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Long-Term Belatacept Exposure Maintains Efficacy and Safety at 5 Years: Results From the Long-Term Extension of the BENEFIT Study

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The Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial randomized patients receiving a living or standard criteria deceased donor kidney transplant to a more (MI) or less intensive (LI) regimen of belatacept or cyclosporine A (CsA). The 5-year results of the long-term extension (LTE) cohort are reported. A total of 456 (68.5% of intent-to-treat) patients entered the LTE at 36 months; 406 patients (89%) completed 60 months. Between Months 36 and 60, death occurred in 2%, 1% and 5% of belatacept MI, belatacept LI and CsA patients, respectively; graft loss occurred in 0% belatacept and 2% of CsA patients. Acute rejection between Months 36 and 60 was rare: zero belatacept MI, one belatacept LI and one CsA. Rates for infections and malignancies for Months 36–60 were generally similar across belatacept groups and CsA, respectively: fungal infections (14%, 15%, 12%), viral infections (21%, 18%, 16%) and malignancies (6%, 6%, 9%). No new posttransplant lymphoproliferative disorder cases occurred after 36 months. Mean calculated GFR (MDRD, mL/min/1.73 m^2) at Month 60 was 74 for belatacept MI, 76 for belatacept LI and 53 for CsA. These results show that the renal function benefit and safety profile observed in belatacept-treated patients in the early posttransplant period was sustained through 5 years.

Keywords: Belatacept, cyclosporine A, kidney, renal function

Abbreviations: BENEFIT, Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial; cGFR, calculated glomerular filtration rate; CNI, calcineurin inhibitor; CI, confidence intervals; CRF, case report form; CsA, cyclosporine A; ESRD, end-stage renal disease; FDA, US Food and Drug Administration; GFR, glomerular filtration rate; HDL, high-density lipoprotein; ITT, intent-to-treat; LDL, low-density lipoprotein; LI, less intensive; LTE, long-term extension; MDRD, Modification of Diet in Renal Disease; MI, more intensive; MMF, mycophenolate mofetil; PTLD, posttransplant lymphoproliferative disorder; SAE, serious adverse event; SD, standard deviation; SE, standard error

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Introduction

Kidney transplant is the most common organ transplant operation performed in the United States, providing improved survival and quality of life for those with end-stage renal disease. One-year patient survival rates of 96% for deceased donor and 99% for living donor grafts are achieved with currently available immunosuppressive regimens (1). These high rates in allograft survival are mainly attributed to improvements in first-year survival that have occurred over the past decade (2). In a study of 252 910 patients in the Scientific Renal Transplant Registry who received single organ kidney transplant between 1989 and 2009, it was found that the graft half-life for deceased donor transplants was 6.6 years in 1989, increasing to 8.8 years by 2005 (2). Over time, however, even with modern immunosuppressive regimens, there is progressive loss of both grafts and patients, with 5-year patient survival rates for deceased donor and living donor kidney transplants of 84% and 91%, respectively, and 10-year patient survival rates of 64% and 77%, respectively (1).

Since the introduction of cyclosporine A (CsA) in the early 1980s, calcineurin inhibitors (CNIs) have been the primary immunosuppressive agents employed in kidney transplant. Tacrolimus, another CNI, was approved by the US Food and Drug Administration (FDA) for liver transplantation rejection in 1994 and for kidney transplant rejection in 1997. However, despite excellent short-term efficacy, the long-term use of CNIs is associated with nephrotoxicity due to vasoconstriction of afferent and efferent glomerular arterioles, thereby reducing renal blood flow and glomerular filtration rate (GFR), resulting in significant decreases in long-term graft function and survival (3,4). Thus, the need exists for an immunosuppression regimen that maintains efficacy over time while avoiding exacerbation of factors that negatively impact long-term outcomes.

Investigations into immunosuppressants that utilize a different mechanism than the CNIs led to the development of belatacept. Belatacept is a second-generation, higher-avidity variant of abatacept. It differs from the parent molecule by two amino acids within the region that binds CD28-B7 (CD80, CD86), important co-stimulatory molecules required for full T cell activation. Belatacept was approved by the US FDA in June 2011 based on the 3-year results of two open-label, randomized, multicenter, Phase III trials: Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) and BENEFIT-EXT (''extended criteria''). These studies compared a more (MI) or less intensive (LI) regimen of belatacept to CsA in patients receiving a kidney transplant from either living or standard criteria deceased donors (BENEFIT) or extended-criteria deceased donors (BENEFIT-EXT) (5,6). The 3-year results demonstrated comparable patient and graft survival between belatacept and CsA, with better renal function despite higher rates and grades of early (within 6 months) acute rejection (7,8). Improved cardiovascular and metabolic risk profiles were also observed with belatacept (7,8). Based upon the findings at Year 3, the LI regimen was approved for use in adult kidney transplant recipients. The results at 4 years for both populations showed a consistent safety profile over time and persistence of the renal function benefit with belatacept (9,10).

The objective of this current analysis is to expand on previous reports by assessing the 5-year (Month 60) results of the BENEFIT study that investigated the efficacy and safety of belatacept versus CsA in patients with kidney transplant from living donors or standard criteria deceased donors.

Methods

Study design

Details of the methodology of the BENEFIT study have been previously published (5). Here we present the 5-year long-term extension (LTE) phase of this study. BENEFIT was a 3-year, multicenter, international, randomized, partially blinded, active-controlled, parallel-group study. Enrollment began in January 2006, and included adult patients who received a living donor or standard criteria deceased donor kidney transplant. Patients were randomized (1:1:1) to one of two regimens of belatacept (MI or LI) or CsA for primary maintenance of immunosuppression (Figure 1). All patients received basiliximab induction, mycophenolate mofetil (MMF) and corticosteroids.

Patients were eligible for the LTE if they completed 36 months of therapy in the original study, were appropriate to continue their assigned therapy according to their physician and signed informed consent. This LTE population is a subset of the original intent-to-treat (ITT) population, and thereby, this analysis does not take into account outcomes in patients who were discontinued from assigned therapy during the initial 36-month period. Patients in the LTE were required to remain on assigned therapy, and those who discontinued the assigned therapy in the LTE were discontinued from the analysis. Clinical outcomes (other than safety) following discontinuation of the LTE were not collected beyond 56 days after discontinuation.

This study was conducted in accordance with the Declaration of Helsinki, and the ethics committee at each site approved the protocol. All patients

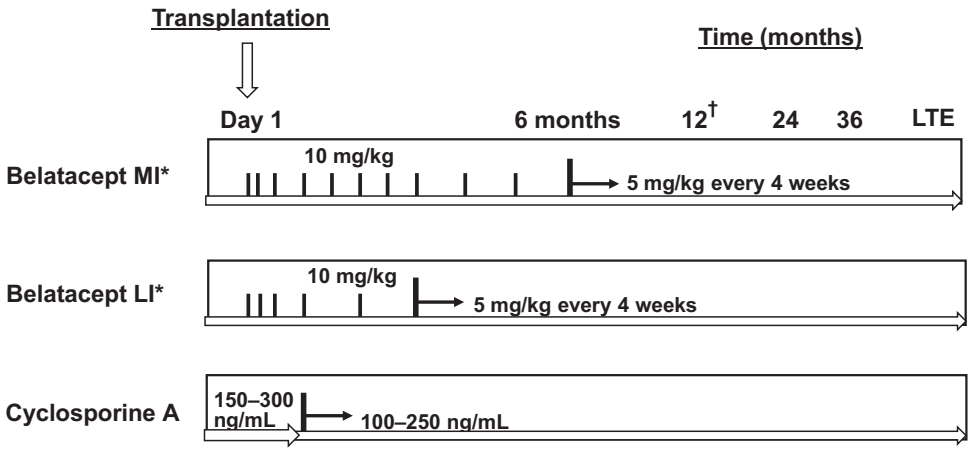

Figure 1: Treatment schema. *All patients received basiliximab induction, mycophenolate mofetil and corticosteroid taper. †Belatacept arms unblinded at 12 months. LI, less intensive; LTE, long-term extension; MI, more intensive.

provided written informed consent prior to inclusion in the study. This trial is registered with ClinicalTrials.gov (ID: NCT00256750).

Outcomes

The primary objective of the LTE was to assess the long-term safety and tolerability of belatacept in subjects who received a kidney transplant, completed 36 months of treatment in the main study and consented to enter the LTE. Other outcomes assessed in this analysis included the proportion of patients surviving with a functioning graft, renal allograft function and acute rejection rates. Independent committees that were blinded to treatment determined the causes of graft loss and death. Renal function was evaluated by calculated GFR (cGFR), using the Modification of Diet in Renal Disease (MDRD) equation, and was derived for an isotope-dilution mass spectrometry traceable assay by dividing the serum creatinine value within the equation by 0.95 (11,12). The original primary endpoints were assessed at 12 months (5). For the LTE, outcomes were assessed from Months 36 to 60, including Months 42, 48 and 54. Laboratory values were assessed every 6 months. Belatacept subjects were seen monthly to receive belatacept infusion. CsA subjects were seen every 3 months and evaluated monthly by phone. Data were recorded at each site on standard paper case report forms (CRFs) provided by Bristol-Myers Squibb, and the data reported on the CRFs were derived from source documents.

Statistical methods

This study assessed the long-term safety and efficacy of belatacept in subjects who had received a kidney transplant and completed the initial study. Those who consented to be included in the LTE continued to receive study medication and were followed for an additional 2 years, and all analyses at 5 years were conducted on the LTE population. Sample sizes were not re-estimated for the LTE. Point estimates and corresponding 95% confidence intervals (CI) with treatment groups were used to summarize the proportion of surviving patients with a functional graft. Data as-observed, without imputation for missing values, were used to calculate mean cGFRs. To assess the trend in renal function over time, an analysis of variance model analyzed the changes in cGFR and metabolic parameters from Months 36 to 60 for each belatacept regimen versus CsA, with treatment as factor and baseline/Month 3 values as covariate, and compared each belatacept regimen to CsA, with randomization group as a factor. Because this was a *post hoc* analysis, the resulting p-values should not be considered conclusive and any conclusions drawn should be considered as hypothesis generating and not hypothesis confirming. Safety was assessed descriptively as frequencies and incidence rates of serious adverse events from Months 36 to 60 in the LTE ($\geq$2% in any group).

Results

Of the 666 patients randomized in the original BENEFIT study, 456 (68.5%) entered the LTE, which included 155 (71%) who received belatacept MI, 165 (73%) who received belatacept LI and 136 (63%) who received CsA (Figure 2). The most common reasons for discontinuing the study before 36 months were lack of efficacy (13.2% belatacept MI, 11.5% belatacept LI and 8.4% CsA) and adverse event (7.3% belatacept MI, 7.1% belatacept LI and 14.9% CsA). A total of 406 patients completed 60 months: 144 (93%) belatacept MI, 151 (92%) belatacept LI and 111 (82%) CsA. Therefore, of the patients who originally entered the BENEFIT study, 65.7%, 66.8% and 50.2% of the belatacept MI, belatacept LI, and CsA groups, respectively, completed the LTE. Of the 320 patients treated with belatacept in the LTE, 96.6% received all of the prescribed infusions, 1.9% missed one infusion, 0.6% missed two infusions and 0.9% missed $\geq$3 infusions. The median daily steroid dose during Months 57–60 was 5.0 mg in all three groups, and the median daily MMF dose in all three groups was 2000 mg; the median trough level at Month 60 of CsA (by TDx assay) was 105 ng/mL.

The demographic characteristics of those patients who entered the LTE were similar to the baseline characteristics of the ITT population (5). The mean age of the LTE population was approximately 43 years; most patients were male (69%), white (55%) and from North America (44%). The most common reason for discontinuation during the LTE was adverse events: 4.5% belatacept MI, 2.4% belatacept LI and 5.1% CsA.

Efficacy assessments

Between Months 36 and 48, there was one case of biopsy-confirmed acute rejection (moderate acute) in the belatacept LI group and one (mild acute) in the CsA group. The belatacept-treated patient had received the transplant from a deceased donor, and the patient in the CsA group had received the transplant from a living donor. Both cases were treated with corticosteroids only. There were no cases in the belatacept MI group. There were no further cases of acute rejection past Months 48 through 60. Of those patients who entered the LTE, 14.2% in the belatacept MI group, 9.1% in the belatacept LI group and 5.9% of the CsA group had experienced acute rejection during the initial 36 months.

Graft loss occurred in zero patients in the belatacept MI and LI groups, and three (2.2%) in the CsA group, of whom two had received transplants from living donors. The causes of graft loss in the CsA group were acute rejection ($n = 2$) and chronic allograft nephropathy ($n = 1$). Death occurred in three (1.9%) patients in the belatacept MI group, of whom two had received transplants from living donors, two (1.2%) patients in the belatacept LI group, both of whom had received transplants from living donors, and seven (5.1%) patients in the CsA group, of whom three had received transplants from living donors. The causes of death in the belatacept MI group were cryptococcosis, dementia and diabetes, and in the belatacept LI group, they were respiratory failure and accidental death. In the CsA group, the causes of death were septic shock, cardiorespiratory arrest, accidental death, peritoneal carcinomatosis, myocardial infarction, cardiac arrest and sudden cardiovascular death.

The mean calculated (MDRD) cGFRs in the LTE cohort were consistently higher from Months 3 to 60 in both belatacept groups compared with CsA (Figure 3). The adjusted mean cGFRs $\pm$ standard deviations (SD) at Month 60 were 74.1 ± 18.9, 76.4 ± 19.0 and 53.0 ± 17.2 mL/min/1.73 m^2

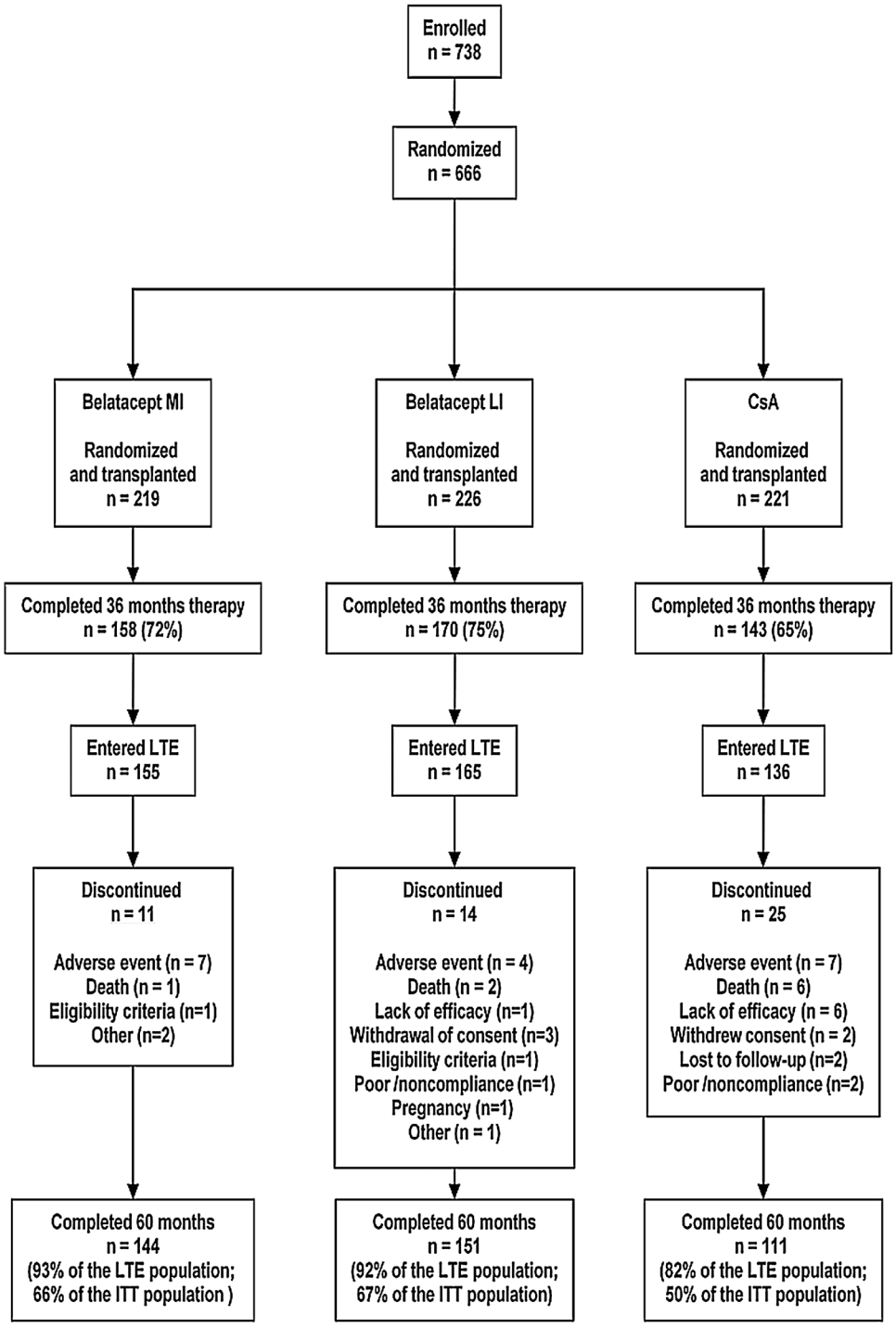

Figure 2: Patient disposition. CsA, cyclosporine A; ITT, intent-to-treat; LI, less intensive; LTE, long-term extension; MI, more intensive.

for the belatacept MI, belatacept LI and CsA groups, respectively ($p < 0.0001$ for belatacept vs. CsA). These values represent adjusted mean (standard error [SE]) changes from Months 3 to 60 of +8.1 (1.4) mL/min/1.73 m^2 for belatacept MI, +10.1 (1.4) mL/min/1.73 m^2 for belatacept LI and −6.6 (1.6) mL/min/1.73 m^2 for CsA ($p < 0.0001$ for belatacept MI and belatacept LI vs. CsA). In those who received a transplant from a living donor, the

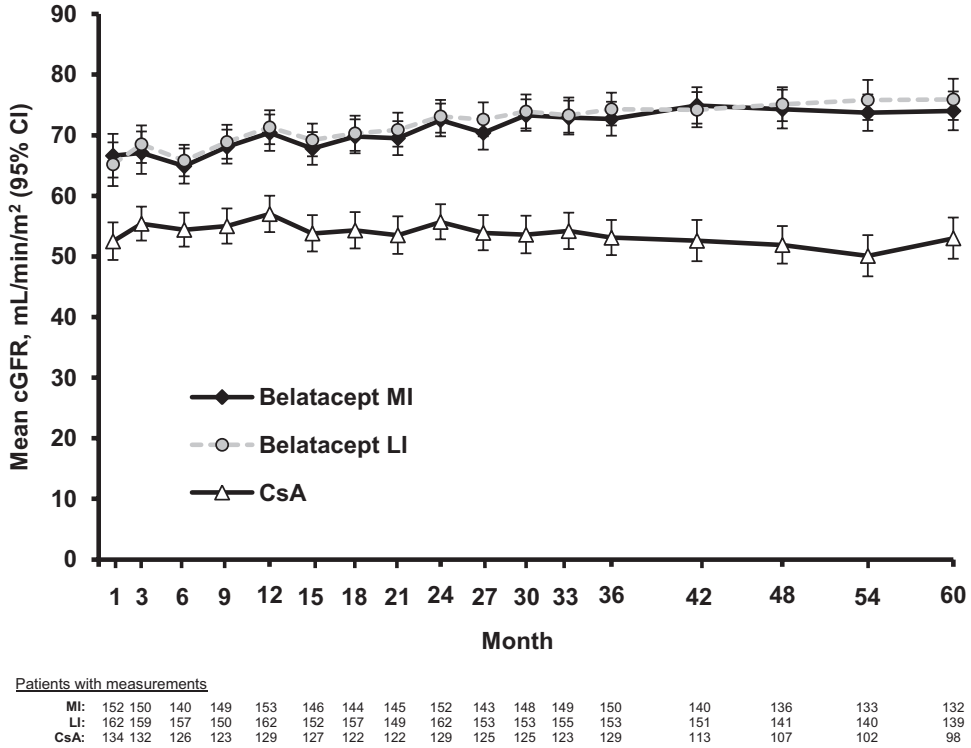

Figure 3: Mean (95% confidence intervals) cGFR (MDRD) over 60 months in the LTE. cGFR values were as observed. CsA, cyclosporine A; cGFR, calculated glomerular filtration rate; LI, less intensive; LTE, long-term extension; MDRD, Modification of Diet in Renal Disease; MI, more intensive.

mean cGFRs ± SD at Month 60 were 72.0 ± 20.4, 74.0 ± 22.1 and 51.6 ± 22.7 mL/min/1.73 m^2, for the belatacept MI, belatacept LI and CsA groups, respectively, and for those who received a transplant from a deceased donor, they were 73.0 ± 23.6, 76.1 ± 19.8 and 42.3 ± 20.6 mL/min/1.73 m^2, respectively.

Of those patients in the LTE population who had a cGFR of ≥30 and <60 mL/min at Month 12, 97% (37/38) in the belatacept MI group, 94% (33/35) in the belatacept LI group and 77% (40/52) in the CsA group either sustained or improved their cGFR through Month 60. Of these patients, 39% (15/38), 40% (14/35) and 14% (7/52) of patients in the belatacept MI, belatacept LI and CsA groups, respectively, improved their cGFR to ≥60 mL/min by Month 60. In addition, only three (2%) patients each in the belatacept MI and LI groups had cGFR <30 mL/min compared with 16 (12%) CsA patients at Month 60.

Decreases in total cholesterol and non-high-density lipoprotein (HDL) cholesterol were observed in both belatacept groups, while the CsA group showed increases in both parameters. Greater decreases in triglycerides were also seen with belatacept compared with CsA. Similar increases in HDL cholesterol were observed across all three groups. Table 1 shows the adjusted mean change in lipid parameters from baseline to Month 60 in the LTE cohort.

Mean systolic and diastolic blood pressures were lower in the belatacept groups compared with the CsA group at Month 60. Mean ± SD systolic blood pressures were 125.6 ± 14.6 and 126.1 ± 17.6 mmHg in the belatacept MI and LI groups, respectively, versus 134.0 ± 19.7 mmHg in the CsA group. Mean ± SD diastolic blood pressures in the belatacept MI, belatacept LI and CsA groups were 73.5 ± 9.5, 75.5 ± 11.6 and 80.2 ± 10.9 mmHg, respectively. A total of 82.3%, 82.8%, and 96.3% of patients in the belatacept MI, belatacept LI and CsA groups were receiving at least one antihypertensive medication at Month 60, and 31.2%, 29.7% and 43.0% of patients, respectively, were receiving three or more antihypertensive agents.

Safety assessments

Between Months 36 and 60, serious adverse events were experienced by 35.5% (55/155) of belatacept MI patients, 31.5% (52/165) of belatacept LI patients and 39.0% (53/136) of CsA patients (Table 2). Fungal

Table 1: Adjusted mean change in lipid parameters from randomization to Month 60 in the LTE cohort[1]

Parameter, mg/dL (SE)	Belatacept MI (n = 155)	Belatacept LI (n = 165)	Cyclosporine A (n = 136)
Total cholesterol	n = 133	n = 143	n = 100
Mean value at 60 months	165.7	165.6	189.8
Change	−4.7 (3.4)	−3.8 (3.3)	18.9 (3.9)
p-Value[2]	<0.0001	<0.0001	
LDL cholesterol	n = 108	n = 115	n = 79
Mean value at 60 months	86.5	90.8	105.7
Change	−4.0 (3.0)	1.0 (2.9)	14.5 (3.5)
p-Value[2]	<0.0001	0.0035	
Non-HDL cholesterol	n = 133	n = 143	n = 100
Mean value at 60 months	115.5	116.8	139.4
Change	−9.7 (3.0)	−7.4 (2.9)	13.1 (3.4)
p-Value[2]	<0.0001	<0.0001	
HDL cholesterol	n = 133	n = 143	n = 100
Mean value at 60 months	50.2	48.7	50.4
Change	4.9 (1.2)	3.6 (1.2)	6.0 (1.4)
p-Value[2]	0.5547	0.1828	
Triglycerides	n = 108	n = 115	n = 79
Mean value at 60 months	133.8	134.7	175.0
Change	−40.7 (6.4)	−37.0 (6.2)	−0.7 (7.5)
p-Value[2]	<0.0001	0.0003	

LI, less intensive; MI, more intensive; SE, standard error; LDL, low-density lipoprotein; LTE, long-term extension; HDL, high-density lipoprotein.

[1]Data represent ∼82% (total cholesterol, HDL cholesterol, non-HDL cholesterol) and ∼66% (LDL cholesterol and triglycerides) of LTE cohort.

[2]p-Values are belatacept versus cyclosporine A.

infections (serious and nonserious) were observed in 14.2% (22/155), 15.2% (25/165) and 11.8% (16/136) of belatacept MI, belatacept LI and CsA patients, respectively, between Months 36 and 60. Most were nonserious, with oral candidiasis, onychomycosis and tinea versicolor as the most common fungal infections overall. Viral infection (serious and nonserious), including BK polyomavirus, cytomegalovirus and herpes (simplex, zoster, other) viruses occurred in 21.3% (33/155) belatacept MI patients, 17.6% (29/165) belatacept LI patients and 16.2% (22/136) CsA patients. Of the LTE cohort, three patients in the belatacept MI group, zero patients in the belatacept LI group, and two patients in the CsA group reported tuberculosis from Months 36 to 60; four of the five cases (two belatacept MI, two CsA) were pulmonary tuberculosis. All cases of tuberculosis occurred in areas known to be endemic (India and South America). Between Months 36 and 60, malignancies occurred in 5.8% (9/155), 6.1% (10/165) and 8.8% (12/136) of belatacept MI, belatacept LI and CsA patients in the LTE cohort. The most common malignancies were squamous cell carcinoma of the skin, basal cell carcinoma and Bowen's disease (squamous cell carcinoma *in situ*).

No patients in the LTE cohort reported posttransplant lymphoproliferative disorder (PTLD) from Month 36 up to database lock. Patients who experienced PTLD in the ITT cohort (0–36 months) did not enter the LTE.

Discussion

This analysis showed that the renal and safety function benefits observed in belatacept-treated patients over the first 3 years posttransplant (5,7,13) were sustained through 5 years of follow-up. Acute rejection episodes were rare in all groups (one each in the LI and CsA groups) in this analysis between 3 and 5 years. At 1 year, rates and grades of acute rejection were higher with belatacept than with CsA (22% in the MI group, 17% in the LI group and 7% in the CsA group) (5), but through 3 years, only four additional cases occurred in the belatacept MI group and five additional cases in the CsA group (7,13). Previous analyses have established that acute rejection episodes with belatacept occurred early, did not tend to recur and were diagnosed and treated via conventional means. cGFR was lower in patients with acute rejection versus those without, irrespective of treatment with belatacept or CsA. Acute rejection in patients receiving belatacept was not typically associated with donor-specific antibodies (7,13). In contrast, CsA was more frequently associated with the development of donor-specific antibodies (5). The development of donor-specific antibodies has been linked to decreases in long-term graft survival (14); however, at the end of 5 years in this study, no differences in graft survival between belatacept and CsA were observed. This is not surprising, since the graft losses that occurred up to Month 36 were not counted toward the cumulative graft losses up to Year 5. Those subjects with graft loss prior to Month 36 were discontinued from the study, leaving only those patients who were doing well entering the LTE.

In this LTE population, mean cGFRs at Month 60 were significantly higher in both belatacept groups compared with CsA, maintaining the difference seen at Month 3 in the belatacept groups versus the CsA group. At Months 48 and 60, the estimated differences from CsA were about 21–23 mL/min/1.73 m^2 for both belatacept MI and LI groups, suggesting persistence of differential GFR between belatacept and CsA with time during the LTE. Moreover, of those patients who had a cGFR $\geq$30 and <60 mL/min at Month 12, more than double the percentage of patients in the belatacept MI and LI groups achieved cGFR $\geq$60 mL/min by Month 60 compared with the CsA group. Several studies have shown that higher GFR values during the first 12 months of kidney transplant are predictive of better long-term outcomes (15–18). In addition, the rate of renal function decline in the first-year posttransplant is also related to long-term outcomes, with more rapid declines associated with a greater risk of graft loss (15). While no appreciable difference was observed between belatacept and CsA on patient and graft survival, the numerical trend

Table 2: Incidence of serious adverse events from beginning of the LTE to Month 60 (≥2% in any group)

	Belatacept MI (n = 155)		Belatacept LI (n = 165)		Cyclosporine A (n = 136)	
	n (%)	Incidence rate[1]	n (%)	Incidence rate[1]	n (%)	Incidence rate[1]
Total subjects with SAE	55 (35.5)	22.5	52 (31.5)	19.8	53 (39.0)	28.0
Infections and infestations	26 (16.8)	9.4	25 (15.2)	8.5	26 (19.1)	11.8
Urinary tract infection	6 (3.9)	2.1	5 (3.0)	1.6	5 (3.7)	2.1
Pneumonia	3 (1.9)	1.0	4 (2.4)	1.3	3 (2.2)	1.2
Pyelonephritis	3 (1.9)	1.0	2 (1.2)	0.6	3 (2.2)	1.2
Gastrointestinal disorders	8 (5.2)	2.8	3 (1.8)	1.0	6 (4.4)	2.5
Neoplasms[2]	8 (5.2)	2.8	12 (7.3)	3.9	12 (8.8)	5.1
Skin squamous cell carcinoma	4 (2.6)	1.4	4 (2.4)	1.3	4 (2.9)	1.6
Basal cell carcinoma	3 (1.9)	1.0	6 (3.6)	1.9	4 (2.9)	1.6
General disorders/administration site conditions	6 (3.9)	2.0	7 (4.2)	2.3	6 (4.4)	2.5
Pyrexia	1 (0.6)	0.3	4 (2.4)	1.3	3 (2.2)	1.2
Cardiac disorders	5 (3.2)	1.7	3 (1.8)	1.0	4 (2.9)	1.6
Injury, poisoning and procedural complications	4 (2.6)	1.4	5 (3.0)	1.6	8 (5.9)	3.3
Nervous system disorders	3 (1.9)	1.0	2 (1.2)	0.6	4 (2.9)	1.6
Vascular disorders	3 (1.9)	1.0	2 (1.2)	0.6	6 (4.4)	2.5
Metabolism/nutrition disorders	2 (1.3)	0.7	2 (1.2)	0.6	3 (2.2)	1.2
Investigations	1 (0.6)	0.3	5 (3.0)	1.6	2 (1.5)	0.8
Psychiatric disorders	1 (0.6)	0.3	0	0	3 (2.2)	1.2
Renal and urinary disorders	1 (0.6)	0.3	3 (1.8)	1.0	8 (5.9)	3.3

LI, less intensive; LTE, long-term extension; MI, more intensive; SAE, serious adverse event.
[1]Incidence rate = per 100 person-years.
[2]Includes benign, malignant and unspecified (including cysts and polyps).

favoring belatacept warrants further assessment in larger cohorts and with longer follow-up. Also, at Month 60, only 2% of patients in either belatacept group had cGFR <30 mL/min versus 16% in the CsA group. Because GFRs <30 mL/min have been shown to increase the risk of returning to dialysis, graft loss and death, as well as increased associated costs (19,20), these results suggest that the benefits seen with belatacept will continue to be realized with longer follow-up.

The safety profile of belatacept was similar to prior observations, and no new safety signals were detected (5,7,13). The rates of fungal and viral infections, as well as malignancies, were generally similar between groups, with fungal and viral infections being slightly more common in belatacept recipients and nonmelanoma skin cancer being slightly more common in CsA recipients. There were no new cases of PTLD in any group during the LTE.

Because poor renal function is associated with greater risk of cardiac events (21,22), it was important to assess the affect of belatacept on risk factors associated with cardiovascular disease. At Month 60, decreases in total cholesterol and non-HDL-cholesterol were observed in both belatacept groups, while the CsA group showed an increase in both parameters. Greater decreases in triglycerides were also observed in the belatacept groups compared with CsA. In addition, patients treated with belatacept demonstrated lower mean systolic and diastolic blood pressure versus CsA and required less antihypertensive therapy. These results are consistent with a previous investigation of pooled data from BENEFIT and BENEFIT-EXT that assessed cardiovascular and metabolic endpoints at Month 12 (23). Taken together, these results suggest that belatacept has a favorable cardiovascular risk profile in both in the short term and over the long term. This is clinically important because of the direct negative effects of cardiovascular complications on outcomes, and because belatacept could potentially reduce the need for additional medications to treat dyslipidemia, hypertension and diabetes, thereby decreasing the risk of accompanying adverse effects and drug interactions.

A greater proportion of belatacept-treated patients (71–75%) versus 67% for CsA entered the LTE, which may have been due in part to the differences in renal function between the groups at the end of the first 3 years in the BENEFIT study. In addition, a larger proportion of belatacept-treated patients compared with CsA-treated patients completed 60 months (92–93% vs. 82% of the LTE population, respectively). A systematic review of adherence to medications for chronic diseases showed an inverse relationship between dosing frequency and adherence (24), and in studies of bisphosphonates for osteoporosis, weekly dosing was preferred by patients to daily dosing and monthly dosing was preferred to weekly dosing (25).

A limitation of the study is that the LTE population likely represents a select group of patients who were doing well on their assigned therapy after 3 years. Approximately 10% more belatacept-treated patients than CsA-treated patients completed 36 months and the difference in patients who remained in the study between belatacept and CsA groups widened during the LTE. Patients in the ITT population who experienced PTLD (and potentially other serious adverse events or lack of efficacy) were discontinued from the study prior to entering the LTE. Also, at the time this study was conceived, CsA was the CNI of choice. However, use of tacrolimus has eclipsed the use of CsA because it may be associated with better outcomes (26). Although the results achieved with belatacept are valid, comparisons with CsA may not be relevant to current clinical practice. For some of the secondary endpoints, statistical comparisons between groups were not performed, and therefore definitive conclusions regarding the differences between groups cannot be made.

In conclusion, the belatacept LI regimen provided a consistent safety profile and a sustained renal function benefit through 5 years of follow-up in this LTE study. Based upon the evidence to date, belatacept represents an important therapeutic option for long-term immunosuppression in kidney transplant recipients.

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Disclosure

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