably related to the high immunological risk patients included for the conversion in our study: almost one-third of our patients were re-transplants, >20% had a cPRA >30% and 14.7% had a rejection before the conversion. Rejection episodes occurred around 6 months after conversion and most of them were cellular rejection that resolved after steroids pulse. Notably, even with this high rate of rejection, the whole cohort benefitted in terms of kidney function after the conversion.

Although benefits in blood pressure, lipids and glycemic control have been found in other studies with *de novo* belatacept [23], we did not find any differences in our cohort. We also found no benefits in terms of proteinuria or BK viremia.

The safety profile of the medication switch was excellent. With a median follow-up of 21.5 months, we only registered mild viral replications (CMV and BK) and one patient who had multiple urinary infection episodes. No cancers or patient deaths were noticed during the follow-up.

Our study has inherent limitations of a retrospective study such as the heterogeneous timing of conversion and small sample size. Furthermore, reasons of conversion were variable. Therefore, we are unable to assess the potential benefit of an earlier conversion in kidney function. More importantly, the lack of a control group of patients with and without vascular lesions not converted to belatacept prevent us from estimating how eGFR may have behaved in those not switched to belatacept.

In conclusion, our study supports the benefit of belatacept conversion in patients with cv in their allograft biopsies. Late conversion is shown to provide a beneficial effect in terms of

renal function in these KT patients. Whether this benefit might be greater if the conversion is done early after transplant remains uncertain.

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## AUTHORS' CONTRIBUTIONS

M.J.P.-S., L.V.R., S.E.H. and S.G. designed the database and the study. B.Y., A.U. and S.E.H. collected the data. M.J.P.-S. assessed the calculations. M.J.P.-S. and L.V.R. wrote the manuscript. The rest of the authors contributed with the manuscript redaction and valuable input for the analysis and interpretation of the results.

## CONFLICT OF INTEREST STATEMENT

None declared.

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