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Three-Year Outcomes from BENEFIT, a Randomized, Active-Controlled, Parallel-Group Study in Adult Kidney Transplant Recipients

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The clinical profile of belatacept in kidney transplant recipients was evaluated to determine if earlier results in the BENEFIT study were sustained at 3 years. BENEFIT is a randomized 3 year, phase III study in adults receiving a kidney transplant from a living or standard criteria deceased donor. Patients were randomized to a more (MI) or less intensive (LI) regimen of belatacept, or cyclosporine. 471/666 patients completed ≥3 years of therapy. A total of 92% (MI), 92% (LI), and 89% (cyclosporine) of patients survived with a functioning graft. The mean calculated GFR (cGFR) was ∼21 mL/min/1.73 m^2 higher in the belatacept groups versus cyclosporine at year 3. From month 3 to month 36, the mean cGFR increased in the belatacept groups by +1.0 mL/min/1.73 m^2/year (MI) and +1.2 mL/min/1.73 m^2/year (LI) versus a decline of −2.0 mL/min/1.73 m^2/year (cyclosporine). One cyclosporine-treated patient experienced acute rejection between year 2 and year 3. There were no new safety signals and no new posttransplant lymphoproliferative disorder (PTLD) cases after month 18. Belatacept-treated patients maintained a high rate of patient and graft survival that was comparable to cyclosporine-treated patients, despite an early increased occurrence of acute rejection and PTLD.

Key words: Belatacept, cyclosporine, kidney, renal function

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; LI, less invasive; MDRD, Modification of Diet in Renal Disease; MI, more intensive; PTLD, posttransplant lymphoproliferative disorder.

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Introduction

Preserving allograft function in kidney transplant recipients is a critical factor in maximizing graft and patient survival. Improved kidney function posttransplant is associated with better long-term outcomes, and poor renal function posttransplant is associated with greater risk of cardiac events and mortality (1–4). There are over 90 000 patients waiting for kidney transplants in the United States alone, with about 15 000 of those relisted and awaiting a repeat transplant (5). It is not only in the best interests of the individual transplant patient to preserve allograft function, but doing so provides more opportunities for the remaining patients on waiting lists to receive a transplant.

The most frequently used immunosuppressive regimens for kidney transplant recipients do not adequately provide long-term preservation of renal function. Regimens based on calcineurin inhibitors may result in both an acute diminution of renal function due to their vasoconstrictive

properties and long-term renal toxicity due to chronic allograft nephropathy/interstitial fibrosis and tubular atrophy (CAN/IFTA) (6,7). General outcomes tend to be similar with either cyclosporine- or tacrolimus-based regimens (8). There has been some success in preserving renal function with regimens that discontinue or taper calcineurin inhibitors early posttransplant (9,10). However, regimens that completely avoid calcineurin inhibitors have been associated with high rates of acute rejection (11,12), poorer renal function (13), and intolerability (14,15). Noncompliance, which is sometimes associated with current immunosuppressive regimens, is implicated as a factor in late, antibody-mediated rejection. Late rejection is costly and increases the risk for graft loss (16–18). Thus, while immunosuppression regimens based on calcineurin inhibitors have diminished the likelihood of acute rejection, they are ultimately nephrotoxic, with few viable alternatives for preserving allograft function.

Belatacept, a selective costimulation blocker, is designed to provide effective immunosuppression and avoid both the renal and many nonrenal side effects associated with calcineurin inhibitors (19). Previously published results demonstrated that belatacept was associated with similar rates of patient and graft survival, better renal function and an improved cardiovascular and metabolic risk profile compared with cyclosporine at 2 years posttransplant (20,21). The similar rates of patient and graft survival were observed despite an increased frequency and severity of early acute rejection episodes in the belatacept groups, and despite an increased frequency of posttransplant lymphoproliferative disorder (PTLD); specifically, PTLD involving the central nervous system. These events were concentrated in patients who were seronegative for the Epstein–Barr virus (EBV) and in those who received the more intensive belatacept dose regimen.

The objective of the current report was to assess the efficacy and safety of belatacept relative to cyclosporine by 3 years after transplantation in the BENEFIT study, as reflected by the rate of patient and graft survival, renal function over time, the rate of acute rejection and the overall safety and tolerability of belatacept.

Methods

Most of the study methodology was previously described (21). BENEFIT is a 3-year, randomized, partially blinded, active-controlled, parallel-group study in adult patients. The study included living donor or deceased donor kidney transplants with an anticipated cold ischemia time of <24 hours. As previously described, patients were randomized to receive a more intensive (MI) regimen of belatacept, a less intensive (LI) regimen of belatacept or cyclosporine for primary maintenance immunosuppression. Patients received basiliximab induction, mycophenolate mofetil and corticosteroids.

Objectives/outcomes

Outcomes assessed at 3 years included patient survival, graft survival, the proportion of patients surviving with a functioning graft, allograft function, the rate of acute rejection and overall safety. Independent committees blinded to treatment assignment adjudicated the causes of graft loss and death. Renal function was assessed by calculated GFR (cGFR), using the Modification of Diet in Renal Disease (MDRD) equation (22,23). In order to assess the differential impact of belatacept versus cyclosporine on critical patient outcomes of time to cGFR <30 mL/min/1.73 m^2, death or graft loss, a *post hoc* Kaplan–Meier survival analysis was conducted. cGFR <30 mL/min/1.73 m^2 was selected as an endpoint in this analysis as an indicator of advanced renal insufficiency (24). The incidence and characteristics of protocol-defined acute rejection (clinically-suspected, biopsy-proven) were assessed as previously described, including the characterization of donor-specific antibodies (21). The current assessment also included the incidence of all biopsy-proven acute rejection, defined as acute rejection based on biopsies read by a central pathologist and performed for any reason, including prespecified protocol biopsies performed at month 12.

Statistical methods

All analyses at year 3 were conducted on the intent-to-treat population, defined as randomized patients who received a transplant. The proportion of patients surviving with a functioning graft up to year 3 was summarized using point estimates and corresponding 95% confidence intervals within treatment groups, and using two-sided 97.3% confidence intervals for the difference between each belatacept regimen and cyclosporine. The mean cGFR was calculated using an imputation method where missing cGFR values due to death or graft loss were set to 0, and two-sided 97.3% confidence intervals were used for the difference between each belatacept regimen and cyclosporine. Each of the individual tests of cGFR comparing a belatacept regimen to the cyclosporine was conducted by an analysis of variance (ANOVA) model with randomization group as a factor. As *post hoc* analyses, the resulting p-values were not considered conclusive and any conclusions drawn should be considered as hypothesis generating and not hypothesis confirming. To assess the trend in renal function over time, a linear mixed model was used to analyze the changes in cGFR from month 3 to month 36 for each belatacept regimen versus cyclosporine with terms for treatment as fixed effects and month as a random effect. Population mean slopes were estimated for each treatment group. Safety was assessed descriptively.

Results

Six hundred sixty-six patients (n = 219 MI; n = 226 LI; n = 221 cyclosporine) who were randomized and transplanted comprised the intent-to-treat population (Figure 1), and 471 patients (n = 158 MI [72%]; n = 170 LI [75%]; n = 143 cyclosporine [67%]) completed at least 3 years of study therapy. Between years 1 and 3, cyclosporine trough levels remained stable (mean ~149–170 ng/mL) and within the protocol-specified range of 100–250 ng/mL. Patients in each treatment group who discontinued belatacept or cyclosporine were most commonly switched to tacrolimus.

Patient and graft survival

The vital status was available for all but 9 patients at year 3. The proportion of patients surviving with a functioning graft by year 3 was 92% (95% CI 88.7–95.8), 92% (88.5–95.6) and 89% (84.5–92.9) in the MI, LI and cyclosporine groups, respectively. By year 3, death-censored graft loss occurred in 10 (5%) patients in the MI group, 9 (4%) in the LI group and 10 (5%) in the cyclosporine group. Nine (4%) patients in the MI group, 10 (4%) in the LI group and 15

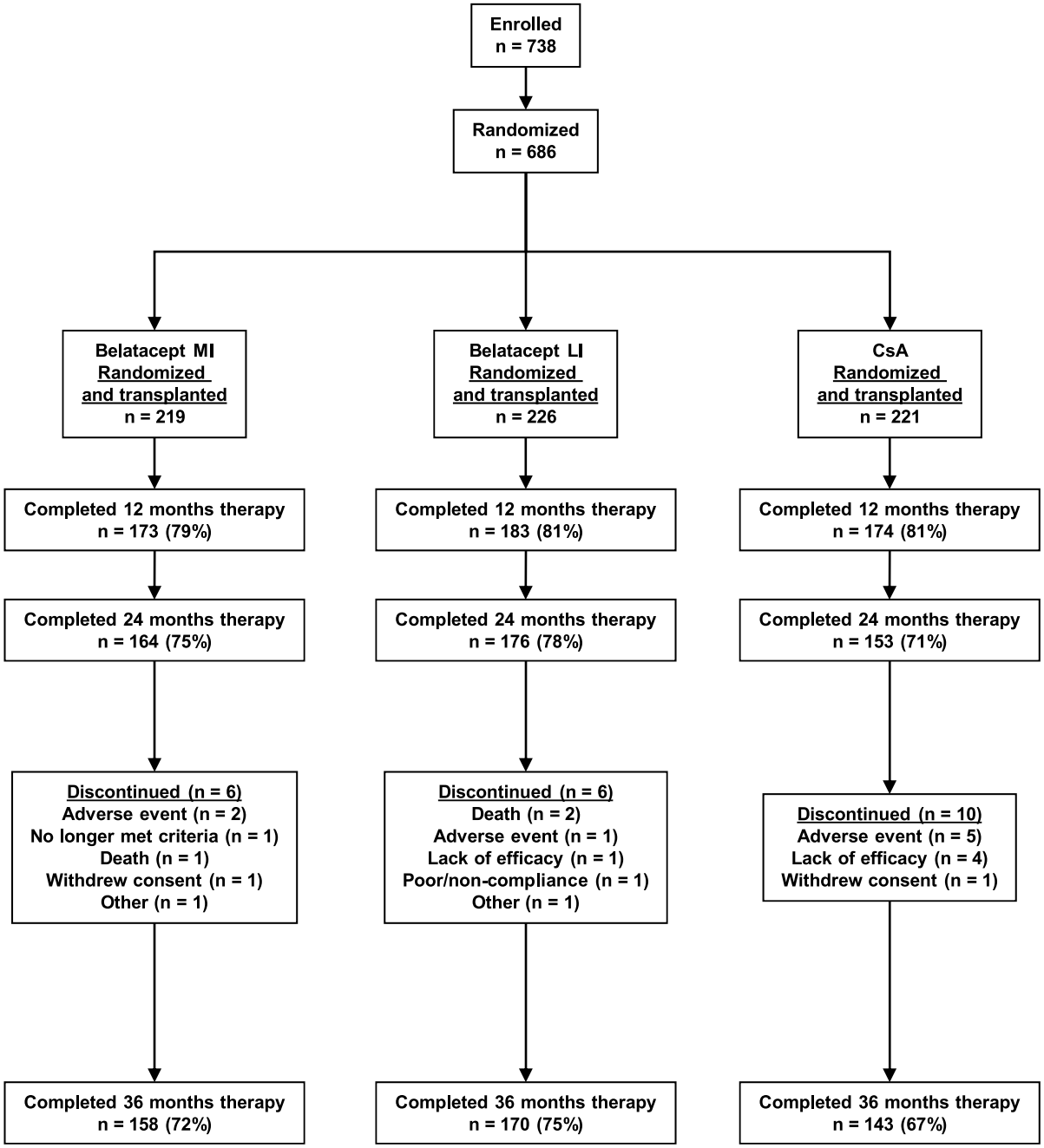
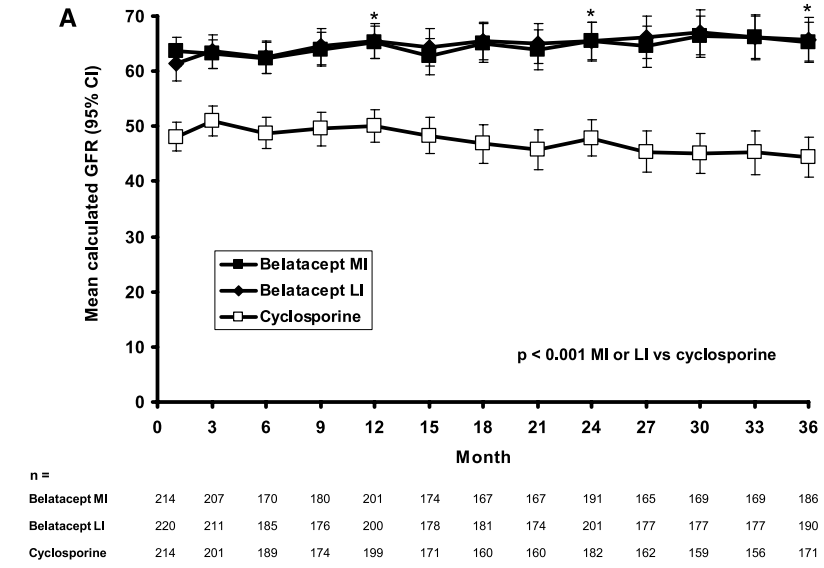


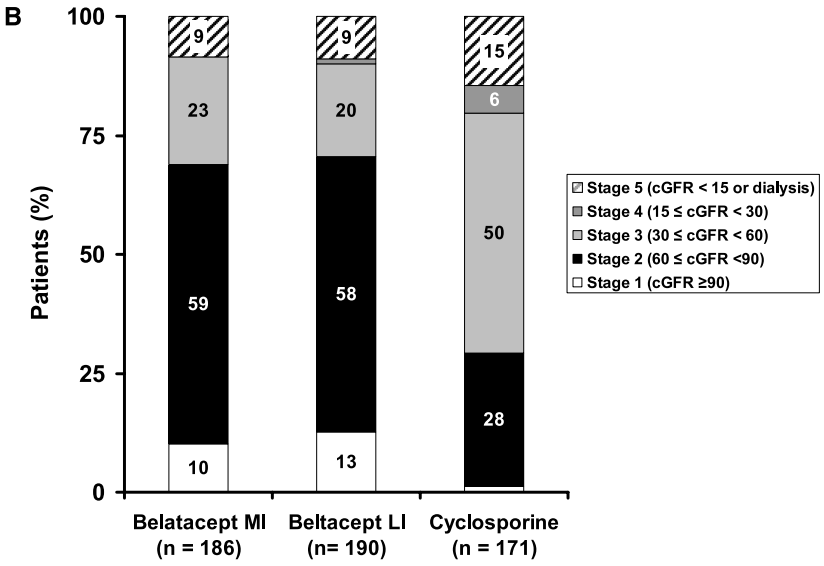
Figure 1: Patient disposition.

(7%) in the cyclosporine group died. Most deaths or graft losses occurred in the first 12 months, as only 6 patients died (n = 2 MI; n = 2 LI; n = 2 cyclosporine) and 9 patients lost their graft (n = 3 MI; n = 4 LI; n = 2 cyclosporine) from year 2 to year 3.

Renal function—cGFR

cGFR data with imputation were available for 85%, 84% and 77% of the MI, LI and cyclosporine patients, respectively, at year 3. The mean ± SD cGFR at year 3 was 65.2 ± 26.3 mL/min/1.73 m^2 (MI), 65.8 ± 27.0 mL/min/1.73 m^2 (LI), and 44.4 ± 23.6 mL/min/1.73 m^2 (cyclosporine) ($p < 0.0001$ MI or LI vs. cyclosporine). The mean cGFR was consistently higher over time in the belatacept groups compared to cyclosporine (Figure 2A; $p < 0.0001$ MI or LI vs. cyclosporine at years 1, 2 and 3). The difference between both belatacept groups and cyclosporine in the mean cGFR increased from ∼15 mL/min/1.73 m^2 at year 1





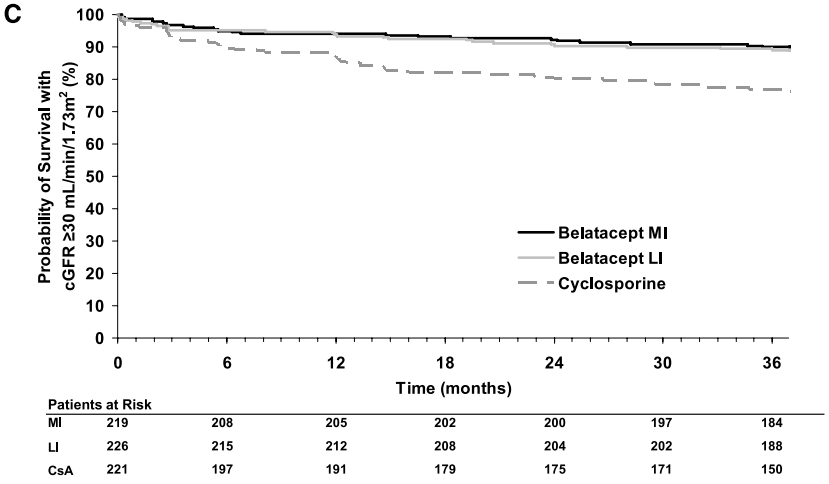


Figure 2: Renal function outcomes. (A) Mean cGFR (95% CI) over time. cGFR was calculated using the modification of diet in renal disease (MDRD) equation (22,23). Missing values due to death or graft loss were imputed as 0. (B) CKD stages (renal function) at year 3. Figure depicts the percentage of patients at various levels of renal activity, defined by the Kidney Disease Outcomes Quality Initiative chronic kidney disease stages. (C) Kaplan–Meier plot of time to cGFR <30 mL/min/1.73 m^2, death or graft loss. Plot depicts the estimated time to cGFR <30 mL/min/1.73 m^2 (CKD stage 4 or 5), death or graft loss through year 3.

to 21 mL/min/1.73 m^2 at year 3. A slope analysis suggested that the mean cGFR increased over time (month 3 to month 36) in the belatacept MI (1.0 ± 0.48 mL/min/1.73 m^2/year) and LI (1.2 ± 0.47 mL/min/1.73 m^2/year) groups, while the mean cGFR declined by −2.0 ± 0.48 mL/min/1.73 m^2/year in the cyclosporine group.

An on-treatment analysis of the mean cGFR at year 3 yielded a similar degree of difference between the belatacept groups and the cyclosporine group: 72.7 ± 17.49 mL/min/1.73 m^2 (MI) and 74.5 ± 16.98 mL/min/1.73 m^2 (LI), versus 52.4 ± 16.44 mL/min/1.73 m^2 (cyclosporine).

Renal function—chronic kidney disease stages

The percentage of patients at various stages of renal function, defined by the Kidney Disease Outcomes Quality Initiative chronic kidney disease stages, is depicted in Figure 2B (24). At year 3, more belatacept patients were in stage 2 (cGFR 60–90 mL/min/1.73 m^2) while more cyclosporine patients were in stage 3 (cGFR 30–60 mL/min/1.73 m^2). Patients with stage 4–5 chronic kidney disease (cGFR <30 mL/min/1.73 m^2) have advanced renal dysfunction, and are at increased risk of morbidity and mortality (24,25). Figure 2C presents the results of a *post hoc* Kaplan–Meier analysis of time to cGFR <30 mL/min, graft loss, or death, in which the survival curves demonstrated an advantage for patients receiving belatacept.

Acute rejection

There were no new cases of acute rejection in the belatacept groups from year 2 to year 3. One patient experienced acute rejection in the cyclosporine group after year 2. The cumulative rate of acute rejection was 24% (MI), 17% (LI), 10% (cyclosporine) at year 3, and the rate of biopsy-proven acute rejection was 27% (MI), 22% (LI) and 14% (cyclosporine). By year 3, the proportion of patients who met the composite endpoint of graft loss, death, lost-to-follow-up or biopsy-proven acute rejection was 32% (MI; 95% confidence interval 25.8, 38.1), 26% (LI; 95% confidence interval 20.0, 31.4) and 26% (cyclosporine; 95% confidence interval 20.0, 31.6).

Impact of acute rejection

An analysis of 113 patients (n = 53 MI; n = 39 LI; n = 21 cyclosporine) who experienced an acute rejection episode by year 3 found that 8 (MI), 10 (LI) and 1 (cyclosporine) died or lost their graft by year 3. Conversely, among patients who did not experience an acute rejection episode by year 3, 9 (MI), 8 (LI) and 23 (cyclosporine) died or lost their graft by year 3.

Calculated GFR data were available or could be imputed for a total of 111/113 patients (n = 53 MI; n = 39 LI; n = 19 cyclosporine) who experienced an acute rejection episode by year 3. In this analysis, patients with missing cGFR values due to death or graft loss had their cGFR values imputed as 0, and a last observation carried forward imputation was utilized for other missing values, except if the last cGFR measurement was before the acute rejection episode. Among these patients, the mean cGFR values at year 3 were 52.8 mL/min/1.73 m^2 (MI), 40.1 mL/min/1.73 m^2 (LI) and 36.4 mL/min/1.73 m^2 (cyclosporine).

Limited information on cGFR was available on patients who remained on assigned therapy following acute rejection and had data available. An as-observed analysis (no imputation for death or graft loss) of 64 patients (n = 32 MI; n = 21 LI; n = 11 cyclosporine) who had an acute rejection episode by year 3 and who had cGFR data available at year 3 found that mean cGFR values were 66.8 mL/min/1.73 m^2 (MI), 57.8 mL/min/1.73 m^2 (LI) and 40.9 mL/min/1.73 m^2 (cyclosporine).

Safety

By year 3, 9 (4%), 10 (4%) and 15 (7%) patients died in the MI, LI and cyclosporine groups, respectively. The most common adverse events occurred with a similar rate across groups, and were similar to those reported at year 2 (26). Sixteen patients (7%) in the MI and LI groups discontinued study therapy due to adverse events, compared to 31 (14%) in the cyclosporine group.

The frequencies of the most common malignancies are listed in Table 1. The incidence rate (per 100 patient-years) of overall malignancies remained stable over time in each group. No new cases of PTLD were reported between years 2 and 3, yielding 6 total cases to date (n = 3 MI; n = 2 LI; n = 1 cyclosporine), including 2 cases involving the central nervous system.

The overall rate of infections as an adverse event was similar among treatment groups (MI: 80%; LI: 82%; cyclosporine: 80%). The most common infections included urinary tract infection (30%–36% across groups), upper respiratory tract infection (17%–20% across groups), and influenza (10%–14% across groups). The rates of cytomegalovirus (CMV), polyoma and fungal infections were generally similar across groups (Table 1). Seven cases of tuberculosis were reported (n = 4 MI; n = 2 LI; n = 1 cyclosporine); 6 of the cases were reported from study sites in India. The rate of serious infections was 28% (MI), 32% (LI) and 33% (cyclosporine). The most common serious infections included urinary tract infection (6%–11% across groups), CMV infection (3%–6% across groups), gastroeneritis (1%–3% across groups) and pyelonephritis (2%–3% across groups). As expected, the incidence rate (per 100 patient-years) of most types of infection diminished over time in each group (data not shown).

Donor-specific antibodies

Donor-specific antibodies occurred in 6% (MI), 5% (LI), and 11% (cyclosporine) of patients by year 3. Among patients who did not have an acute rejection episode, donor-specific antibodies occurred in 5% (MI), 5% (LI) and 10%

Table 1: Rates of malignancies and infections through year 3

n (%)	Belatacept MI n = 219	Belatacept LI n = 226	Cyclosporine n = 221
All malignancies	18 (8)	10 (4)	12 (5)
PTLD	3 (1)	2 (1)	1 (<1)
Most common malignancies*			
Basal cell carcinoma	5 (2)	3 (1)	4 (2)
Squamous cell carcinoma of skin	4 (2)	1 (<1)	3 (1)
EBV-associated PTLD	2 (1)	1 (<1)	1 (1)
Breast cancer	2 (1)	0	0
Bowen's disease	1 (1)	0	2 (1)
Thyroid cancer	0	0	2 (1)
Renal cell carcinoma	0	2 (1)	0
All infections	175 (80)	185 (82)	176 (80)
CMV infections	22 (10)	26 (12)	25 (11)
BK polyoma virus	18 (8)	10 (4)	18 (8)
BK virus infection	13 (6)	8 (4)	12 (5)
Polyoma test positive	6 (3)	5 (2)	4 (2)
Human polyoma virus infection	1 (1)	1 (<1)	1 (1)
Polyomavirus-associated nephropathy	1 (1)	1 (<1)	4 (2)
Herpes virus	29 (13)	26 (12)	21 (10)
Oral herpes	13 (6)	15 (7)	7 (3)
Herpes zoster	10 (5)	8 (4)	11 (5)
Herpes simplex	5 (2)	1 (<1)	2 (1)
Fungal infections	50 (23)	46 (20)	45 (20)
Oral candidiasis	17 (8)	9 (4)	14 (6)
Onchomycosis	9 (4)	10 (4)	6 (3)
Candidiasis	7 (3)	7 (3)	2 (1)
Body tinea	6 (3)	2 (1)	1 (1)
Tuberculosis	4 (2)	2 (1)	1 (1)

*Malignancies occurring in ≥2 patients in any treatment group, reported by MeDRA preferred terms; "PTLD" includes multiple individual terms, including "EBV-associated PTLD," "B-cell lymphoma," "CNS lymphoma" and "lymphoma."

(cyclosporine) of patients. In patients who had an acute rejection episode by year 3, the proportion of patients with donor-specific antibodies was 12% (MI), 8% (LI) and 19% (cyclosporine).

Discussion

At 3 years, a high rate of patient and graft survival and improved renal function was sustained in kidney transplant recipients treated with belatacept versus cyclosporine. Belatacept, which is intravenously administered, appeared to be well tolerated, with more patients on therapy at 3 years compared to cyclosporine, in agreement with observations from a phase II study (27). No belatacept-treated patients experienced acute rejection between years 2 and 3, and there were no new safety signals.

Renal function remained stable over time in the belatacept groups, while function declined in the cyclosporine group (28). The rate of decline in the cyclosporine group agrees with other studies showing a ∼1–2 mL/min/year loss of function with either cyclosporine or tacrolimus-based regimens (29–33). In a report of over 1000 kidney transplant recipients, both renal function at 1 year and the rate of renal function decline during the first year were associated with increased risk for late graft loss (34). The risk increased by sevenfold in patients with cGFR <45 mL/min/1.73 m^2 and in those who had the highest rates of decline. The preservation of renal allograft function observed with belatacept may ultimately contribute to fewer late graft losses.

The observed data by year 3 (Figure 2C) show a reduction in key outcomes (progression to advanced renal dysfunction, death, graft loss) in belatacept-treated patients. Much of this difference is due to the improved renal function in the belatacept groups versus cyclosporine. Based on a validated prediction model, described in detail elsewhere (35; see also Supporting Information), the improved renal function observed in belatacept-treated patients versus cyclosporine projects to a median graft survival difference of 1.9 years (95% CI: 1.5 to 2.2), and potentially ∼9 graft loss events averted at 10 years posttransplant. These projections suggest that treatment with belatacept may delay a return to dialysis and the need for retransplantation. Transplant patients who return to dialysis have significantly higher mortality risk compared to patients on waiting lists. Additionally, the resumption of dialysis results in increased morbidity and mortality, increased health care costs, and negative impacts on patients' quality of life (36,37).

There were no cases of acute rejection after year 2 in the belatacept groups. The results confirm that acute rejection in the belatacept groups tended to occur early and did

not typically recur. The presentation of acute rejection was consistent with clinical expectations, and episodes were treated according to existing clinical practice. Acute rejection had an impact on a number of long-term outcomes. For example, acute rejection was associated with reduced renal function in all treatment groups. At year 3, more deaths and graft losses were observed in acute rejection patients receiving belatacept than in those receiving cyclosporine, although interpretation is limited by the high rate (~50%) of belatacept discontinuation in patients who developed acute rejection. Despite higher rates and grades of acute rejection, the overall proportion of patients surviving with a functioning graft remained comparable between the belatacept groups and cyclosporine by year 3.

There were no new cases of PTLD between years 2 and 3. Previous analyses indicated that the greatest risk of PTLD with belatacept was associated with EBV negative serostatus in the recipient. A higher rate of PTLD was also observed in EBV seropositive patients; however, the magnitude of risk was ~10-fold lower than that in EBV(−) patients. The risk of PTLD involving the central nervous system was also highest in EBV(−) patients and in patients treated with the more intensive belatacept regimen (38). The data in the belatacept phase III studies support the general observation that the risk for PTLD appears to be highest within the first 18 months posttransplant (39).

In conclusion, the 3-year results from BENEFIT confirm the persistence of the renal function benefits of belatacept over time. These benefits balance the early risks associated with belatacept in the study population, namely acute rejection and PTLD. The totality of data suggests that belatacept offers an important therapeutic advance in the care of renal transplant recipients.

Acknowledgments

The BENEFIT study was supported by Bristol–Myers Squibb. The study was conducted in accordance with ethical principles that have their origin in the current Declaration of Helsinki, and was consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements. The study protocol and any amendments were reviewed and approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for each site prior to initiation of the study. BENEFIT is registered with ClinicalTrials.gov (id: NCT00256750). The authors would like to acknowledge Kathy Soucek, Protocol Manager, Bristol Myers Squibb, for her support of the BENEFIT study and Brian Atkinson, PhD, Bristol–Myers Squibb, for writing and editorial assistance.

Disclosure

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Dr. Larsen has received research grants/contracts from Bristol–Myers Squibb and Genentech.

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Drs. Xing and Agarwal are employees of Bristol–Myers Squibb.

Drs. Charpentier, Alberu, Bresnahan, Garcia, Kothari, Lang, Mancilla-Urrea, Massari, Mondragon-Ramirez, Reyes-Acevedo, Rostaing and Steinberg have nothing to disclose.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1: Projected graft survival based on clinical profile by 3 years

All-Cause Graft Failure Risk Prediction Model

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