Article

Switching from Calcineurin Inhibitor-based Regimens to a Belatacept-based Regimen in Renal Transplant Recipients: A Randomized Phase II Study

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Summary

Background and objectives Prolonged use of calcineurin inhibitors (CNIs) in kidney transplant recipients is associated with renal and nonrenal toxicity and an increase in cardiovascular risk factors. Belatacept-based regimens may provide a treatment option for patients who switch from CNI-based maintenance immunosuppression.

Design, setting, participants, & measurements This is a randomized, open-label Phase II trial in renal transplant patients with stable graft function and receiving a CNI-based regimen. Patients who were ≥6 months but ≤36 months after transplantation were randomized to either switch to belatacept or continue CNI treatment. All patients received background maintenance immunosuppression. The primary end point was the change in calculated GFR (cGFR) from baseline to month 12.

Results Patients were randomized either to switch to belatacept ($n = 84$) or to remain on a CNI-based regimen ($n = 89$). At month 12, the mean (SD) change from baseline in cGFR was higher in the belatacept group *versus* the CNI group. Six patients in the belatacept group had acute rejection episodes, all within the first 6 months; all resolved with no allograft loss. By month 12, one patient in the CNI group died with a functioning graft, whereas no patients in the belatacept group had graft loss. The overall safety profile was similar between groups.

Conclusions The study identifies a potentially safe and feasible method for switching stable renal transplant patients from a cyclosporine- or tacrolimus-based regimen to a belatacept-based regimen, which may allow improved renal function in patients currently treated with CNIs.

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Introduction

The calcineurin inhibitors (CNIs) have been an important component of renal transplant immunosuppression since the introduction of cyclosporine and tacrolimus (1). The introduction of CNIs reduced the incidence of acute rejection (AR) episodes and improved early patient and graft survival. However, CNIs contribute to acute and chronic impairment of graft function and are associated with side effects that increase cardiovascular risk such as hypertension and diabetes (2–7). Their effect on allograft function is worrisome because impaired renal function has been associated with poorer long-term graft survival (8). Thus, the use of CNIs in immunosuppression has largely overcome the problem of early graft loss from rejection, but at the cost of increased cardiovascular risk and late graft loss from CNI nephrotoxicity (9,10).

There are limited treatment options to avoid CNIs and their associated toxicities. In kidney transplantation, the only currently approved CNI-sparing agent is sirolimus. In this indication, sirolimus, in combination with cyclosporine and corticosteroids, is given for approximately 3 months followed by withdrawal of cyclosporine in low-risk patients and is given in combination with cyclcosporine and corticosteroids for at least the first 12 months in high-risk patients (11). Immunosuppressive doses of sirolimus are associated with dose-dependent side effects that limit the drug's tolerability (12). These side effects include hyperlipidemia, new onset diabetes, anemia, thrombocytopenia, proteinuria, edema, impaired wound healing, and mouth ulcers. Everolimus, a related mammalian target of rapamycin inhibitor, is used in combination with basiliximab induction and with reduced doses of cyclosporine and corticosteroids but not as part of a CNI-avoiding regimen (13).

Belatacept, a costimulation blocker that selectively inhibits T cell activation, has been studied in kidney transplant patients as a *de novo* immunosuppressant (14–16). Treatment with belatacept was associated with better renal function, less chronic allograft nephropathy, and an improved cardiovascular risk fac-

tor profile compared with cyclosporine. Although belatacept's overall safety profile was similar to cyclosporine, in the *de novo* setting it was associated with more severe early AR episodes and an increased risk for post-transplant lymphoproliferative disorder affecting the central nervous system.

Kidney transplant patients are switched from CNIs for various reasons, including AR, adverse events (*e.g.* hirsutism, gingival hypertrophy, and neurotoxicity), and chronic factors such as nephrotoxicity, diabetes, and dyslipidemia (17–19). However, there are challenges to switching immunosuppressive regimens, including increased risk of AR or graft loss and the introduction of new adverse events. Although the therapeutic profile of belatacept supports its use in *de novo* transplant recipients, it is not established whether stable renal transplant patients on CNI maintenance therapy can be safely switched to belatacept and whether allograft function would be improved. This study was conducted to investigate the safety and efficacy of switching stable renal transplant patients from maintenance CNI therapy (either cyclosporine or tacrolimus) to a belatacept-based regimen.

Materials and Methods

This is a randomized, open-label, multicenter, Phase II clinical trial of kidney transplant patients receiving a CNI-based regimen (cyclosporine or tacrolimus) who were randomly allocated 1:1 to switch to belatacept or remain on their existing therapy. The study, which began in January 2007, was conducted at 34 centers in the Americas, Europe, Australia, and India. Primary and secondary outcomes were assessed at month 12, and patients were eligible to enter a long-term study extension. The study is being conducted in accordance with ethical principles that have their origin in the current Declaration of Helsinki and is consistent with International Conference on Harmonization Good Clinical Practice and other applicable regulatory requirements. Institutional review boards or independent ethics committees for each site reviewed and approved the study protocol and informed consent forms before the start of the study. A data monitoring committee periodically evaluated accrued efficacy and safety data. The study is registered with ClinicalTrials.gov (id: NCT00402168).

Patients

Enrolled patients were adult recipients of a renal allograft from a living or deceased donor at least 6 months but no longer than 36 months before enrollment. To be eligible for inclusion, patients needed to be receiving CNI-based maintenance immunosuppression at a stable dose during the month immediately before randomization and have a cGFR between 35 and 75 ml/min per 1.73 m^2 at enrollment, based on the Modification of Diet in Renal Disease formula (20). Patients also received stable doses of background immunosuppression (mycophenolate mofetil, mycophenolic acid, sirolimus, or azathioprine); patients receiving corticosteroids at enrollment continued at a stable dose. Female patients of child-bearing potential were required to use an adequate method of contraception throughout the study.

Principal exclusion criteria included a history of recent, recurrent, or severe AR in the current allograft or a history of graft loss due to AR. A single AR episode was not exclusionary if it occurred >3 months before randomization, was Grade IB (Banff 97 criteria) or milder, did not recur, and had been successfully reversed with corticosteroids. Other exclusion criteria included a positive T or B cell crossmatch, a C4d-positive biopsy in the current allograft, recent >30% serum creatinine (SCr) increase, underlying renal disease that could adversely effect the current graft, current infection, and a history of malignancy (other than nonmelanoma skin cancer cured by local resection) in the past 5 years.

Randomization and Interventions

The patients were randomized 1:1 to belatacept or to remain on their existing therapy. Randomization was stratified by patients' current CNI regimens (cyclosporine- or tacrolimus-based) and by site. Belatacept 5 mg/kg was given by intravenous infusion on days 1, 15, 29, 43, and 57, and then every 28 days thereafter. This dosage was derived from studies in *de novo* renal transplant immunosuppression and was designed to provide a similar target trough concentration during maintenance treatment (10 to 12 μg/ml) and additional exposure during the first month of dosing (16,21). For those patients randomized to belatacept, the CNI dose was tapered as follows: 100% on day 1, to 40 to 60% on day 15, 20 to 30% on day 23, and none on day 29 and beyond. Patients allocated to the comparator group continued receiving cyclosporine or tacrolimus according to local practice and the respective package inserts. Cyclosporine doses were maintained at trough serum concentrations of 100 to 250 ng/ml; tacrolimus doses were maintained at trough serum concentrations of 5 to 10 ng/ml. Any adjunctive immunosuppressive or corticosteroids treatments a patient had been receiving were maintained at existing doses unless dose modification was medically necessary. Per protocol, AR episodes were treated with bolus corticosteroids, except for episodes that were Banff Grade IIB or higher and/or corticosteroid-resistant; those episodes were recommended to be treated with lymphocyte-depleting therapy.

Outcomes

The primary end point was the change in cGFR from baseline to month 12, calculated using the Modification of Diet in Renal Disease formula (22). Secondary end points included the incidence of AR, patient and graft survival, new onset diabetes after transplantation (NODAT), BP, serum lipids, and Kidney Disease Outcomes Quality Initiative chronic kidney disease stage. Patients with signs and symptoms suspicious for AR (defined in the protocol as unexplained rise of SCr ≥25% from baseline, unexplained decreased urine output, or fever and graft tenderness)

underwent a renal biopsy. Although local biopsies (Banff 97 criteria) (23) guided treatment of AR, all biopsy specimens were sent to a blinded central pathologist to minimize bias in grading for the AR protocol end point. The presence of anti-donor HLA antibodies was assessed by a central laboratory at study baseline, at months 6 and 12, and at the time of any suspected rejection episode (24–26).

Statistical Methods

The efficacy data were analyzed according to the intention to treat, with all randomized patients included whether or not they remained on treatment. Safety data were analyzed for all patients treated after randomization. Enrollment of 85 subjects per treatment group would be sufficient to reveal a difference between treatment groups of 5.71 ml/min per 1.73 m^2, assuming a SD of 19 ml/min per 1.73 m^2. Calculated GFR and its change from baseline were summarized descriptively, and an imputed value of 10 used in the event of death or graft loss. Other missing cGFR values were imputed, wherever possible, using linear regression calculations from two or more other post-baseline time points taken at least 4 months apart. The study was not powered to assess the statistical significance of the change from baseline in cGFR between the belatacept and CNI groups. As a *post hoc* analysis, the *P* value was calculated for the change from baseline in cGFR using the adjusted mean based on an analysis of covariance model with treatment as factor and baseline value and prerandomization CNI regimen as covariates. Patient and graft survival, incidence of AR, and the incidence of NODAT were summarized within treatment groups using point estimates and the corresponding 95% confidence intervals (CIs). Two-sided CIs were also generated for the difference between treatment groups. BP and serum lipid concentrations were summarized descriptively.

Results

Patient Demographics and Disposition

The two treatment groups had similar demographic and clinical characteristics except that more belatacept patients had end-stage renal disease secondary to glomerulonephritis (Table 1). Nearly two-thirds of the patients were male, and the mean patient age was 44 to 45 years. About half had received a kidney from a living donor. Seven of 84 patients in the belatacept group and nine of 89 patients in the CNI group were Epstein-Barr virus-negative at baseline. Donor characteristics were also well balanced between treatment groups (not shown). Figure 1 summarizes the flow of patients through the study. Eighty-four patients were randomized to switch to belatacept, and 89 patients remained on their CNI-based treatment. Ninety-eight percent of patients in each group completed 1 year of treatment. The two patients who discontinued belatacept had AR episodes but did not experience graft loss. Mean trough levels of cyclosporine and tacrolimus were within treatment target levels at baseline in both groups, decreasing to zero by 3 months in the belatacept group, and remaining within target levels through month 12 in the CNI group. Mean and median trough levels in the CNI group at month 12 were 173.7 and 133 ng/ml, respectively, for cyclosporine and 7.1 and 7 ng/ml, respectively, for tacrolimus.

Renal Function

Improvements in renal function were greater in the belatacept group compared with the CNI group ($P = 0.0058$ for the difference between groups). The mean cGFR values at month 12 (Table 2) were 60.5 ml/min per 1.73 m^2 in the belatacept group and 56.5 ml/min per 1.73 m^2 for the CNI group, increases of 7.0 and 2.1 ml/min per 1.73 m^2 from baseline, respectively. Similar results favoring belatacept were observed for data based on observed values and on the last observation carried forward method (data not shown). The mean cGFR over time is depicted in Figure 2. Improvements in cGFR from baseline were typically higher with belatacept than in the CNI group across a range of patient types (Table 2). The increase in cGFR was 7.7 ml/min per 1.73 m^2 in belatacept patients who had originally received cyclosporine at baseline and 6.4 ml/min per 1.73 m^2 with those who received tacrolimus. At month 12, 54% of the belatacept group and 39% of the CNI group had a cGFR of $\geq$60 ml/min (corresponding to stage 1 or 2 CKD; Figure 3), compared with 33 and 37% at baseline, respectively.

Acute Rejection

Mild or moderate centrally-confirmed AR episodes occurred in six patients in the belatacept group on days 43, 59, 71, 88, 113, and 126 after initiation of the switch (Table 3). Of these six patients, four were originally maintained on tacrolimus, and two were on cyclosporine. Four of the six AR patients remained on belatacept therapy. Two of the patients experienced their AR episode after discontinuing belatacept. Two AR patients (one Grade IIA and one corticosteroid-resistant Grade IIA) received treatment with lymphocyte-depleting therapy. Two others were treated successfully with corticosteroids: one received no treatment, and one (Grade IA) received rituximab. One patient who experienced an AR episode had donor-specific anti-HLA alloantibodies; this patient was positive at baseline and at all subsequent time points. After the AR episodes, the SCr concentration returned to baseline or improved from baseline in four of six patients; the concentration was worse than baseline or not recorded in two patients. AR episodes were associated with a >20% increase in SCr in two patients.

Graft and Patient Survival

No grafts were lost in the first 12 months. One patient in the CNI group died with a functioning graft (because of myocardial infarction) on day 142 (Table 3).

Cardiovascular and Metabolic Changes

NODAT occurred in two patients receiving CNIs (2.9%; 95% CI 0.4, 10.2) and one receiving belatacept (1.7%; 95%

Table 1. Transplant recipient demographic and baseline characteristics

Recipient Characteristic	Belatacept (n = 84)	CNI (n = 89)
Mean age, years (SD)	45.3 (13.5)	44.3 (13.0)
Male	66 (79)	60 (67)
Race		
white	44 (52)	53 (60)
black/African American	6 (7)	4 (5)
Asian	16 (19)	12 (14)
other	18 (21)	20 (22)
Geographic region		
North America	28 (33)	25 (28)
South America	28 (33)	31 (35)
Europe	15 (18)	22 (25)
other	13 (16)	11 (12)
Reported cause of ESRD		
glomerulonephritis	23 (27)	14 (16)
diabetes	7 (8)	10 (11)
polycystic kidneys	9 (11)	9 (10)
renovascular/hypertensive nephrosclerosis	7 (8)	10 (11)
congenital, familial, and metabolic	3 (4)	3 (3)
other causes	35 (42)	43 (48)
Previous number of transplants		
0	74 (88)	77 (87)
1	10 (12)	10 (11)
2	0	2 (2)
Categorized highest PRA		
<20%	63 (75)	64 (72)
≥20%	3 (4)	5 (6)
Missing	18 (21)	20 (23)
Mean baseline cGFR, ml/min per 1.73 m^2 (SD)	53.5 (11.0)	54.5 (10.3)
Mean time from transplantation to randomization, months (SD)	19.4 (9.2)	20.1 (9.4)
CNI agents		
cyclosporine	37 (44.0)	39 (43.8)
mean trough serum cyclosporine level, ng/ml (SD)	160.2 (41.81)	154.4 (38.08)
Tacrolimus	47 (56.0)	50 (56.2)
Mean trough serum tacrolimus level, ng/ml (SD)[a]	7.2 (1.77)	7.5 (1.44)
Adjunctive immunosuppressive agents[b]		
azathioprine	6 (7.2)	3 (3.4)
MMF/MPA	77 (92.8)	83 (94.3)
sirolimus	1 (1.2)	0
Systemic corticosteroids[b]	73 (88.0)	71 (80.7)

The values given indicate n (%), unless specified. PRA, panel reactive antibodies; MMF, mycophenolate mofetil; MPA, mycophenolic acid.
[a]Cyclosporine trough levels based on data for 36 (belatacept) and 37 (CNI) patients who had available measurements; tacrolimus trough levels based on data available for 45 (belatacept) and 46 (CNI) patients.
[b]Prerandomization data on adjunctive agents were not available for three patients in the CNI group; data were based on randomized, treated patients (n = 83 belatacept; n = 88 CNI).

CI 0.0, 9.1). Use of antidiabetic medication, whether in the whole study population or in the subgroups with and without diabetes at baseline, did not differ between treatment groups. Decreases in systolic and diastolic BP over the 12 months tended to be greater in the belatacept group (4.0/3.5 mmHg) than in the CNI group (1.6/1.7 mmHg). Use of antihypertensive medication was similar between groups. Changes in serum lipids were minimal, and there were no clinically significant differences between groups.

Safety

Most adverse events reported during the first 12 months of the study were mild and occurred with similar frequency in the two treatment groups. Few serious

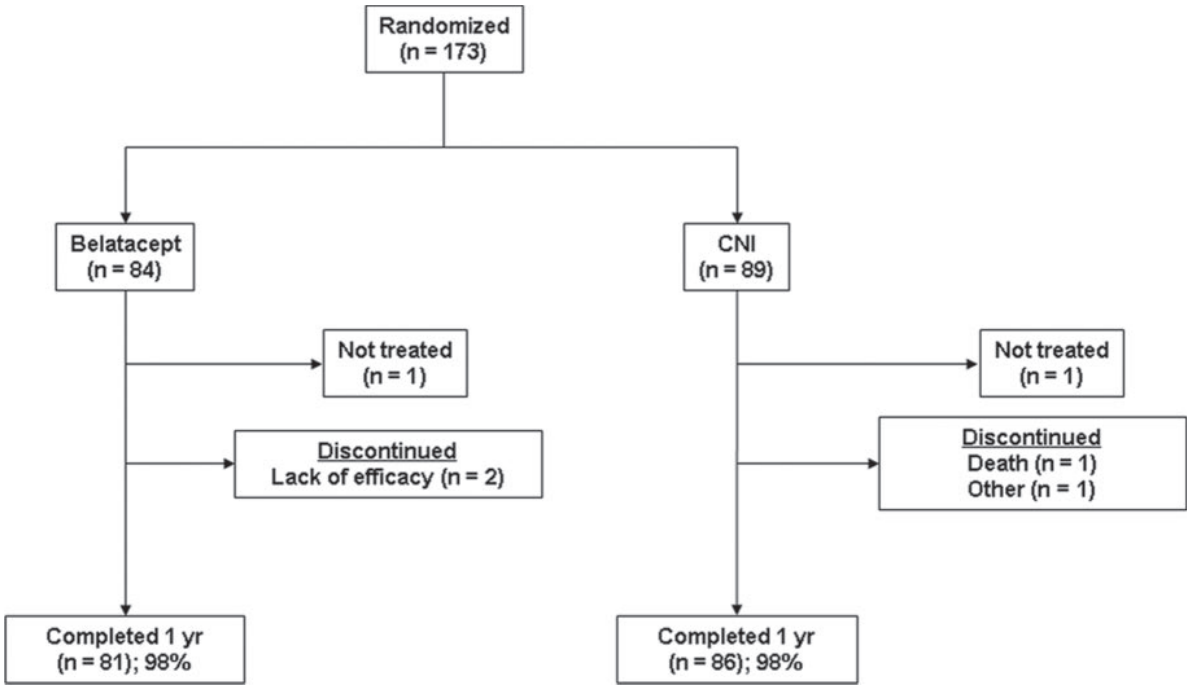

Figure 1. | Patient disposition.

Table 2. Mean cGFR at month 12 and mean change in cGFR from baseline to month 12

	Belatacept (n = 84)			CNI (n = 89)		
	Baseline	Month 12	Mean Change from Baseline	Baseline	Month 12	Mean Change from Baseline
Mean cGFR, ml/min per 1.73 m^2 (SD)	53.5 (11.01)	60.5 (16.19)	7.0 (11.99)[a]	54.5 (10.26)	56.5 (14.42)	2.1 (10.34)[a]
Baseline cGFR						
<45 (n = 40)	40.2 (3.87)	43.9 (10.56)	3.7 (11.01)	41.1 (3.35)	43.9 (7.43)	2.8 (8.17)
45 to 60 (n = 70)	51.7 (3.98)	61.7 (13.88)	10.0 (13.41)	51.4 (3.67)	53.2 (12.84)	1.9 (11.72)
>60 (n = 59)	66.2 (4.98)	71.8 (11.38)	5.7 (10.17)	65.8 (4.20)	67.8 (10.81)	2.0 (10.13)
Baseline CNI						
CsA (n = 74)	51.9 (10.11)	59.2 (18.17)	7.7 (14.51)	53.1 (11.66)	53.1 (16.18)	0 (10.86)
TAC (n = 95)	54.8 (11.61)	61.5 (14.59)	6.4 (9.70)	55.6 (8.98)	59.2 (12.41)	3.7 (9.73)
Time from transplantation to randomization						
6 to 12 months (n = 48)	54.2 (10.31)	59.6 (16.24)	5.4 (12.56)	54.5 (8.43)	56.1 (14.23)	1.6 (11.80)
12 to 18 months (n = 25)	49.7 (10.27)	53.8 (19.28)	4.1 (13.57)	53.3 (12.10)	51.8 (16.05)	−1.5 (11.41)
>18 months (n = 85)	53.8 (11.66)	61.4 (15.02)	7.6 (10.68)	54.5 (10.93)	57.1 (14.03)	2.8 (9.49)
Diabetes status						
diabetic (n = 45)	53.5 (13.27)	55.5 (16.73)	2.7 (11.17)	54.6 (10.61)	54.6 (17.60)	−0.1 (12.64)
nondiabetic (n = 124)	53.5 (10.02)	62.5 (15.66)	8.8 (11.95)	54.5 (10.22)	57.1 (13.35)	2.8 (9.51)
Type of transplant						
living donor (n = 83)	54.9 (10.66)	60.5 (14.07)	5.9 (11.34)	56.1 (10.43)	57.5 (15.86)	1.6 (11.58)
deceased donor (n = 86)	52.2 (11.29)	60.5 (18.16)	8.0 (12.62)	52.9 (9.94)	55.5 (12.97)	2.6 (9.09)

The values are the mean changes in cGFR from baseline by patient subsets, ml/min per 1.73 m^2 (SD). n for patient subsets may not add up to the overall population because of missing values or information. CsA, cyclosporine; TAC, tacrolimus.

[a]P = 0.0058 for difference between treatment groups in change from baseline (post-hoc analysis).

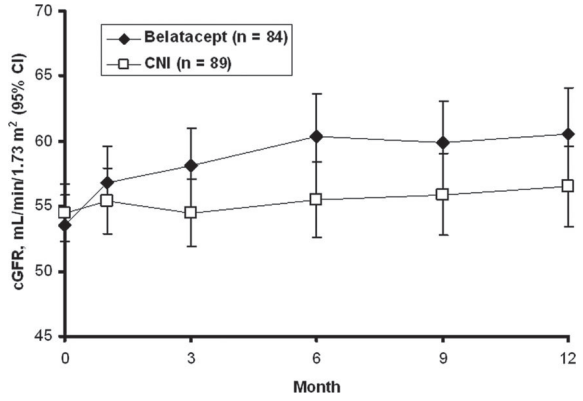

Figure 2. | **Mean cGFR values over time.**

adverse events were reported; serious events occurring in >1 patient in either group included pyelonephritis ($n = 2$ belatacept, $n = 1$ CNI), pyrexia ($n = 3$ belatacept), basal cell carcinoma ($n = 1$ belatacept, $n = 2$ CNI), cytomegalovirus infection ($n = 2$ CNI), and urinary tract infection ($n = 2$ belatacept) (Table 4).

Proteinuria was uncommon ($n = 1$ in each group). At month 12, the mean (SD) urinary protein-creatinine ratio was 0.25 ± 0.472 in the belatacept group and 0.18 ± 0.178 in the CNI group. The mean change from baseline in the ratio was low and similar between groups.

The overall incidence of viral infections over the 12 months was 13% in each group. The most frequently reported viral infection was influenza. Cytomegalovirus infection occurred in two patients in each group, and BK virus infection occurred in three patients in the belatacept group. Fungal infections were more frequent with belatacept (11 patients [13%]) than with

Table 3. Secondary outcomes at month 12

	Belatacept ($n = 84$)	CNI ($n = 89$)
Acute rejection incidence, *n* (%)	6 (7)	0
95% CI	1.6 to 12.7	
Banff grade, *n* (%)		
mild acute (IA)	1 (1)	0
mild acute (IB)	1 (1)	0
moderate acute (IIA)	3 (4)	0
moderate acute (IIB)	1 (1)	0
severe acute (III)	0	0
Patient/graft survival, *n* (%)	84 (100)	88 (99)
95% CI		96.7 to 100.0
Graft loss or death, *n* (%)	0	1 (1)
graft loss	0	0
death	0	1 (1)
death with functioning graft	0	1 (1)

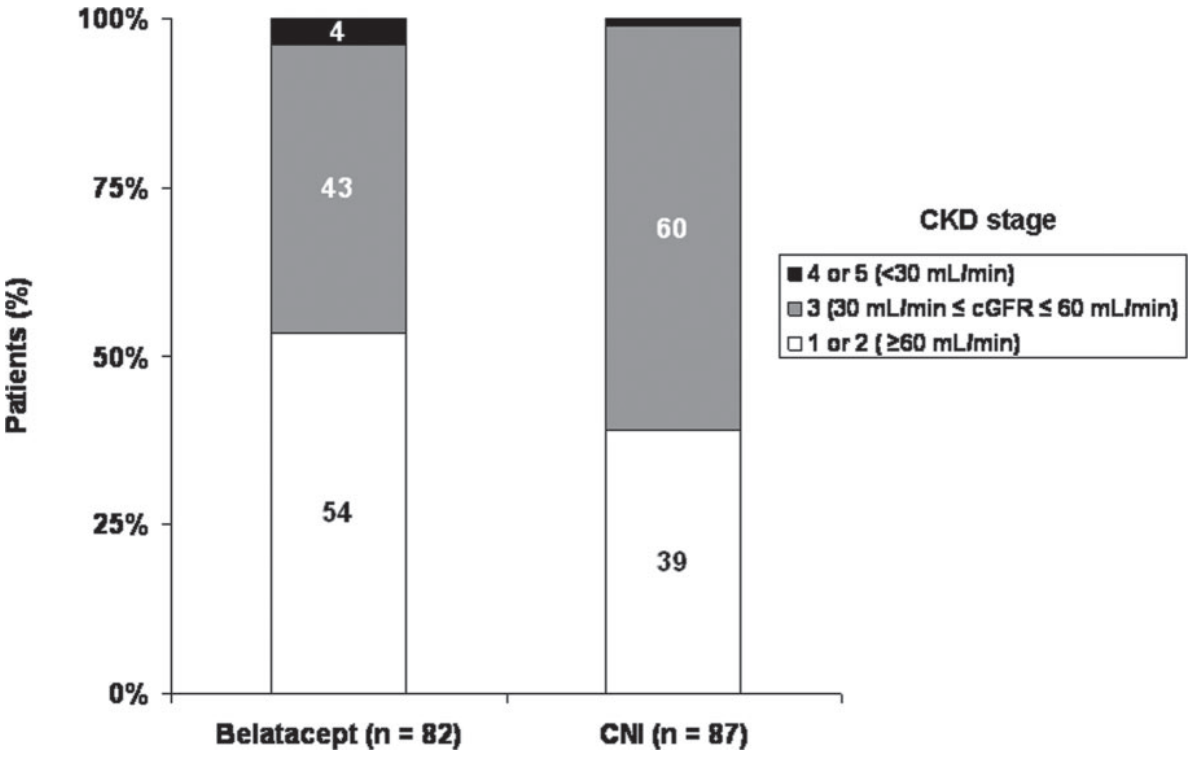

Figure 3. | **Proportion of patients at chronic kidney disease stages based on cGFR. cGFR data for two patients in each group could not be imputed, and those patients were excluded from the analysis.**

Table 4. Most common serious adverse events, malignancies, selected viral infections, and fungal infections by month 12

Event, *n* (%)	Belatacept (*n* = 83)	CNI (*n* = 88)
Total patients with serious adverse events	20 (24)	17 (19)
pyrexia	3 (4)	0
pyelonephritis	2 (2)	1 (1)
urinary tract infection	2 (2)	0
basal cell carcinoma	1 (1)	2 (2)
CMV infection	0	2 (2)
Total patients with malignancies	2 (2)	2 (2)
basal cell carcinoma	1 (1)	2 (2)
Kaposi's sarcoma	1 (1)	0
Total patients with viral infections	11 (13)	12 (14)
herpes infections	4 (5)	3 (3)
herpes zoster	2 (2)	1 (1)
oral herpes	1 (1)	1 (1)
herpes virus infection	1 (1)	0
varicella	0	1 (1)
BK polyoma virus infection	3 (4)	0
BK virus infection	2 (2)	0
polyomavirus-associated nephropathy	1 (1)	0
CMV infection	2 (2)	2 (2)
CMV infection	1 (1)	2 (2)
CMV viremia	1 (1)	0
Total patients with fungal infections	11 (13)	3 (3)
tinea versicolor	5 (6)	0
fungal infection	1 (1)	1 (1)
fungal skin infection	1 (1)	1 (1)
onychomycosis	1 (1)	1 (1)
body tinea	1 (1)	0
skin candida	1 (1)	0
tinea curis	0	1 (1)
vulvovaginal mycotic infection	1 (1)	0

Patients could report more than one event. The table includes patients who were randomized, transplanted, and treated with study drug; one patient from each group was not treated.

CNI therapy (three patients [3%]). These mostly consisted of mild or moderate skin or oral infections, such as tinea versicolor. None were classified as serious or resulted in discontinuation of study drug. There was one tuberculosis case in the belatacept group. The patient, living in Mexico, had no prior history of tuberculosis and was hospitalized as a result of the event. After successful treatment, the patient remained in the study and continued receiving belatacept. There were no cases of progressive multifocal leukoencephalopathy.

Malignancies were reported in four patients: two in the belatacept group (one with Kaposi's sarcoma and one with basal cell carcinoma) and two in the CNI group (basal cell carcinoma). There were no cases of post-transplant lymphoproliferative disorder.

Discussion

This exploratory study of belatacept in stable renal transplant patients demonstrated that switching from a CNI-based therapy to a belatacept-based regimen appeared to be feasible and well tolerated, with a low frequency of AR, no graft loss, and an improvement in renal function compared with CNI-based regimens.

The potential to avoid CNI-associated toxicities is important for transplant recipients, especially those who cannot tolerate CNI-based therapy. However, there are risks inherent with switching immunosuppressive regimens, including increased risk for AR, graft loss, and the introduction of new side effects (27). The most common reason for discontinuing CNI-based therapy is typically nephrotoxicity (18,19,28), although discontinuation because of non-nephrotoxic side effects is not uncommon (28). A study of 157 liver and kidney transplant recipients who could not continue tacrolimus-based therapy found that the most common reasons necessitating a therapy switch were neurotoxicity, diabetes, gastrointestinal intolerance, and nephrotoxicity (17). Few therapeutic options currently exist for patients maintained on a CNI-based immunosuppressive regimen who might benefit from switching to a different agent.

In this study, the switch from a CNI-based to a belatacept-based regimen was associated with a high rate of patient/graft survival and was associated with improved renal function. Belatacept was well tolerated, with 98% of patients continuing on therapy through 1 year. Subgroup analysis showed that most patient groups experienced an improvement in renal function after introduction of belatacept and discontinuation of CNI, including those who were switched sooner and later after transplantation and those with lower GFR at the time of switch. The improvement in cGFR was greater for those patients with better renal function at baseline, with the greatest increase occurring in patients with baseline cGFR of 45 to 60 ml/min per 1.73 m^2. In contrast, patients in the CONVERT trial with cGFRs of 20 to 40 ml/min per 1.73 m^2 experienced a decline in renal function as a result of switching from CNIs to sirolimus (29). Although some acute hemodynamic effects of CNIs are at least partially reversible, there is also longer-term damage to the structure of the allograft that may not be reversible (2). The results of the current study emphasize that a broad range of patients may benefit from switching from CNI to belatacept, although allograft function

may be better preserved by switching from a CNI-based regimen before nephrotoxicity irreversibly diminishes allograft function. The renal function benefit for belatacept compared with cyclosporine in kidney transplant recipients appears to be greater when used *de novo* (15,16), and data from a Phase II study indicate that allograft function remains stable over time with longer-term belatacept treatment (30).

A subgroup analysis showed that the improvement in cGFR after switching to belatacept was similar for cyclosporine-treated patients and tacrolimus-treated patients (7.7 and 6.4 ml/min per 1.73 m^2, respectively). However, patients treated with tacrolimus who did not switch also had an improvement in GFR, whereas those treated with cyclosporine who did not switch had a stable GFR. Both tacrolimus and cyclosporine are associated with long-term allograft damage and dysfunction, although the relative effects of tacrolimus *versus* cyclosporine are uncertain (2,31–33).

The 7% AR rate in this study is comparable with the rates observed in other CNI-sparing switch studies (29,34–36). The lack of AR episodes in the comparator arm is not surprising, because these patients did not switch therapy and had been on stable CNI-based therapy for as long as 3 years. In the current study, all of the AR episodes occurred within the first 6 months, all but one had resolved by 12 months, and none led to graft loss. None of the AR episodes were associated with the development of donor-specific antibodies; in general, the development of donor-specific antibodies was not associated with switching to belatacept. The pattern of AR is also consistent with studies of *de novo* use of belatacept in which AR episodes tended to occur early, did not recur, and responded to treatment (14–16).

The safety profile of belatacept in this switch study appears to be consistent with the available data on belatacept and with few differences between treatment groups in adverse events. There were no differences between groups in the incidence of malignancies or serious infections.

Limitations of the study include its open-label design. The use of a central GFR lab and a central pathologist blinded to treatment allocation eliminated the potential for observer bias for some key end points; it is possible that knowledge of treatment assignment by patients and study staff may have influenced decisions on dosing of study medication and other treatments. In addition, the relatively small number of subjects in the study limits the conclusions that can be made from the subgroup analyses. Results on the relative clinical benefit of belatacept in a switch paradigm, and particularly in different patient categories, should be considered exploratory and require confirmation in future studies.

Conclusions

The study has identified a belatacept switching regimen that at 1 year appears to be safe for renal allograft patients currently maintained on CNIs and offers the potential for better renal function. The results suggest that belatacept may offer an important advantage by avoiding the CNIs and their associated toxicities and corresponding loss of renal function. The overall profile suggests that belatacept may have potential as primary maintenance therapy as part of an immunosuppressive regimen in renal transplantation.

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