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ORIGINAL ARTICLE

Improvement in renal function in kidney transplant recipients switched from cyclosporine or tacrolimus to belatacept: 2-year results from the long-term extension of a phase II study

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Summary

Kidney transplant recipients who switched from a calcineurin inhibitor (CNI) to belatacept demonstrated higher calculated glomerular filtration rates (cGFRs) at 1 year in a Phase II study. This report addresses whether improvement was sustained at 2 years in the long-term extension (LTE). Patients receiving cyclosporine or tacrolimus were randomized to switch to belatacept or continue CNI. Of 173 randomized patients, 162 completed the 12-month main study and entered the LTE. Two patients (n = 1 each group) had graft loss between Years 1–2. At Year 2, mean cGFR was 62.0 ml/min (belatacept) vs. 55.4 ml/min (CNI). The mean change in cGFR from baseline was +8.8 ml/min (belatacept) and +0.3 ml/min (CNI). Higher cGFR was observed in patients switched from either cyclosporine (+7.8 ml/min) or tacrolimus (+8.9 ml/min). The frequency of acute rejection in the LTE cohort was comparable between the belatacept and CNI groups by Year 2. All acute rejection episodes occurred during Year 1 in the belatacept patients and during Year 2 in the CNI group. There were more non-serious mucocutaneous fungal infections in the belatacept group. Switching to a belatacept-based regimen from a CNI-based regimen resulted in a continued trend toward improved renal function at 2 years after switching.

Introduction

Calcineurin inhibitors (CNIs) provide a well-characterized benefit/risk profile in kidney transplantation – decreasing the risk for acute rejection, but over time contributing to nephrotoxicity that can accelerate graft loss [1–4]. In addition, the non-immunologic toxicities of CNIs can exacerbate hypertension and dyslipidemia, and may be associated with new-onset diabetes after transplant [5–9]. The avoidance of CNI-based regimens in *de novo* transplants or switching patients from a CNI-based regimen to preserve renal function while maintaining immunosuppressive efficacy has been clinically difficult to achieve. Several studies utilizing mammalian target-of-rapamycin inhibitors (mTORs) have

been hampered by high rates of discontinuation and/or increased risk for acute rejection versus CNI-based therapy [10–14]. Other well-tolerated CNI-avoiding regimens do not exhibit adequate immunosuppressive efficacy [15,16].

Belatacept, a selective co-stimulation blocker that prevents T-cell activation, has demonstrated better preservation of renal structure and function compared with CNIs in *de novo* kidney transplant recipients [17–24]. At Year one, this exploratory Phase II study found that switching stable patients maintained on a CNI-based regimen to a belatacept-based regimen may be associated with a similar rate of survival and trends toward better renal function among those switched to belatacept. There was a 7% rate of acute rejection episodes within the first 6 months after the switch [25].

This manuscript summarizes the 2-year safety and efficacy profile of belatacept after switching from a CNI-based regimen for patients who completed the 12-month main study and entered the long-term extension phase.

Materials and methods

As previously described, this was a randomized, open-label, multicenter, Phase II clinical trial of kidney transplant patients receiving a CNI-based regimen (CsA or TAC) who were randomly allocated 1:1 to switch to belatacept or remain on their existing therapy. Primary and secondary outcomes were assessed at month 12, after which patients were eligible to enter the LTE [25]. All patients who completed the 12-month main study and who consented to participate in the LTE continued their original treatment assignment. The study was 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 (ICH GCP) 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 evaluates accrued efficacy and safety data. The study is registered with ClinicalTrials.gov (id: NCT00402168).

Patients

The study included adult recipients of a renal allograft from a living or deceased donor at least 6 months, but no longer than 36 months prior to enrollment. CNI-based maintenance immunosuppression was to have been maintained at a stable dose during the month immediately before randomization, and patients were to have had a cGFR between 35 and 75 ml/min/1.73 m^2 at enrollment, based on the Modification of Diet in Renal Disease formula [26]. Patients received stable doses of background immunosuppression (mycophenolate mofetil, mycophenolic acid, sirolimus, or azathioprine); patients receiving corticosteroids at enrollment continued at a stable dose. Other inclusion/exclusion criteria were as previously described [25].

Interventions

Patients were randomized 1:1 to belatacept or to remain on their existing therapy. Belatacept 5 mg/kg was given by intravenous infusion on Days 1, 15, 29, 43, and 57, and then every 28 days thereafter. For those patients randomized to belatacept, the CNI dose was tapered as follows: 100% on Day 1, to 40–60% on Day 15, 20–30% on Day 23, and none on Day 29 and beyond. Patients allocated to the comparator group continued receiving CsA or TAC according to local practice and the respective package inserts. Cyclosporine doses were maintained at trough serum concentrations of 100–250 ng/ml; tacrolimus doses were maintained at trough serum concentrations of 5–10 ng/ml.

Statistical analyses

All efficacy and safety analyses were conducted on the ITT-LTE population, defined as patients who completed 12-month main study treatment and entered the long-term extension phase with their original treatment assignment. Calculated GFR and its change from baseline were summarized descriptively. For patients who died or had graft loss, GFR was imputed as 0. The study was not powered to assess the statistical significance of the change from baseline in cGFR between the belatacept and CNI groups. The percent of patients surviving with a functioning graft, the frequency of acute rejection, and adverse events were summarized descriptively.

Results

Of 173 patients originally randomized to switch to belatacept ($n = 84$) or remain on CNI-based therapy ($n = 89$), 167 completed 1 year of treatment ($n = 81$ belatacept; $n = 86$ CNI). One hundred sixty-two patients ($n = 81$ belatacept; $n = 81$ CNI) entered the LTE and constituted the intent-to-treat population for the LTE (ITT-LTE). Among the ITT-LTE population, three patients discontinued study medication by year 2 (CNI: $n = 1$ withdrew consent, $n = 1$ lack of efficacy; belatacept: $n = 1$ adverse event). Baseline characteristics of patients entering the LTE, including calculated GFR (cGFR), were similar to the original ITT population [25].

Ninety-nine percent of patients in each group survived with a functioning graft by Year 2. There was one graft loss in each group approximately 18 months postrandomization. There was one previously-reported death due to myocardial infarction in the CNI arm 5 months postrandomization [24].

Acute rejection

Among the ITT-LTE population, four of 81 patients in the belatacept group (5%) had an acute rejection episode by Year 2. All acute rejection episodes occurred within the first 6 months after switch. None of the patients with acute rejection died, and one had a graft loss by Year 2 (associated with BK virus). There were no additional acute rejection episodes from 6 to 24 months in the belatacept group. Of note, the ITT-LTE population did not include two patients who experienced an acute rejection episode during the 6 months, discontinued study therapy, and did not enter the LTE.

Three of 81 patients in the CNI group (4%) had an acute rejection episode from Year 1 to Year 2. Two of the three patients were treated for their acute rejection episode – one with corticosteroids alone and one with steroids and lymphocyte depleting therapy. None died and one (with an AR episode treated with corticosteroids alone) experienced a functional graft loss. Figure 1 depicts the timing of acute rejection episodes in each treatment group through Year 2.

Change in cGFR from baseline

Among the ITT-LTE population, the mean change in cGFR from baseline to Year 1 was +7.1 ml/min/1.73 m^2 in the belatacept group and was +2.8 ml/min/1.73 m^2 in the CNI group. At 2 years, the mean change from baseline was +8.8 ml/min/1.73 m^2 in the belatacept group, and was +0.3 ml/min/1.73 m^2 in the CNI group. The difference in the mean change in cGFR between the belatacept group and the CNI group was 4.3 ml/min/1.73 m^2 at Year 1 and was 8.5 ml/min/1.73 m^2 at Year 2.

The difference in the change in cGFR from baseline between the belatacept group and the CNI group was observed whether patients were initially on CsA or TAC. At Year 2, the mean change in cGFR from baseline was +8.9 ml/min/1.73 m^2 in patients switched from CsA to belatacept and was +1.1 ml/min/1.73 m^2 in those who remained on CsA. At Year 2, the mean change in cGFR from baseline was +8.7 ml/min/1.73 m^2 in patients switched from TAC to belatacept and was −0.2 ml/min/1.73 m^2 for those who remained on TAC. The cGFR over time among patients who had initially been maintained on a CsA- or TAC-based regimen is depicted in Fig. 2 (top and bottom).

The change in cGFR from baseline among patients converting from CNI to belatacept was evident across a range of baseline cGFR. (Figure 3) Among patients with high baseline renal function (cGFR >60), patients switched to belatacept had a mean increase in cGFR of 8.5 ml/min/1.73 m^2 from baseline to Year 2, while patients remaining

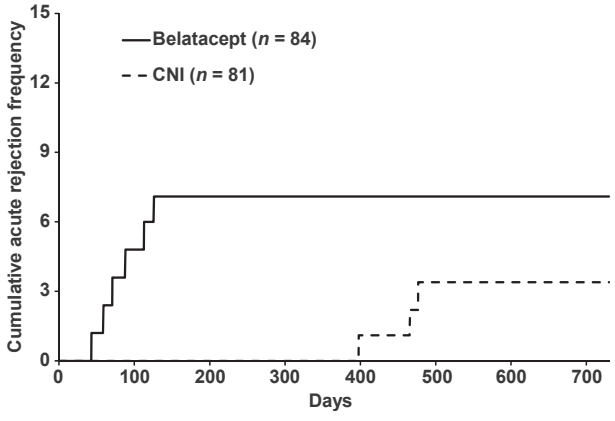

Figure 1 Cumulative acute rejection frequency over time.

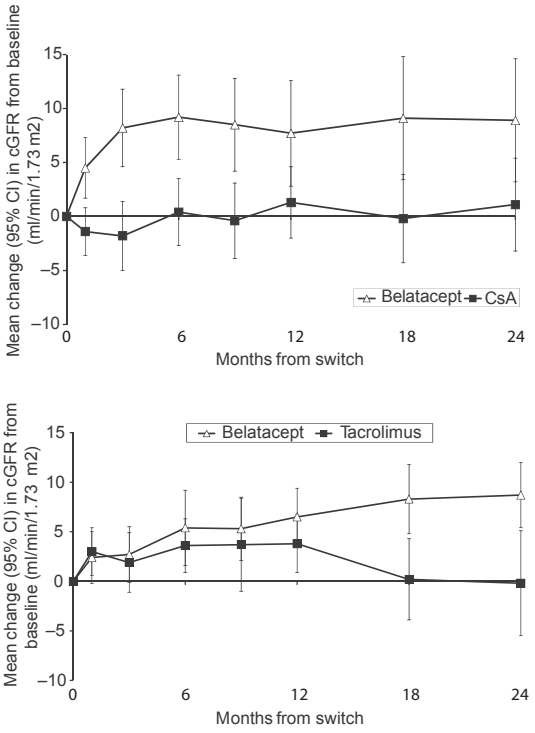

Figure 2 Mean change in calculated glomerular filtration rate from baseline to year 2. (top) Patients who were stably maintained on a CsA-based immunosuppressive regimen were either switched to a belatacept-based regimen or continued on CsA. (bottom) Patients who were stably maintained on a TAC-based immunosuppressive regimen were either switched to a belatacept-based regimen or continued on TAC.

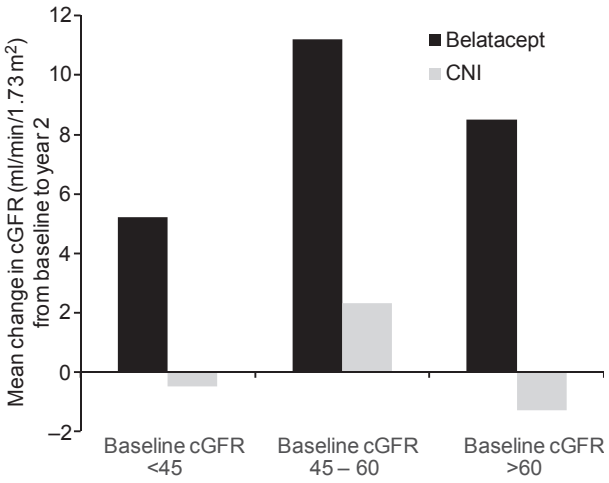

Figure 3 Mean change from baseline to year 2 in calculated glomerular filtration rate (cGFR) by baseline cGFR.

on a CNI had a mean decrease of 1.3 ml/min/1.73 m^2. Among patients with baseline renal function between 45 and 60 ml/min/1.73 m^2, patients switched to belatacept had a mean increase in cGFR of 11.2 ml/min/1.73 m^2 from baseline to Year 2, while patients remaining on a CNI had a mean increase of 2.3 ml/min/1.73 m^2. Among patients with baseline renal function cGFR <45 ml/min/1.73 m^2, patients switched to belatacept had a mean increase in cGFR of 5.2 ml/min/1.73 m^2 from baseline to Year 2, whereas patients remaining on a CNI had a mean decrease of 0.5 ml/min/1.73 m^2.

Safety

The most common serious adverse events are listed in Table 1, along with selected events of interest. More fungal infections were observed in the belatacept group; however, most cases were not serious and were typically mucocutaneous. There were no cases of post-transplant lymphoproliferative disorder reported. There was 1 case of tuberculosis in the belatacept group; the patient remained on belatacept and the infection resolved with treatment.

Discussion

The results from this LTE of a Phase II study showed that patients switched from a CNI to belatacept may experience improved renal function. There were no new acute rejection episodes in the belatacept group from Year 1 to Year 2, and the switch appeared to be well tolerated, with a low rate of discontinuation. The safety profile appeared to be similar between the two groups. There were fungal infections in the belatacept group, but as in the Phase III studies of belatacept, they were typically mucocutaneous and mild in nature.

Table 1. Frequency of the most common serious adverse events, serious infections, overall malignancies, fungal infections, and viral infections.

n (%)	Belatacept (*n* = 81)	CNI (*n* = 81)
Serious adverse events*	30 (37)	27 (33)
Pyrexia	4 (5)	0
Basal cell carcinoma	3 (4)	4 (5)
Gastroenteritis	3 (4)	2 (2)
Urinary tract infection	3 (4)	1 (1)
Serious infections	16 (20)	15 (19)
Gastroenteritis	3 (4)	2 (2)
Urinary tract infection	3 (4)	1 (1)
Pyelonephritis	2 (2)	2 (2)
Upper respiratory tract infection	2 (2)	0
Malignancies	4 (5)	6 (7)
Fungal infections	14 (17)	3 (4)
Tinea versicolor	5 (6)	0
Fungal infection	3 (4)	1 (1)
Body tinea	2 (2)	0
Viral infections	16 (20)	18 (22)
Influenza	6 (7)	8 (10)
Herpes zoster	3 (4)	2 (2)
Oral herpes	2 (2)	2 (2)
Herpes virus infection	2 (2)	1 (1)
BK virus infection	2 (2)	0
CMV viremia	2 (2)	0

*Serious adverse events in ≥3 patients in either group, ordered by frequency in the belatacept group. Adverse events were classified by investigators using MedRA terms.

The changes in renal function observed by switching to belatacept at Year 1 were evident at 2 years, with similar differences in belatacept-treated patients and those who continued treatment with either CsA or TAC. This difference in the mean change in cGFR from baseline reached approximately 9 ml/min/1.73 m^2 at Year 2, an increase that has been described as clinically meaningful in a CNI switch setting [27]. Switching from a CsA-based regimen to a sirolimus-based regimen was associated with a 4–5 ml/min improvement in cGFR by 52 weeks in the CONCEPT study [28].

However, while conversion from CsA-based therapy to mTOR-based regimens has demonstrated some ability to preserve renal function, tolerability remains a concern [10,29–31]. An open-label, randomized trial reported that early (10–24 days post-transplant) conversion from a CsA-based regimen to a sirolimus-based regimen was associated with approximately 10 ml/min better cGFR at 1 year [32]. However, almost twice as many more patients in the sirolimus-based arm discontinued therapy, usually due to adverse events. In the CONVERT study, patients with a baseline GFR of 20–40 ml/min/1.73 m^2

were discontinued from the study due to a disproportionate number of patients converted from CNI- to sirolimus-based therapy experienced acute rejection, graft loss, or death [33]. In the current study, high patient retention was notable, and only one patient in the belatacept ITT-LTE arm discontinued therapy due to adverse events.

In this study, the rate and timing of acute rejection are consistent with results expected when switching patients who are maintained on a stable CNI-based regimen. Acute rejection episodes were limited to the first several months after switch, with no additional acute rejection episodes observed from months 6 to 24. In the ZEUS study, acute rejection rates were approximately 10% from month 4.5 through Month 12 after conversion from CsA to everolimus, and was 15% from baseline to Month 12 [27]. Conversion from CNI-based therapy to everolimus-based immunosuppression with either CNI elimination or minimization was associated with 5–6% acute rejection rates at 24 months [34]. Biopsy-confirmed acute rejection occurred in approximately 6–7% of patients in the Spare the Nephron trial during the first 12 months and in approximately 10–12% of patients during the first 24 months. Of note, however, the renal function benefits observed at 12 months in the group switched to a sirolimus-based regimen in Spare the Nephron had diminished by 24 months, in contrast to the continuing improvement observed in this study [35].

This study has limitations that restrict the conclusions. The study was an exploratory, open-label trial with a limited number of patients and lack of statistical power, which limits the conclusions that can be drawn regarding differences in renal function. Centrally read biopsies mitigate some risk for bias based on local reading for acute rejection.

Conclusions

The results of this exploratory study suggest that switching from either CsA- or TAC-based therapy to belatacept may result in improved renal function. Acute rejection episodes were limited to the first 6 months post-switch. There were more non-serious fungal infections in the belatacept group. Although belatacept is not currently indicated as part of a conversion regimen, switching from CNI-based therapy to belatacept appears to be an approach in kidney transplant recipients, which may help preserve renal function and lead to better long-term outcomes. These results should be confirmed in a Phase III study.

Authorship

GJ and VF: participated in the design of the study. All authors participated in the conduct of the study, collection of the data, and analysis of the data. Professor Grinyo had primary responsibility for writing the manuscript with the input, review, and approval of all authors.

Funding

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Conflicts of Interest

Dr Grinyo has served as an advisor for Novartis, Bristol-Myers-Squib, Adsorva and Life Cycle Pharma. Dr Alberu has received research grants/contracts from Pfizer and Bristol-Myers Squibb. Dr Manfro has received research grants from Bristol-Myers Squibb, Novartis, and Wyeth. Dr Rial has received fees for expert testimony from Astellas, Bristol-Myers Squibb, Novartis, and Pfizer/Wyeth, and Roche, and has received payment for development of educational presentations from Novartis and Pfizer/Wyeth. Dr Kamar has received honoraria from Novartis, Roche, Pfizer, Genzyme, Astellas, and Amgen. Dr Vincenti has received research grants/contracts from Bristol-Myers Squibb, Pfizer, Novartis, Astellas Pharma, Genzyme, Genentech, and Roche. Drs Contieri, Mondragon, Nainan, and Steinberg have nothing to disclose. Drs Dong and Thomas are employees of Bristol-Myers Squibb.

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