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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.

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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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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