Belatacept: An Update of Ongoing Clinical Trials

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Belatacept is a fusion protein that acts as an antagonist of the costimulatory pathway of T-cell proliferation and activation. Major trials comparing belatacept with cyclosporine-based regimens have shown the two drugs to be clinically equivalent for immunosuppression. Use of belatacept in kidney-transplant recipients is associated with increased rates of early post-transplant lymphoproliferative disorder and acute rejection; however, cardiovascular and metabolic profiles and post-transplant renal function appear to be better with belatacept therapy than with other immunosuppressive treatments. This report includes a summary of the pivotal clinical trials involving belatacept, updates on several ongoing clinical trials, and data on several new studies involving safety and outcomes that were presented at the 2014 World Transplant Congress in San Francisco, California. Although long-term data are lacking, early results with belatacept are promising. Apparently, belatacept therapy may be a viable option for maintenance immunosuppression in the future. Clearly, additional randomized, controlled trials with belatacept and ongoing safety monitoring are needed.

Abstract

Belatacept is a fusion protein that acts as an antagonist of the costimulatory pathway of T-cell proliferation and activation. Major trials comparing belatacept with cyclosporine-based regimens have shown the two drugs to be clinically equivalent for immunosuppression. Use of belatacept in kidney-transplant recipients is associated with increased rates of early post-transplant lymphoproliferative disorder and acute rejection; however, cardiovascular and metabolic profiles and post-transplant renal function appear to be better with belatacept therapy than with other immunosuppressive treatments. This report includes a summary of the pivotal clinical trials involving belatacept, updates on several ongoing clinical trials, and data on several new studies involving safety and outcomes that were presented at the 2014 World Transplant Congress in San Francisco, California. Although long-term data are lacking, early results with belatacept are promising. Apparently, belatacept therapy may be a viable option for maintenance immunosuppression in the future. Clearly, additional randomized, controlled trials with belatacept and ongoing safety monitoring are needed.

Belatacept has been approved by the US Food and Drug Administration (FDA) for prophylaxis of organ rejection in adults receiving a kidney transplant. Belatacept is administered via monthly infusion and is used in combination with basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids. Its effects are believed to be highly specific for the B7-CD28 pathway. Therefore, it ultimately may serve as a therapeutic alternative to avoid the long-term toxicity of calcineurin inhibitors (CNIs). However, belatacept should be used only in patients who are Epstein-Barr virus (EBV) seropositive. Use of this drug in liver-transplant recipients is controversial because some early studies demonstrated an increase in the risk of graft loss and death. The drug’s benefits and safety in recipients of other transplanted organs have not been established, although clinical studies in simultaneous pancreas-kidney transplant recipients are ongoing.

Although belatacept therapy has been associated with increased rates of post-transplant lymphoproliferative disorder (PTLD) and early acute rejection, its use in kidney-transplant recipients may lead to fewer late acute-rejection episodes. The cardiovascular and metabolic profiles of this drug and its impact on renal function appear to be superior to those of cyclosporine-based regimens. Rates of patient and graft survival appear to be comparable between belatacept and cyclosporine.

OUTCOMES OF PIVOTAL CLINICAL TRIALS

FDA approval of belatacept rested largely on the results of two phase 3, multinational, partially blinded, parallel-group studies, BENEFIT and BENEFIT-EXT. The BENEFIT trial studied patients who received a kidney from a living donor or standard-criteria deceased donor. The BENEFIT-EXT trial studied patients who received a kidney from an extended-criteria deceased donor. In both studies, patients received corticosteroids and basiliximab for induction therapy intraoperatively and MMF and tapering doses of the steroid postoperatively. Patients then were randomized 1:1:1 to receive a more intensive regimen of belatacept (10 mg/kg every 4 weeks for 6 months), a less intensive regimen of belatacept (10 mg/kg every 4 weeks for 3 months, followed by 5 mg/kg every 4 weeks), or cyclosporine. After 6 months, both belatacept groups were continued on 5 mg/kg of the drug every 4 weeks, whereas patients in the cyclosporine arm were continued on 100–250 mg/mL of cyclosporine (Figure 1).

In both studies, the mean calculated glomerular filtration rate (GFR) was significantly higher in both belatacept treatment groups when compared with the GFR in cyclosporine-treated patients at 3 years and 5 years after transplantation. The belatacept-treated patients also may have had better control of their blood pressure and needed fewer antihypertensive medications than did the cyclosporine control group. In addition,
patients in the belatacept arms of both studies had significantly better metabolic profiles than did patients who received cyclosporine.

In the BENEFIT trial, no significant differences in serious adverse events and late onset of PTLD were detected across the three treatment groups. However, belatacept recipients had a higher rate of early-onset PTLD.\textsuperscript{11,12} The most notable risk factor for developing PTLD was pretransplant EBV seronegativity.

A post hoc analysis of 3-year outcomes of EBV-seropositive transplant recipients who received a deceased-donor kidney in the BENEFIT and BENEFIT-EXT trials revealed no significant differences in patient- and graft-survival rates across all three treatment groups, although the survival rate was numerically highest among patients who had been randomized to the less-intensive belatacept regimen. All groups showed similar rates of acute graft rejection, and renal function at 3 years was superior in patients who had received either regimen of belatacept compared with those who had been treated with cyclosporine. These results are consistent with the observations made at 3 years in the full global BENEFIT and BENEFIT-EXT study populations.\textsuperscript{13}

The results of a similar ad hoc study of EBV-seropositive European subpopulations extracted from the BENEFIT and BENEFIT-EXT trials were comparable to those found among all the patients in those trials who were treated with belatacept or cyclosporine.\textsuperscript{14}

\section{LONG-TERM SAFETY OF BELATACEPT}

Recently, results of a detailed vascular function analysis comparing 23 belatacept recipients with 23 cyclosporine recipients over a median of 81 months (nearly 7 years) were reported.\textsuperscript{15} There was no difference between the two groups in systolic or diastolic blood pressure or pulse wave velocity, a measure of arterial stiffness. However, central aortic augmentation pressure—a strong independent cardiovascular risk factor—was significantly higher in the cyclosporine group.

Another recent study examined the 10-year outcomes of 218 patients randomized to the belatacept arm of a phase 2 clinical trial.\textsuperscript{16} Of 44 remaining patients, 46% missed a single infusion or less. In all, 84% of patients had serious adverse events, including 36% with significant infections and 23% with malignancies; however, there were no cases of PTLD in this group. Only one episode of acute rejection occurred during year 9. In the belatacept cohort, the mean calculated GFR was 70 ± 21 mL/min/1.73 m\textsuperscript{2} (Figure 2).\textsuperscript{16} The efficacy and safety profile of belatacept after 10 years was consistent, and the belatacept group showed high treatment adherence. However, this study had a small sample size.

As a part of the post-approval monitoring for belatacept, the ENLiST registry was created to survey recipients for PTLD, central nervous system PTLD, and progressive multifocal leukoencephalopathy (PML). In all, 365 adult transplant recipients treated with belatacept agreed to participate in the registry. There were no reports of PTLD, central nervous system PTLD, or PML. All study participants were EBV seropositive, and 69% were cytomegalovirus (CMV) seropositive. The mean duration of belatacept exposure was 240 ± 172 days. There were a total of three deaths and two additional graft losses among the study group.

The ENLiST registry is intended to be an ongoing monitoring system for the long-term safety of belatacept as its use becomes more widespread.\textsuperscript{17} This is important, especially in the setting of the known increased rate of development of early-onset PTLD in patients who received this drug in clinical trials.

\section{DEVELOPMENT OF DONOR-SPECIFIC ANTIBODIES (DSAs)}

Increased DSA levels following transplantation (ie, de novo DSA levels) clearly is a risk factor for antibody-mediated rejection and, ultimately, graft loss.\textsuperscript{18} Co-
stimulatory pathway blockade inhibits T cell-dependent antibody production in nonhuman primate models. Results of the BENEFIT trial revealed surprisingly low rates (5%–6%) of DSA formation at 3 years for all kidney-transplant recipients. Bray and others examined the rates of development of de novo DSAs in the BENEFIT and BENEFIT-EXT long-term extension trials through 5 years. Lower rates of de novo DSA formation were seen in patients who had been randomized to both the more-intensive and less-intensive belatacept regimens than among the group treated with cyclosporine; these results were consistent with the 3-year results of both clinical trials (Table 1).

## BELATACEPT VS TACROLIMUS AND STEROID AVOIDANCE

In the BENEFIT and BENEFIT-EXT trials, use of belatacept was compared with cyclosporine therapy rather than with tacrolimus administration, which may be more relevant to the immunosuppression regimens of today. Ferguson et al conducted a 1-year, randomized, controlled trial of live- and deceased-donor kidney recipients who were randomized 1:1:1 to treatment with belatacept and MMF, belatacept and sirolimus, or tacrolimus and MMF with steroid avoidance. All recipients received antilymphocyte globulin. By month 6, acute rejection rates were numerically very low in all three study arms, compared with the rates observed in the BENEFIT trial, but within this study were slightly higher in the belatacept-MMF arm. The rates of graft survival were higher among the tacrolimus-MMF group (100%) than among the belatacept-MMF (91%) and belatacept-sirolimus (92%) groups. Renal function, as measured by calculated GFR, was 8–10 mL/min/1.73 m² higher in both belatacept treatment groups at month 12 than in the tacrolimus-MMF group.

Four-year follow-up studies of this phase 2, randomized trial showed similar results. Patients in the belatacept-MMF and belatacept-sirolimus arms had higher mean calculated GFRs through 48 months than did those in the tacrolimus-MMF arm (59.6, 72.2, and 55.7 mL/min/1.73 m², respectively; Figure 3). There was no difference in the proportion of patients alive with functioning grafts among the groups, and the safety profiles of all three drug regimens were similar. The rates of serious adverse events also were similar across all three arms, and there were no differences among the three regimens in rates of new-onset diabetes, dyslipidemia, or hypertension. Thus, when used with T-cell depleting induction, belatacept-based regimens show promise in allowing for avoidance of steroids and CNIs, although the numbers of patients who participated in this study were small.

A small study by Wongsaroj et al reported on a 12-month follow-up of deceased-donor kidney-transplant recipients. Of the 13 recipients treated with belatacept, induction was accomplished with basiliximab in 6 patients and with rabbit antithymocyte globulin in 7 individuals. Findings in this group were compared with those of 26 retrospective controls maintained with tacrolimus matched 2:1. Outcomes in the belatacept and tacrolimus groups were not significantly different. Two deaths related to infection were noted in the belatacept group and likely were associated with treatment for acute rejection. The rate of death-censored graft survival was lowest in the tacrolimus/basiliximab group. Acute rejections were more frequent in the belatacept group and highest in the belatacept/basiliximab group. The belatacept/basiliximab group also had the highest incidence of CMV and BK viremia. Sample sizes were likely too small to draw significant conclusions, but the provocative incidence of viremia and infection in the belatacept group suggested that more intense viral monitoring in these recipients may be prudent.

## CONVERSION FROM CNI-BASED THERAPY TO BELATACEPT

An alternative option for integrating belatacept into maintenance immunosuppression protocols, rather than starting with belatacept post transplant, is converting from a CNI-based regimen to one that relies on belatacept. One study described results from 18 patients who were converted to belatacept for at least 1 month after 6 weeks to 12 years

![Mean calculated glomerular filtration rate (cGFR) after 4 years' follow-up comparing belatacept with tacrolimus and steroid avoidance. GFR calculated using the Levey MDRD (Modification of Diet in Renal Disease) study equation. MMF = mycophenolate mofetil. Adapted, with permission, from Woodle et al.](image)

**FIGURE 3** Mean calculated glomerular filtration rate (cGFR) after 4 years’ follow-up comparing belatacept with tacrolimus and steroid avoidance. GFR calculated using the Levey MDRD (Modification of Diet in Renal Disease) study equation. MMF = mycophenolate mofetil. Adapted, with permission, from Woodle et al.

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**TABLE 1** Development of De Novo DSAs in the BENEFIT and BENEFIT-EXT Trials from Baseline to 5 Years

<table>
<thead>
<tr>
<th></th>
<th>BENEFIT</th>
<th>BENEFIT-EXT</th>
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<tbody>
<tr>
<td></td>
<td>Bela MI (n = 155)</td>
<td>Bela LI (n = 165)</td>
</tr>
<tr>
<td></td>
<td>Bela MI (n = 136)</td>
<td>Bela LI (n = 113)</td>
</tr>
<tr>
<td>Subjects, n (%)</td>
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<td>6 (3.6)</td>
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<tr>
<td>95% CI</td>
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</tr>
<tr>
<td>Class II DSAs, n</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Both class I and class II DSAs, n</td>
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<td>0</td>
</tr>
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DSAs = donor-specific antibodies; Bela = belatacept; MI = more-intensive regimen; LI = less-intensive regimen; CI = confidence interval

Source: Bray et al

![Mean calculated glomerular filtration rate (cGFR) after 4 years' follow-up comparing belatacept with tacrolimus and steroid avoidance. GFR calculated using the Levey MDRD (Modification of Diet in Renal Disease) study equation. MMF = mycophenolate mofetil. Adapted, with permission, from Woodle et al.](image)

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(mean, 25 months) of maintenance immunosuppression with CNIs. In all, 15 of 18 patients remained on belatacept for 1–18 months of follow-up. Four patients developed CMV viremia after the conversion; none of the patients developed BK viremia. None of the patients developed DSAs after their immunosuppressive regimen was converted to belatacept, but one episode of acute graft rejection occurred 3 months after the conversion. The average serum creatinine concentration fell from 2.6 mg/dL at the time of the conversion to 2.0 mg/dL at the latest follow-up after transition to belatacept.

Another option for converting patients from CNIs to belatacept is to make the transition after a period of prolonged delayed graft function. Wojciechowski and colleagues recently related their experience with 11 patients who were converted to belatacept after a period of delayed graft function exceeding 14 days (mean, 45 days; range, 18–74 days). This group of patients was compared with a historic control group of 22 patients who continued to use tacrolimus for maintenance immunosuppression. Mean time to biopsy for the belatacept group was significantly later than it was for the tacrolimus group. Mean number of dialysis treatments and mean calculated GFR at 3 and 6 months post transplant were similar between the two groups, although the GFR was slightly higher in the belatacept group. Rates of acute rejection and infection were comparable in both groups.

In another recent study, Gupta et al examined a small group of patients at high immunologic risk who were switched from tacrolimus to belatacept for presumed acute CNI toxicity and/or interstitial fibrosis and tubular atrophy. Four patients were switched at a median of 6 months post transplant. After the transition, peak mean serum creatinine levels fell from 3.1 to 1.8 mg/dL. No new rejection episodes were noted, and there was no de novo development of DSAs at the latest follow-up. These results indicated that it may be safe to transition a highly select patient population to belatacept after transplantation and use of maintenance immunosuppression including CNIs. However, these data are clearly preliminary and involved only four patients and therefore should be interpreted with caution.

Rostaing et al published a key study on conversion to belatacept. Patients receiving a CNI-based regimen within 6–36 months post transplant were randomized to switch to belatacept (n = 84) or remain on their CNI regimen (n = 89). At 1 year of follow-up, the mean calculated GFR and mean increase in calculated GFR were both higher in the group that had been converted to belatacept. However, more episodes of acute graft rejection, but no graft losses, occurred in the belatacept arm. Safety profiles were similar between the group that had converted to belatacept and the group that had remained on CNI therapy.

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**The Potential for Belatacept Monotherapy**

One of the goals of post-transplant immunosuppression is to safely minimize exposure to the agents used to avoid unwanted side effects and, perhaps, eventually to maintain transplant recipients on a single immunosuppressive agent. Preliminary work by Kirk and others may represent the first strides toward this goal. Twenty live-donor kidney-transplant recipients received alemtuzumab induction and maintenance immunosuppression with monthly infusions of belatacept and daily sirolimus. These patients were randomized 1:1 to receive unfractionated donor bone marrow; after 1 year, all patients were allowed to wean off their sirolimus regimen. Graft function was similar at 12 and 36 months, and no graft rejections were observed in either group. Ten patients elected to wean from sirolimus. Donor-specific hyporesponsiveness was noted in 16 of 19 recipients tested using serial in vitro intracellular cytokine production measurements. An additional 16-patient cohort was sampled, this time using 8 deceased-donor kidney-transplant recipients. This second cohort achieved similar results with excellent graft function at latest follow-up, and all remained rejection-free.

The possibilities of belatacept monotherapy are promising with both live- and deceased-donor kidney transplants. This therapeutic option presents an exciting opportunity for prospective, randomized, controlled clinical trials.

**Strategies to Improve the Efficacy of Belatacept**

Studies in nonhuman primates have suggested a synergism with the combined use of belatacept and mammalian target of rapamycin (mTOR) inhibitors. This synergy has not been extensively studied in a human kidney-transplant recipient cohort. Wojciechowski et al retrospectively studied 19 renal-transplant recipients who were given induction therapy using belatacept with thymoglobulin induction therapy and maintenance therapy with MMF and subsequent conversion to everolimus at 1 month post transplant, with or without corticosteroids. This group was compared with a historic control group of 38 low-immunologic-risk patients, which met the belatacept inclusion and exclusion criteria. There was an increased rate of delayed graft function in the belatacept group, but the mean calculated GFR and rates of acute rejection and infection were similar between the groups at 1, 3, and 6 months. Longer follow-up time and a larger patient cohort clearly will be needed to assess the efficacy and safety of this approach.
CONCLUSION

Belatacept is a promising new immunosuppressant approved for maintenance therapy in adult EBV-seropositive kidney transplant recipients. Some concerns regarding early acute rejection and PTLD exist, but graft survival does not seem to be affected. A main benefit is the increased calculated GFR noted with belatacept therapy when compared with the use of other maintenance immunosuppression regimens.

Future directions for belatacept research should include continued follow-up from the BENEFIT and BENEFIT-EXT trials along with further safety monitoring and updates. Other clinical trials are needed to assess the efficacy and safety of long-term belatacept in conjunction with T-cell depleting induction by combining it with other immunosuppressive agents, such as MMF, sirolimus, or everolimus, to avoid the chronic use of steroids and/or CNIs. In addition, more study of belatacept use in the above-mentioned settings with high-risk patients is needed.

REFERENCES