AJKD

Original Investigation

Safety and Efficacy Outcomes 3 Years After Switching to Belatacept From a Calcineurin Inhibitor in Kidney Transplant Recipients: Results From a Phase 2 Randomized Trial

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Background: In a phase 2 study, kidney transplant recipients of low immunologic risk who switched from a calcineurin inhibitor (CNI) to belatacept had improved kidney function at 12 months postconversion versus those continuing CNI therapy, with a low rate of acute rejection and no transplant loss.

Study Design: 36-month follow-up of the intention-to-treat population.

Setting & Participants: CNI-treated adult kidney transplant recipients with stable transplant function (estimated glomerular filtration rate [eGFR], 35-75 mL/min/1.73 m^2).

Interventions: At 6 to 36 months posttransplantation, patients were randomly assigned to switch to belatacept-based immunosuppression (n = 84) or continue CNI-based therapy (n = 89).

Outcomes: Safety was the primary outcome. eGFR, acute rejection, transplant loss, and death were also assessed.

Measurements: Treatment exposure–adjusted incidence rates for safety, repeated-measures modeling for eGFR, Kaplan-Meier analyses for efficacy.

Results: Serious adverse events occurred in 33 (39%) belatacept-treated patients and 36 (40%) patients in the CNI group. Treatment exposure–adjusted incidence rates for serious infections (belatacept vs CNI, 10.21 vs 9.31 per 100 person-years) and malignancies (3.01 vs 3.41 per 100 person-years) were similar. More patients in the belatacept versus CNI group had any-grade viral infections (14.60 vs 11.00 per 100 person-years). No posttransplantation lymphoproliferative disorder was reported. Belatacept-treated patients had a significantly greater estimated gain in mean eGFR (1.90 vs 0.07 mL/min/1.73 m^2 per year; P for time-by-treatment interaction effect = 0.01). The probability of acute rejection was not significantly different for belatacept (8.38% vs 3.60%; HR, 2.50 [95% CI, 0.65-9.65; $P = 0.2$). HR for the comparison of belatacept to the CNI group for time to death or transplant loss was 1.00 (95% CI, 0.14-7.07; $P = 0.9$).

Limitations: Exploratory post hoc analysis with a small sample size.

Conclusions: Switching patients from a CNI to belatacept may represent a safe approach to immunosuppression and is being further explored in an ongoing phase 3b trial.

Am J Kidney Dis. ■(■):■-■.

INDEX WORDS: Kidney transplant; renal transplantation; belatacept; calcineurin inhibitor (CNI); switch; conversion study; immunosuppression; safety; adverse events; kidney function; acute rejection; graft loss; phase 2 randomized controlled trial.

The principal immunosuppressive therapies for kidney transplantation—the calcineurin inhibitors (CNIs) cyclosporine and tacrolimus—may contribute to patient comorbidity via nephrotoxicity and to cardiovascular risk (eg, hypertension, hypercholesterolemia, and diabetes mellitus)[1] and transplant loss via chronic transplant injury.[2] There is a need for immunosuppressive agents that control the alloimmune response to an extent similar to that seen with CNIs, but without the renal and cardiovascular toxicities that contribute to transplant loss and patient death.[3,4]

Some CNI-avoiding or CNI-minimizing immunosuppressive regimens, many involving the mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus, have been evaluated in kidney transplant recipients.[5] In prospective studies, patients

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Received January 13, 2016. Accepted in revised form September 26, 2016.

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0272-6386

http://dx.doi.org/10.1053/j.ajkd.2016.09.021

switching from CNI-based to mTOR inhibitor–based immunosuppression showed significant improvements in kidney function at 12 months postconversion versus patients who continue treatment with cyclosporine or tacrolimus. However, mTOR inhibitor–treated patients are more likely to have adverse events (AEs), especially dyslipidemia and proteinuria.[6-14]

The frequency of proteinuria observed with mTOR inhibitor–based immunosuppression is of concern because proteinuria is associated with poor long-term outcomes in kidney transplant recipients.[15,16] Moreover, the early improvements in kidney function seen with everolimus or sirolimus may not be sustained over the long term (ie, beyond 1 year); some randomized controlled studies have shown the significant differences favoring mTOR inhibitor–based over CNI-based immunosuppression being maintained for as long as 48 months postconversion,[6,10,17-19] whereas others have reported loss of statistical significance as early as 24 months postconversion.[8,11,20]

Belatacept is the first immunosuppressant that selectively inhibits T-cell activation via costimulation blockade to have been tested in kidney transplant recipients. Accumulating evidence suggests that belatacept avoids the renal, cardiovascular, and metabolic toxicities of CNI-based regimens. In 2 phase 3 studies (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial [BENEFIT] and BENEFIT–extended criteria donors [BENEFIT-EXT]), patients treated de novo with belatacept had comparable patient/transplant survival and superior kidney function versus cyclosporine-treated patients at 12[21,22] and 36 months posttransplantation.[23,24] Long-term follow-up data from the intention-to-treat populations of BENEFIT and BENEFIT-EXT have shown that belatacept provides sustained benefit to kidney function and a favorable safety profile through 7 years of treatment.[25,26] In addition, at 7 years post-transplantation, belatacept was associated with a 43% reduction in risk for death or transplant loss in recipients of standard-criteria donor kidneys.[25]

Belatacept was studied as conversion therapy in patients maintained on CNI-based immunosuppression (cyclosporine or tacrolimus) in a phase 2 trial,[27,28] the primary outcome of which was change in estimated glomerular filtration rate (eGFR) from baseline to 12 months postrandomization.[27] At 12 months postconversion, kidney function improvements relative to baseline were statistically significantly greater in patients who switched to belatacept-based immunosuppression versus those who continued CNI therapy (7.0 vs 2.1 mL/min/1.73 m^2; $P = 0.006$). Moreover, the switch from a CNI to belatacept was not associated with increased risk for death or transplant loss. Acute rejection occurred in 6 of 84 (7%) patients in the belatacept treatment group, all within the first 6 months of treatment, and in no patient in the CNI treatment group.[27] Among patients who continued to participate in the study beyond month 12, mean change in eGFR from baseline to month 24 remained greater in patients randomly assigned to switch to belatacept versus those who remained on CNI treatment (8.8 vs 0.3 mL/min/1.73 m^2). Between months 12 and 24, acute rejection occurred in no belatacept-treated patient and in 3 patients who remained on CNI-based immunosuppression.[28] We summarize outcomes at 36 months postrandomization in the intention-to-treat population of this phase 2 conversion study.

METHODS

Phase 2 Study Design

The design of this open-label multicenter study has been described (ClinicalTrials.gov study number NCT00402168).[27,28] Briefly, study participants were adults receiving a living or deceased donor kidney transplant in the 6 to 36 months prior to trial enrollment. To be eligible, patients had to be receiving CNI-based maintenance immunosuppression and have stable kidney function (eGFR, 35-75 mL/min/1.73 m^2). Patients were randomly assigned (1:1) to switch to 5 mg/kg of belatacept (intravenous; days 1, 15, 29, 43, and 57 and every 28 days thereafter) or to remain on existing CNI-based therapy, with randomization stratified by CNI regimen (cyclosporine or tacrolimus) and site.[27] To ensure that all patients had the opportunity to receive belatacept, patients randomly assigned to continuous CNI-based immunosuppression who consented to participate in the long-term extension were allowed to switch to belatacept after month 24, if deemed clinically appropriate by the study investigator (n = 16). The study was approved by the ethics committees/institutional review boards at participating centers and conformed to Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Outcomes and Analyses

The primary objective of this analysis was to assess the ongoing safety and tolerability of belatacept in the intention-to-treat population. AEs and serious AEs were mapped to Medical Dictionary for Regulatory Activities (MedDRA), version 14.0. Because treatment duration varied between patients, incident rates of AEs and serious AEs were adjusted for each patient's treatment exposure and calculated as number of AEs and serious AEs divided via duration of treatment exposure in 100 person-years. Secondary end points included eGFR (determined using the 6-variable MDRD [Modification of Diet in Renal Disease] Study equation[29]), acute rejection, death, and transplant loss.

Mean eGFRs and 95% confidence intervals (CIs) were determined from month 1 to month 36 using a repeated-measures model with an unstructured covariance matrix. This model takes into account between-patient variability and the intrapatient correlation of eGFR measurements over time and included time, treatment, and a time-by-treatment interaction (no adjustment was made for other potentially confounding covariates). Time was regarded as a categorical variable (intervals of 3 months up to month 12 and every 6 months thereafter). Missing data were assumed to be missing completely at random. Sensitivity analysis was performed in which eGFR values that were missing due to death or transplant loss were imputed as zero.

A slope-based model was also used to determine whether there was a difference between the slope for the belatacept group and the

slope for the CNI group. The slope-based model assumed that the relationship between eGFR values over time was linear. The difference between slopes was tested with the use of a contrast statement within the SAS model (SAS software, version 9.2; SAS Institute Inc). Time was regarded as a continuous variable; treatment, as a fixed effect; and intercept and time, as random effects (no adjustment was made for other potentially confounding covariates). Sensitivity analysis was performed in which eGFR values that were missing due to death or transplant loss were imputed as zero.

The cumulative event rate for acute rejection was calculated for each treatment group using the Kaplan-Meier method. Time to death and/or time to transplant loss in each treatment group were determined using the Kaplan-Meier method and compared using log-rank test. No adjustment was made for multiplicity testing. The development of donor-specific antibodies was assessed centrally at baseline; months 6, 12, 24, and 36; and the time of suspected acute rejection episodes. Hazard ratios (HRs) and 95% CIs for the efficacy end points were derived using Cox regression.

RESULTS

Patient Disposition

In total, 74 of 84 (88%) belatacept-treated patients and 72 of 89 (81%) patients in the CNI group were followed up for the full 36-month period. Five belatacept-treated patients discontinued treatment by month 36 due to lack of efficacy (n = 2), AE (n = 1 [polyoma virus–associated nephropathy]), death (n = 1), and other (n = 1). Fourteen patients in the CNI treatment group discontinued treatment by month 36 for unknown reasons (n = 4), withdrawal of consent (n = 3), AE (n = 2 [pulmonary edema and nephropathy, n = 1; cellulitis, n = 1]), other (n = 2), administrative reason (n = 1), death (n = 1), and lack of efficacy (n = 1). The CNI group also included 16 patients who switched to belatacept after month 24, as permitted in the study protocol. Overall, treatment groups were balanced in baseline demographics, immunologic factors, and donor characteristics (Table 1).

Safety

At 36 months postrandomization, the cumulative frequency of serious AEs was similar for the belatacept (33 of 84 [39%]) and CNI (36 of 89 [40%]) groups. The incidence rate of serious infections per 100 person-years of treatment exposure was similar for the belatacept and CNI groups (10.21 and 9.31 per 100 person-years, respectively; Table 2). However, more belatacept-treated patients had any-grade viral infections (14.60 per 100 person-years) versus those in the CNI (11.00 per 100 person-years) treatment group. The most common any-grade viral infections were influenza, herpes, and cytomegalovirus viremia. More patients had any-grade fungal infections in the belatacept group (9.73 per 100 person-years) than in the CNI group (2.58 per 100 person-years); the most common types of fungal infections were onychomycosis and tinea versicolor. The frequency of any-grade malignancies was similar in the belatacept (3.01 per 100 person-years) and CNI (3.41 per 100 person-years) groups; the most common malignancies were basal cell carcinoma and squamous cell carcinoma. No patient in either treatment group developed posttransplantation lymphoproliferative disorder. Serious proteinuria occurred in 1 belatacept-treated patient (0.42 per 100 person-years) and no patient in the CNI treatment group.

Kidney Function

From month 1 to month 36, mean eGFR increased for the belatacept treatment group, but not for the CNI treatment group (Fig 1). Mean eGFRs at months 12, 24, and 36 in the belatacept group were 60.3, 62.4, and 62.4 mL/min/1.73 m^2, respectively. Corresponding values in the CNI group were 56.9, 55.0, and 55.6 mL/min/1.73 m^2, respectively. The estimated difference in eGFRs significantly favored belatacept-based versus continued CNI-based immunosuppression ($P = 0.01$ for the overall treatment effect). In terms of change in mean eGFR from month 1 to month 36, the slope-based analysis showed that patients randomly assigned to the belatacept group had an estimated gain in eGFRs of 1.90 (95% CI, 0.89-2.92) mL/min/1.73 m^2 per year, whereas those randomly assigned to the CNI treatment group had an estimated gain in eGFRs of 0.07 (95% CI, −0.96 to 1.09) mL/min/1.73 m^2 per year. eGFR slopes diverged significantly between the 2 treatment groups over time (P for the time-by-treatment interaction effect = 0.01).

Sensitivity analysis in which eGFRs that were missing due to death or transplant loss were imputed as zero yielded similar results. Mean eGFRs at months 12, 24, and 36 in the belatacept group were 60.3, 61.9, and 61.0 mL/min/1.73 m^2, respectively. Corresponding values in the CNI group were 56.4, 54.3, and 54.7 mL/min/1.73 m^2, respectively. The estimated difference in eGFRs significantly favored belatacept-based versus continued CNI-based immunosuppression ($P = 0.02$ for the overall treatment effect). In terms of change in mean eGFR from month 1 to month 36, the slope-based analysis with imputation showed that patients randomly assigned to the belatacept group had an estimated gain in eGFRs of 1.39 (95% CI, 0.153-2.626) mL/min/1.73 m^2 per year, whereas those randomly assigned to the CNI group had an estimated change of −0.215 (95% CI, −1.453 to 1.023) mL/min/1.73 m^2 per year. In contrast to the slope-based analysis without imputation, eGFR slopes deriving from sensitivity analysis did not diverge significantly between the belatacept and CNI treatment groups (P for the time-by-treatment interaction effect = 0.07).

Acute Rejection

At month 36 postrandomization, cumulative rates for the proportion of patients with acute rejection in

Table 1. Baseline Characteristics

	Belatacept (n = 84)	CNI (n = 89)
Mean age, y	45.3 ± 13.5	44.3 ± 13.0
Male sex	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	35 (42)	43 (48)
Previous no. of transplants		
0	74 (88)	77 (87)
1	10 (12)	10 (11)
2	0 (0)	2 (2)
Highest panel-reactive antibodies		
<20%	63 (75)	64 (72)
≥20%	3 (4)	5 (6)
Missing	18 (21)	20 (23)
Baseline eGFR, mL/min/1.73 m^2	53.5 ± 11.0	54.5 ± 10.3
Time from transplantation to randomization, mo	19.4 ± 9.2	20.1 ± 9.4
CNI		
Cyclosporine	37 (44)	39 (44)
Trough serum cyclosporine level, ng/mL[a]	160.2 ± 41.81	154.4 ± 38.08
Tacrolimus	47 (56)	50 (56)
Trough serum tacrolimus level, ng/mL[a]	7.2 ± 1.77	7.5 ± 1.44
Adjunctive immunosuppressive agents[b]		
Azathioprine	6 (7)	3 (3)
MMF/MPA	77 (93)	83 (94)
Sirolimus	1 (1)	0 (0)
Systemic corticosteroids[b]	73 (88)	71 (81)

Note: Continuous variables given as mean ± standard deviation; categorical variables, as count (proportion).

Abbreviations: CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MMF, mycophenolate mofetil; MPA, mycophenolic acid.

[a]Cyclosporine trough levels based on data available for 36 patients in the belatacept group and 37 patients in the CNI group; tacrolimus trough levels based on data available for 45 patients in the belatacept group and 46 patients in the CNI group.

[b]Prerandomization data for adjunctive agents were not available for 3 patients in the CNI group; data were based on randomly assigned treated patients (belatacept, n = 83; CNI, n = 88).

Adapted with permission from Rostaing et al.[27]

the belatacept and CNI groups were 8.38% and 3.60%, respectively. HR for the comparison of belatacept-based versus continuous CNI-based immunosuppression for the probability of acute rejection was 2.50 (95% CI, 0.65-9.65; p = 0.2; Fig 2). In the belatacept group, 1 patient each had grade IA, grade IB, and grade IIB acute rejection, and 4 patients had grade IIA acute rejection by month 36. In the CNI group, 1 patient had grade IB acute rejection, and 2 patients had grade IIA acute rejection by month 36. No patient in either treatment group had grade III acute rejection.

Table 2. Cumulative Incidence Rates of Selected Adverse Events

Event	Belatacept (n = 84)	CNI (n = 89)
Serious infections	10.21	9.31
Urinary tract infection	2.57	0.41
Gastroenteritis	2.13	0.82
Pyelonephritis	0.84	0.83
Upper respiratory tract infection	0.84	0.00
Escherichia spp urinary tract infection	0.41	0.83
Pneumonia	0.41	0.82
Cellulitis	0.00	0.82
Cytomegalovirus infection	0.00	0.83
Any-grade viral infections	14.60	11.00
Influenza	4.45	4.54
Herpes virus infection	1.71	0.84
Cytomegalovirus viremia	1.71	0.00
Oral herpes	1.28	1.27
Herpes zoster	1.29	0.85
Epstein-Barr viremia	1.27	0.00
Cytomegalovirus infection	0.84	0.85
BK virus infection	0.85	0.00
Anogenital warts	0.00	0.84
Any-grade fungal infections	9.73	2.58
Onychomycosis	2.13	1.27
Tinea versicolor	2.19	0.00
Fungal infection	1.28	0.42
Fungal skin infection	0.85	0.84
Body tinea	0.85	0.00
Vulvovaginal candidiasis	0.84	0.00
Any-grade malignancies	3.01	3.41
Basal cell carcinoma	1.27	2.11
Squamous cell carcinoma of the skin	0.41	1.23

Note: Values given are incidence rates per 100 person-years of treatment exposure. Only adverse events occurring in ≥2% of patients in either treatment group are reported.

Abbreviation: CNI, calcineurin inhibitor.

Patient and Transplant Survival

By month 36, one patient in each treatment group died and one patient in each group had transplant loss. Kaplan-Meier–estimated rates of death or transplant loss in the belatacept group at months 12, 24, and 36 were 0.00%, 1.23%, and 2.47%, respectively. Corresponding values in the CNI group were 1.14%, 2.37%, and 2.37%, respectively. HR for the comparison of the belatacept group with the CNI group was 1.00 (95% CI, 0.14-7.07; $P = 0.9$; Table 3).

Kaplan-Meier–estimated rates of death in the belatacept group at months 12, 24, and 36 were 0.00%, 0.00%, and 1.25%, respectively. Corresponding values in the CNI group were 1.14%, 1.14%, and 1.14%, respectively. HR for the comparison of the belatacept group with the CNI group was 1.02 (95% CI, 0.06-16.27; $P = 0.9$; Table 3).

Kaplan-Meier–estimated rates of death-censored transplant loss in the belatacept group at months 12, 24, and 36 were 0.00%, 1.23%, and 1.23%, respectively. Corresponding values in the CNI group were 0.00%, 1.25%, and 1.25%, respectively. HR for the comparison of the belatacept group with the CNI group was 0.98 (95% CI, 0.06-15.69; $P = 0.9$; Table 3).

Donor-Specific Antibodies

The development of donor-specific antibodies was infrequent and similar between treatment groups. Cumulative rates for the proportion of patients who developed de novo donor-specific antibodies by month 36 in the belatacept and CNI groups were 0.00% and 2.30%, respectively.

DISCUSSION

This analysis demonstrated the potential for kidney transplant recipients with stable transplant function to convert from CNI-based to belatacept-based immunosuppression. Overall, conversion to belatacept was well tolerated and was associated with improved kidney function over 36 months.

Compared to the continuous CNI treatment group, numerically fewer patients randomly assigned to switch to belatacept-based immunosuppression

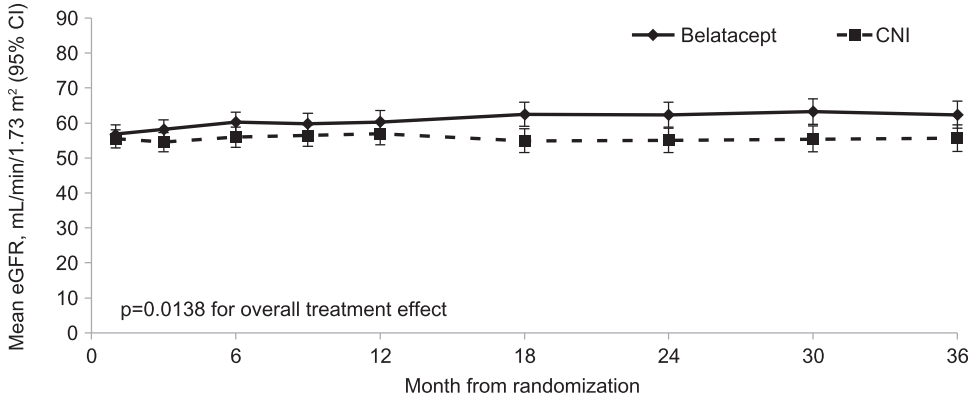

Figure 1. Mean estimated glomerular filtration rate (eGFR) from month 1 to month 36. Abbreviations: CI, confidence interval; CNI, calcineurin inhibitor.

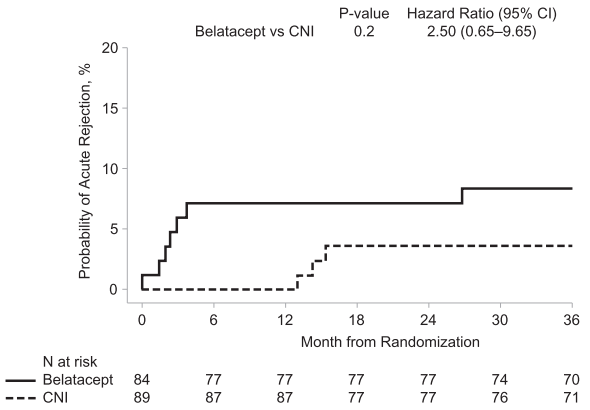

Figure 2. Probability of acute rejection. Abbreviations: CI, confidence interval; CNI, calcineurin inhibitor.

discontinued treatment prior to month 36 (6% vs 16%, respectively). Safety profiles of both treatment groups were similar over 36 months, although treatment exposure−adjusted incidence rates of any-grade viral infections and any-grade fungal infections were numerically higher with belatacept-based versus continued CNI-based therapy. These data support the favorable tolerability of belatacept that was observed in this cohort at 12 and 24 months postconversion.[27,28] Dyslipidemia and proteinuria, which can lead to treatment discontinuation, are AEs common to mTOR inhibitor–based immunosuppression.[9,12,14,15,19] Serious proteinuria was an infrequent event in this study, occurring in only 1 belatacept-treated patient and in no patient who continued CNI-based immunosuppression.

Compared with patients who remained on tacrolimus or cyclosporine treatment, those who switched to belatacept sustained early improvements in kidney function for up to 36 months postconversion. Based on results from the mixed model, belatacept-treated patients had an estimated gain in eGFRs of 1.90 mL/min/1.73 m^2 per year. This increase is both clinically and statistically significant and was supported by sensitivity analysis in which eGFR values that were missing because of death or transplant loss were imputed as zero. However, statistical significance was not reached in this slope-based sensitivity analysis, likely due in part to the increased variability introduced by adding zero values. In addition, differences in kidney function measured at 36 months postrandomization may have been confounded by the 16 patients who switched from CNI-based to belatacept-based immunosuppression after month 24. However, given the kidney function improvements observed in the belatacept treatment group, this would diminish the statistical and clinical differences between treatment arms in favor of CNI-based immunosuppression.

Table 3. Time to Death and/or Transplant Loss

	Belatacept vs CNI
Time to death or transplant loss	1.00 (0.14-7.07)
Time to death	1.02 (0.06-16.27)
Time to death-censored transplant loss	0.98 (0.06-15.69)

Note: Values are given as hazard ratio (95% confidence interval). $P = 0.9$ for all.

Abbreviation: CNI, calcineurin inhibitor.

Improvements in kidney function have also been observed in kidney transplant recipients converting from CNI-based to mTOR inhibitor–based immunosuppression; in the ZEUS and CENTRAL studies of everolimus and the SMART study of sirolimus, patients who switched to a CNI-free regimen had significantly higher GFRs at 12 months postswitch versus those who continued CNI-based therapy.[9,12,13] Statistically significant differences in favor of mTOR inhibitor–based therapy were seen in the ZEUS and SMART studies at 36 months postswitch,[17,18] but not in the CENTRAL study.[20] Thus, mTOR inhibitor–based regimens may not consistently sustain improvements in kidney function over the long term. This is supported by the randomized ASCERTAIN (Assessment of Everolimus in Addition to Calcineurin Inhibitor Reduction in the Maintenance of Renal Transplant Recipients) and Spare-the-Nephron (sirolimus) studies, in which no statistically significant differences in measured GFRs were seen between the CNI and mTOR inhibitor treatment groups at 24 months postswitch.[6,8]

Cumulative rates of acute rejection up to month 36 were low; however, acute rejection rates were numerically higher and occurred earlier among patients randomly assigned to the belatacept versus the continued CNI treatment group. There were few deaths and few transplant losses, with no statistically significantly differences between treatment groups in risk for death and/or transplant loss over 36 months.

The development of de novo donor-specific antibodies was an infrequent occurrence in this phase 2 study. This finding, coupled with the fact that few patients receiving first-line treatment with belatacept-based immunosuppression in the phase 3 clinical trials developed de novo donor-specific antibodies,[21-26] suggest that belatacept may be associated with a lower incidence of donor-specific antibody formation. Data for the incidence of donor-specific antibody formation following conversion from CNI-based to mTOR inhibitor–based immunosuppression are limited; however, a retrospective subanalysis of the ZEUS and CRAD001ADE13 trials found that conversion to everolimus was associated with increased risk for both de novo donor-specific antibody development and antibody-mediated rejection.[30]

There are limitations associated with the present analysis that may preclude definitive interpretation of the results. First, sample sizes were small. Second, the trial design was open label, which may have introduced bias. Last, the large range of times between transplantation and conversion (6-36 months) may have confounded results; studies have demonstrated that patient outcomes may be improved with earlier conversion from CNI-based regimens.[16]

Despite these limitations, our results suggest that the improvements in kidney function seen in patients who switched from CNI-based to belatacept-based immunosuppression were sustained over 36 months and may help preserve long-term transplant function. This exploratory analysis indicates that switching from a CNI-based to a belatacept-based regimen may represent a safe and effective clinical approach to long-term immunosuppression, one that is being further explored in an ongoing phase 3b trial (ClinicalTrials.gov study number NCT01820572).

ACKNOWLEDGEMENTS

Some of the data in this study were presented at the American Transplant Congress, Boston, MA, June 11-15, 2016.

Support: This study was supported by Bristol-Myers Squibb, which markets belatacept. Medical writing and editorial assistance (provided by Tiffany DeSimone, PhD, of CodonMedical, an Ashfield Company, part of UDG Healthcare plc) was funded by Bristol-Myers Squibb.

Financial Disclosure: Dr del Carmen Rial reports grants and nonfinancial support from Bristol-Myers Squibb related to the submitted work, as well as grants and personal fees from Pfizer, Bristol-Myers Squibb, Novartis, and Astellas. Dr Alberu reports grants from Pfizer and Bristol-Myers Squibb and has received personal fees from Pfizer, Roche, Genzyme, and Bristol-Myers Squibb. Dr Manfro reports grants from Bristol-Myers Squibb. Dr Vincenti reports grants from Bristol-Myers Squibb, Alexion, Pfizer, Astellas, Novartis, and Genetech. Dr Jones-Burton is an employee of Bristol-Myers Squibb. Dr Kamar reports personal fees from Novartis, Sanofi, Astellas, Amgen, and MSD and nonfinancial support from Fresenius and Roche. The other authors declare that they have no other relevant financial interests.

Contributions: Data acquisition: JMG, MdCR, JA, SMS, RCM, GN, FV, NK; data analysis/interpretation: all authors. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Peer Review: Evaluated by 2 external peer reviewers, a Statistical Editor, a Co-Editor, and Editor-in-Chief Levey.

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