PERSONAL VIEWPOINT

Optimization of de novo belatacept-based immunosuppression administered to renal transplant recipients

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Kidney transplant recipients administered belatacept-based maintenance immunosuppression present with a more favorable metabolic profile, reduced incidence of de novo donor-specific antibodies (DSAs), and improved renal function and long-term patient/graft survival relative to individuals receiving calcineurin inhibitor (CNI)-based immunosuppression. However, the rates and severity of acute rejection (AR) are greater with the approved belatacept-based regimen than with CNI-based immunosuppression. Although these early co-stimulation blockade-resistant rejections are typically steroid sensitive, the higher rate of cellular AR has led many transplant centers to adopt immunosuppressive regimens that differ from the approved label. This article summarizes the available data on these alternative de novo belatacept-based maintenance regimens. Steroid-sparing, belatacept-based immunosuppression (following T cell–depleting induction therapy) has been shown to yield AR rates comparable to those seen with CNI-based regimens. Concomitant treatment with belatacept plus a mammalian target of rapamycin inhibitor (mTORi; sirolimus or everolimus) has yielded AR rates ranging from 0 to 4%. Because the optimal induction agent and number of induction doses; blood levels of mTORi; and dose, duration, and use of corticosteroids have yet to be determined, larger prospective clinical trials are needed to establish the optimal alternative belatacept-based regimen for minimizing early cellular AR occurrence.

KEYWORDS
clinical research / practice, editorial / personal viewpoint, immunosuppressant - fusion proteins and monoclonal antibodies, immunosuppression / immune modulation, immunosuppressive regimens - maintenance, kidney transplantation / nephrology, kidney transplantation: living donor, off-label drug use, rejection: acute

1 | INTRODUCTION

In the United States (US), more than 90% of renal transplant recipients are maintained on calcineurin inhibitor (CNI)-based immunosuppressive regimens.[1] CNIs (cyclosporine or tacrolimus) have been associated with systemic adverse effects (AEs), including dyslipidemia, diabetes, nephrotoxicity, and neurotoxicity,[2-14] and have the potential to negatively impact both patient and graft survival.[9,15]

Belatacept is a soluble fusion protein composed of the human IgG1 Fc domain linked to the modified extracellular domain of

cytotoxic T-lymphocyte–associated antigen 4, a homolog of CD28.[16] Activated T cells are central to transplant rejection.[17,18] Belatacept binds to CD80 and CD86 on antigen-presenting cell surfaces and inhibits CD28-mediated T cell co-stimulation.[16] Compared with CNI-treated patients, kidney transplant recipients administered belatacept present with a more favorable metabolic profile, reduced chronic allograft nephropathy and incidence of de novo donor-specific antibodies (DSAs), and improved renal function and long-term patient and graft survival.[19-24] Additionally, because belatacept is intravenously (IV) infused, adherence may be better monitored relative to oral agents and the risk of occult nonadherence eliminated. The lower incidence of DSAs—both pre-existing[25] and de novo[24]—seen with belatacept-based versus CNI-based immunosuppression may be related to treatment adherence, as well as to mechanism of action.

Among renal transplant recipients, the rates and severity of cellular acute rejection (AR) are greater with the approved belatacept-based regimen than with cyclosporine-based immunosuppression.[19,22,26] Although these early co-stimulation blockade–resistant rejections are typically steroid sensitive,[19,20,27,28] the higher AR rate with belatacept has led many transplant centers to adopt treatment regimens that differ from the approved label. This article reviews the available data on these alternative belatacept-based regimens.

2 | APPROVED REGIMEN

Belatacept is approved for use in combination with basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids for the prophylaxis of organ rejection in adult renal transplant recipients seropositive for Epstein-Barr virus (EBV).[29] The 2011 approval of belatacept by the US Food and Drug Administration (FDA) and European Medicines Agency was partly based on results from the randomized phase 3 BENEFIT (NCT00256750) and BENEFIT-EXT (NCT00114777) studies.[19,20,26,30] In these studies, two belatacept dosing regimens (more intense [MI] and less intense [LI]) were compared with cyclosporine-based immunosuppression. All kidney transplant recipients received basiliximab induction, MMF, and corticosteroids (initiated at 500 mg pre-operatively and tapered to no less than 2.5 mg/day by day 15).[19,20]

There was no difference in efficacy between the belatacept MI and LI regimens in BENEFIT and BENEFIT-EXT,[19,20] but belatacept LI was associated with a lower AR incidence and fewer AEs.[19] Thus, belatacept LI is the regulatory-approved regimen. Under this regimen, patients receive IV belatacept 10 mg/kg on days 1 and 5 and weeks 2, 4, 8, and 12 posttransplantation, and IV belatacept 5 mg/kg every 4 weeks thereafter.[19,20]

In BENEFIT, patients were transplanted with a living or standard criteria deceased (SCD) donor kidney.[19] At 12 months posttransplantation, the AR rate was 17% (39/226) for belatacept LI, and 7% (16/221) for cyclosporine with a greater proportion of belatacept LI-treated patients developing Banff grade IIB AR (26% [10/39] vs. 13% [2/16]); one belatacept LI-treated patient experienced Banff grade III AR. Of note, mean measured glomerular filtration rate (GFR)

at month 12 was higher in belatacept LI-treated patients with AR (61 mL/min/1.73 m^2) than in cyclosporine-treated patients without AR (51 mL/min/1.73 m^2).

Patients enrolled to BENEFIT-EXT were recipients of extended criteria donor kidneys (donors aged ≥60 years or those aged ≥50 years with ≥2 other risk factors [death due to cerebrovascular accident, history of hypertension, or serum creatinine >1.5 mg/dL], kidneys with an anticipated cold ischemia time ≥24 hours, or kidneys donated after cardiac death).[20] At 12 months posttransplantation, 18% (31/175) and 14% (26/184) of patients randomized to belatacept LI and cyclosporine, respectively, experienced AR. As in BENEFIT, a numerically greater proportion of patients treated with belatacept LI than with cyclosporine developed Banff grade IIB AR (26% [8/31] vs. 19% [5/26]); no patient in BENEFIT-EXT experienced Banff grade III AR.

AR episodes under belatacept-based treatment tend to occur early in the posttransplantation period, with a low incidence of late rejections. Across BENEFIT and BENEFIT-EXT, the majority (81% to 82%) of AR episodes occurred within 3 months posttransplantation,[19,20] with few events reported after month 12.[26,30-32] The AR rate at 3 years posttransplantation among belatacept LI-treated and cyclosporine-treated patients in BENEFIT was 17% and 10%, respectively[26]; the corresponding values in BENEFIT-EXT were 19% and 16%.[30]

Importantly, the increased rate of AR in the early posttransplantation period has not been shown to negatively impact 7-year overall patient or graft survival. In 7-year posttransplantation analyses of BENEFIT, belatacept LI-based immunosuppression was associated with a 43% risk reduction in death or graft loss compared with cyclosporine-based immunosuppression (hazard ratio [HR] 0.57; 95% confidence interval [CI] 0.35–0.94; p = .02).[22] The risk of death or graft loss at 7 years posttransplantation was similar for the two regimens in BENEFIT-EXT (HR 0.93; 95% CI 0.63–1.36; p = .70).[23] In addition, belatacept LI-based immunosuppression was associated with superior renal function: estimated GFR (eGFR) increased by +1.39 mL/min/1.73 m^2 per year in BENEFIT and +1.51 mL/min/1.73 m^2 per year in BENEFIT-EXT, in contrast with cyclosporine-based treatment (eGFR decreased by −1.04 mL/min/1.73 m^2 per year in BENEFIT and −0.01 mL/min/1.73 m^2 per year in BENEFIT-EXT). The difference in renal function favored belatacept LI-based immunosuppression in both studies (both p < .001).[22,23] Racial disparities in kidney transplant outcomes are well documented, with Blacks/African Americans having increased rates of graft loss relative to whites.[33,34] However, in post hoc analyses of BENEFIT and BENEFIT-EXT data performed at 7 years posttransplant, clinical outcomes (rates of death or graft loss, AR rates, graft function) were similar in belatacept-treated Black and non-Black renal transplant recipients.[35]

3 | ALTERNATIVE REGIMEN: BELATACEPT PLUS AN MTORI

The clinical evaluation of belatacept-based immunosuppression was informed by preclinical research (Table S1). The early cellular

AR episodes associated with belatacept have been attributed to al-loreactive memory T cells (T_{MEM}).[36,37] In primates, but not in mice, T cells lose CD28 during maturation, and most T cells do not ex-press this key belatacept-targeted molecule.[27] However, rapamycin targets more differentiated cells, including mature T cells otherwise resistant to belatacept. In mice, concomitant co-stimulation block-ade and rapamycin treatment was shown to trigger the apoptosis of activated alloreactive T cells, promoting allograft tolerance.[38] In addition, long-term belatacept use has been shown to lower the sur-vival and immunosuppressive capacity of regulatory T cells (T_{REG}), as CD28 signaling is critical to T_{REG} survival.[39] Therefore, combining belatacept with other therapies may help to preserve T_{REG} function and lower AR rates. To this end, clinical studies have examined com-bination treatment with belatacept and a mammalian target of ra-pamycin inhibitor (mTORi) (sirolimus or everolimus) in de novo renal transplant recipients[40-42] (Table 1).

In a 12-month phase 2 study (NCT00455013), 89 kidney (living or deceased donor) transplant recipients were randomized to re-ceive belatacept-MMF, belatacept-sirolimus, or tacrolimus-MMF.[40] All patients received rabbit anti-thymocyte globulin (rATG) induc-tion and corticosteroids in tapering doses for 4 days, and belata-cept was dosed per the approved regimen. The 12-month AR rate for belatacept-MMF, belatacept-sirolimus, and tacrolimus-MMF was 15% (5/33), 4% (1/26), and 3% (1/30), respectively; all AR episodes were Banff grade IIA or IIB. Compared with tacrolimus-MMF, the 12-month AR rate was only 0.5% higher for belatacept-sirolimus, but 12% higher for belatacept-MMF. Patients with AR were treated suc-cessfully with either corticosteroids (57% [4/7]) or lymphocyte-de-pleting therapy (43% [3/7]), and all but one patient (treated with belatacept-MMF) survived with a functioning graft to month 12. Mean eGFR at month 12 in patients administered belatacept-MMF, belatacept-sirolimus, and tacrolimus-MMF was 63.6, 61.8, and 54.0 mL/min/1.73 m^2, respectively. Thus, eGFR at month 12 was 8–10 mL/min/1.73 m^2 greater for belatacept-based versus tacrolim-us-based immunosuppression.

Like CNIs, corticosteroids are associated with systemic AEs, including dyslipidemia, diabetes, and cardiovascular events.[43] Therefore, CNI- and corticosteroid-free regimens are being sought for the long-term treatment of renal transplant recipients. In the above phase 2 trial (NCT00455013),[40] patients received only a 4-day corticosteroid course. At month 12, 73% (24/33), 77% (20/26), and 93% (28/30) of patients randomized to belatacept-MMF, be-latacept-sirolimus, and tacrolimus-MMF, respectively, remained corticosteroid-free, and 73% (24/33) and 69% (18/26) of patients randomized to belatacept-MMF and belatacept-sirolimus, respec-tively, were both corticosteroid- and CNI-free.[40] Importantly, the safety profile of belatacept (dosed per the approved regimen) was consistent with that observed in BENEFIT and BENEFIT-EXT.[19,20,40] At various time points during this 12-month study, belatacept-si-rolimus–treated patients presented with a greater number of T_{REG} cells relative to those treated with either belatacept-MMF or tac-rolimus-MMF. As the T_{MEM} cell numbers were comparable for the three regimens, the ratio of T_{MEM}-to-T_{REG} cells shifted.[44] However,

short-term treatment with everolimus does not result in an in-crease in T_{REG} cells.[45] These data suggest that long-term treatment with both belatacept and sirolimus may promote the survival and/or expansion of T_{REG} cells, which may contribute to immunologic tolerance.

The effects of CNI- and corticosteroid-free immunosuppression were further explored in a single-center, nonrandomized phase 2 study (NCT00565773) of 20 living donor kidney transplant recip-ients administered belatacept (approved dosing regimen) plus si-rolimus following induction with the lymphocyte-depleting, CD52 monoclonal antibody alemtuzumab.[41] Although approved by the US FDA for multiple sclerosis and B-cell chronic lymphocytic leukemia, alemtuzumab is not indicated for renal transplant recipients. In this phase 2 study, there were no reports of AR in the first 12 months posttransplantation, and no patient required readmission for an op-portunistic infection or malignancy.[41] However, as expected with alemtuzumab treatment, protective immunity became impaired; 10 patients exhibited transient BK viremia in the first 12 months posttransplantation, all cases of which resolved. Following induc-tion, peripheral T cells and B cells were depleted (as expected), but absolute lymphocyte counts returned to baseline levels by month 12. Lymphocyte repopulation was characterized by a T_{REG} cell in-crease, and a decrease in CD28$^-$CD8$^+$ T cells, accompanied by an increase in naïve T cells that express CD28.[16,41] Following the initial report, an additional 20 patients were recruited, none of whom ex-perienced AR in the 12 months posttransplant. Among all 40 study participants, 5-year posttransplant graft and patient survival rates were 95% and 100%, respectively, and eGFR was stable (1 year: 70 ± 23 mL/min/m^2; 5 years: 71 ± 19 mL/min/1.73 m^2).[46] Patients were allowed to taper and ultimately discontinue daily sirolimus be-ginning at month 12, resulting in the use of once-monthly belatacept only. Of 26 patients who satisfied the criteria for transitioning to belatacept monotherapy, seven elected not to wean from sirolimus, 19 attempted weaning, and 12 (63%) successfully transitioned.[46]

The phase 1 TEACH study (NCT03504241; currently recruiting) is designed to further evaluate the use of alemtuzumab induction in combination with belatacept-based immunosuppression and corti-costeroids in living donor kidney transplant recipients[47] to promote a state of immunologic tolerance, thus enabling immunosuppres-sion withdrawal. In this study, patients will receive alemtuzumab induction, belatacept-sirolimus maintenance, and an infusion of do-nor-derived mesenchymal stromal cells on day 42, day 56, and every 4 weeks thereafter. Patients will be eligible to withdraw from bela-tacept after ≥24 weeks and sirolimus between weeks 52 and 104. The primary endpoint is operational tolerance to the transplanted kidney (i.e., immunosuppression-free for 52 weeks after complete immunosuppression withdrawal).

In a single-center, nonrandomized trial, clinicians at the University of California, San Francisco, explored de novo belatacept (approved dosing regimen) plus everolimus in 67 renal (living or de-ceased donor) transplant recipients. These patients initially received concomitant mycophenolate but were switched to everolimus at 1 month posttransplantation. All patients received rATG induction

TABLE 1 Overview of clinical studies examining de novo belatacept-based immunosuppressive regimens

	Belatacept-based immunosuppression							Comparator immunosuppression						
Study	Induction	Approach	Regimen	n	AR rate at month 12	Graft survival at month 12	Mean eGFR at month 12, mL/min	Induction	Regimen	n	AR rate at month 12	Graft survival at month 12	Mean eGFR at month 12, mL/min	Biomarker of AR
Ferguson et al.[40]	rATG	Steroid withdrawal	mTORi	26	4%	92%	---	rATG	Tacrolimus-MMF	30	3%	100%	---	---
Kirk et al.[41]	Alemtuzumab			20	0%	100%	89	---						---
Ferguson et al.[40]	rATG		MMF	33	15%	91%	---	rATG	Tacrolimus-MMF	30	3%	100%	---	---
BEST[52]	Alemtuzumab			107	16%	100%	64	rATG	Tacrolimus-MMF	105	5%	99%	64	---
	rATG			104	22%	99%	65							
UCSF[42]	rATG	Prednisone 5–10 mg	mTORi	67	0%	---	---	---						CD28⁻CD8⁺ T cells[48]
BENEFIT[19] (approved regimen)	Basiliximab		MMF[a]	226	17%	98%	63	Basiliximab	CsA-MMF	221	7%	96%	50	---
BENEFIT-EXT[20] (approved regimen)	Basiliximab			175	18%	91%	49.5	Basiliximab	CsA-MMF	184	14%	89%	45	---
UCSF[42]	rATG			67	16%	---	---	---						CD28⁻CD8⁺ T cells[48]
Emory[50]	Basiliximab		MMF +tacrolimus for 5 months	87	33%	100%	---	Basiliximab	Tacrolimus-MMF	205	20.5%	99.5%	---	CD28⁺CD4⁺ T cells[51]
								Basiliximab	Belatacept-MMF	97	50.5%	100%	---	CD28⁺CD8⁺ T cells[51]
Emory[50]	Basiliximab		MMF +tacrolimus for 11 months	356	16%	99.7%	---	Basiliximab	Tacrolimus-MMF	205	20.5%	99.5%	---	---
								Basiliximab	Belatacept-MMF	97	50.5%	100%	---	---

Abbreviations: AR, acute rejection; CsA, cyclosporine A; eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor; rATG, rabbit anti-thymocyte globulin; UCSF, University of California, San Francisco.

[a]In this study, mycophenolate rather than MMF was used.

and, unlike the phase 2 studies described above, maintenance prednisone.[42] At 12 months posttransplantation, 16% (11/67) of patients experienced AR. All 11 AR episodes occurred prior to the everolimus switch, when patients were still receiving mycophenolate treatment. While the AR episodes could be attributed to mycophenolate use, the timing since transplantation (within 1 month) may have been a contributing factor. The AR rate in this study was comparable to BENEFIT and BENEFIT-EXT at 12 months posttransplantation (17% and 18%, respectively),[19,20,42] and biomarker analyses showed that patients with AR had higher levels of CD28⁻CD8⁺ T cells prior to transplantation than those without AR.[48]

Collectively, data from two small, single-center, nonrandomized clinical studies[40,41] showed that belatacept plus mTORi treatment can result in improved AR rates relative to the approved regimen, while the beneficial effects of belatacept on graft function/survival and safety are maintained. The randomized phase 2 Regimen Optimization Study (NCT02137239) that compared de novo belatacept-everolimus with tacrolimus-MMF in renal (living or SCD donor) transplant recipients supported these results.[49] All patients received rATG induction and a 7-day corticosteroid course, and belatacept was dosed per the approved regimen. The original target enrollment was 240 patients, but due to a belatacept supply constraint at the time, enrollment was prematurely halted. Of 68 enrolled patients, 58 were randomized, transplanted, and treated. At 6 months posttransplantation, the AR rate was 8% (2/26) among belatacept-everolimus–treated patients and 9% (3/32) among tacrolimus-MMF–treated patients. In the modified intent-to-treat analysis performed at 24 months posttransplantation, AR rates were 16% (4/25) and 15% (5/33), respectively. No patient experienced Banff grade IIB or III AR.[49] Thus, in this abbreviated, randomized, controlled study, use of belatacept in conjunction with an mTORi resulted in AR rates similar to those seen with tacrolimus-based treatment.

4 | ALTERNATIVE REGIMEN: BELATACEPT PLUS TRANSIENT TACROLIMUS

To minimize the elevated AR rates associated with the approved regimen, clinicians at Emory University tested an alternative belatacept dosing regimen coupled with transient tacrolimus in renal (living or deceased donor) transplant recipients in a retrospective single-center nonrandomized study with historical cohorts administered standard belatacept-based or standard tacrolimus-based treatment as comparators (Table 1).[50] Under the modified dosing regimen, belatacept 10 mg/kg was not delivered on days 4 and 14, and tacrolimus was dosed twice daily for 3 months and then tapered prior to discontinuation at month 5. Patients also received basiliximab induction, MMF, and corticosteroids. The belatacept-tacrolimus, tacrolimus, and belatacept cohorts comprised 87, 205, and 97 renal transplant recipients, respectively. The 3-month AR rate was similar for belatacept-tacrolimus (15%) and tacrolimus (17%) but was approximately twofold higher for belatacept (38%). Following tapered cessation of corticosteroids and tacrolimus, the

12-month AR rate posttransplantation for belatacept-tacrolimus (33%) was intermediate to that observed for tacrolimus (20.5%) and belatacept (50.5%). Banff grade IIB or III AR rates in the three treatment arms were 5%, 4%, and 13%, respectively. Consistent with the 7-year analyses of BENEFIT and BENEFIT-EXT,[22,23] the higher AR rates or severity at 12 months posttransplantation in the Emory study did not negatively impact overall graft or patient survival. At 3 years posttransplantation, patient (graft) survival rates were 92% (91%) in the belatacept-tacrolimus arm and 94% (88%) in the tacrolimus arm.[50]

However, as the 12-month AR rate for belatacept-tacrolimus was higher than for tacrolimus, clinicians examined prolonged tacrolimus exposure under the modified belatacept dosing regimen. With extended-dosing tacrolimus, patients (N = 356) received twice-daily tacrolimus for 9 months, which was then tapered prior to discontinuation at month 11.[50] The belatacept-extended tacrolimus regimen resulted in a lower 12-month AR rate than the historical tacrolimus cohort (16% vs. 20.5%). Overall, 4% of belatacept-extended tacrolimus–treated patients experienced Banff grade IIB or III AR. Over 3 years, mean eGFR was consistently higher for both belatacept-tacrolimus–based regimens than for standard tacrolimus-based treatment (values not specified). Rates for viremia with cytomegalovirus (CMV) and BK virus were similar for the belatacept-tacrolimus and tacrolimus regimens. These results suggest that a belatacept-based immunosuppressive regimen involving transient (11 months) use of tacrolimus has the potential to yield AR rates comparable to those reported with a CNI-based regimen. Retrospective biomarker analysis revealed that patients with increased frequencies of CD4⁺CD28⁺ T_{MEM} and CD8⁺CD28⁺ T_{MEM} had higher rates of AR on this regimen.[51]

5 | ALTERNATIVE REGIMEN: T CELL–DEPLETING INDUCTION PLUS BELATACEPT-MMF AND EARLY STEROID WITHDRAWAL

In the 2-year, multicenter, randomized phase 4 Belatacept Early Steroid Withdrawal Trial (BEST, NCT01729494), two belatacept-based regimens, one involving alemtuzumab induction (n = 107) and the other with rATG (n = 104), were compared with a tacrolimus-based regimen involving rATG induction (n = 105) (Table 1). All patients received MMF, a 5-day corticosteroid course (tapering doses), and belatacept was dosed per the approved regimen.[52] BEST addressed several limitations of prior randomized controlled belatacept trials. First, belatacept-based treatment was compared with tacrolimus-based rather than cyclosporine-based immunosuppression; second, all studied regimens followed T cell–depleting induction; and third, all regimens required early corticosteroid cessation.

The 12-month AR rate in BEST was significantly greater with both belatacept-based regimens than with tacrolimus-based treatment (belatacept-alemtuzumab, 16% [17/107]; belatacept-rATG, 22% [23/104]; tacrolimus-rATG, 5% [5/105]; belatacept-alemtuzumab

vs. tacrolimus-rATG, $p = .024$; belatacept-rATG vs. tacrolimus-rATG, $p < .001$).[52] The absolute difference in AR between each belatacept-based regimen and the tacrolimus-based regimen was similar to that observed with the approved regimen.[19] However, no significant differences in the rate of death, graft loss, or eGFR <45 mL/min/1.73 m^2, the composite primary endpoint, were seen across treatment arms at month 12 (belatacept-alemtuzumab, 8% [9/107]; belatacept-rATG, 14% [15/104]; tacrolimus-rATG, 13% [14/105]),[52] and proportions of patients who were corticosteroid-free at month 12 were not significantly different (belatacept-alemtuzumab, 81% [87/107]; belatacept-rATG, 86% [89/104]; tacrolimus-rATG, 91% [96/105]).

At 24 months posttransplantation, AR rates remained significantly greater for belatacept-alemtuzumab (19% [20/107]; $p = .012$) and belatacept-rATG (25% [26/104]; $p < .001$) than for tacrolimus-rATG (7% [7/105]).[53] As in the 12-month analysis, no significant differences were found for the composite primary endpoint at month 24 (belatacept-alemtuzumab, 10% [11/107]; belatacept-rATG, 13% [13/104]; tacrolimus-rATG, 20% [21/105]). However, a significantly greater proportion of tacrolimus-treated patients had an eGFR <45 mL/min/1.73 m^2 (belatacept-alemtuzumab, 9% [9/96]; belatacept-rATG, 9% [8/92]; and tacrolimus-rATG, 21% [20/97]; belatacept-alemtuzumab vs. tacrolimus-rATG, $p = .043$; belatacept-rATG vs. tacrolimus-rATG, $p = .05$). The proportion of corticosteroid-free patients at month 24 was similar to month 12 (belatacept-alemtuzumab, 84% [90/107]; belatacept-rATG, 88% [92/104]; tacrolimus-rATG, 91% [96/105]). No unexpected safety events were reported over the 2-year study with either belatacept-based regimen.[52,53] BEST was the first multicenter randomized trial to demonstrate the feasibility of a CNI-free regimen coupled with early corticosteroid withdrawal (albeit with an increased AR risk) and the efficacy and safety of CNI-free and corticosteroid-free, belatacept-based immunosuppression in the renal transplantation setting.

In contrast to BEST, the phase 2 Clinical Trials in Organ Transplant-10 (CTOT-10) study results were less favorable. In CTOT-10, de novo kidney (living or deceased donor) transplant recipients were randomized to receive alemtuzumab induction and maintenance treatment with either tacrolimus-MMF (group 1, $n = 6$) or belatacept-MMF (group 2, $n = 6$).[54] A third group of patients ($n = 7$) received basiliximab induction followed by a 3-month course of tacrolimus and maintenance belatacept-MMF. Patients in all three groups received corticosteroids in tapering doses over 4 days, and belatacept was dosed per the approved regimen. Originally planned as a 3-year study with 210 patients, CTOT-10 was terminated early owing to the occurrence of serious thrombotic events in three of six patients in the alemtuzumab-belatacept-MMF group and to increased AR rates among belatacept-treated patients (group 1, 17% [1/6]; group 2, 33% [2/6]; group 3, 71% [5/7]). Two of the three cases of vascular thrombosis in the alemtuzumab-belatacept-MMF group were related to technical issues (distal dissection related to a vascular clamp and renal vein thrombosis due to compression of the IVC). Of note, eGFR at week 52 was similar across treatment groups (group 1, 55.9 ± 8.9 mL/min; group 2, 51.6 ± 23.5 mL/min; group 3, 58.3 ± 12.2 mL/min).[54]

6 | SAFETY CONSIDERATIONS

Because of an increased risk of posttransplant lymphoproliferative disorder,[19,20] belatacept is contraindicated in patients who do not have immunity to EBV.[29] However, CMV-seronegative patients may also be subject to poorer outcomes. In a retrospective analysis of 168 kidney transplant recipients at high risk of CMV (CMV-seronegative, receiving CMV-seropositive donor kidneys), the 2-year cumulative incidence of primary CMV infection (50% vs. 34%; $p = .047$) and the duration of CMV viremia were greater in those administered belatacept-based versus tacrolimus-based immunosuppression (although many belatacept-treated patients in this study received both belatacept and tacrolimus during the first year posttransplant).[55] Although additional studies are needed to establish whether belatacept treatment is optimal for CMV-seronegative patients and whether these patients may need to receive preventative anti-CMV treatment, the situation may be confounded by the concomitant use of MMF, which is itself associated with an increased CMV disease risk.[56-58]

However, the effects of MMF on infection incidence may be countered by mTORi use. In the phase 3 ATHENA study, CMV infection rates over 12 months were significantly lower in kidney (living or deceased donor) transplant recipients receiving everolimus plus either tacrolimus or cyclosporine than those receiving tacrolimus-MMF (tacrolimus-everolimus, 6% [13/210]; cyclosporine-everolimus, 3% [5/198]; tacrolimus-MMF, 21% [42/204]; $p < .001$).[59] Similarly, in the 24-month phase 4 TRANSFORM study, a lower CMV infection rate was observed with an everolimus plus a reduced-exposure CNI regimen compared with an MMF plus a standard-exposure CNI regimen (3% [28/1014] vs. 14% [137/1012]).[60] Although an mTORi can potentially mitigate the risks of CMV infection, this class of agents is associated with dose-limiting toxicities: approximately 25% of renal transplant recipients who initiate treatment with an mTORi resume use of a CNI.[61]

7 | CONCLUDING REMARKS

The approval of belatacept in 2011 represented a major change in the field of renal transplantation, as it provided physicians with a CNI-free treatment option. Despite the favorable effects of belatacept on long-term graft function and survival[22,23] (at least partly attributable to its lack of nephrotoxicity), belatacept-based immunosuppression has consistently been shown to lead to higher AR rates in the early posttransplantation period. Pilot studies of numerous off-label regimens have been undertaken in an effort to reduce these AR rates, with varying success. Given the limitations (e.g., single-center, uncontrolled, small patient numbers) of many of the aforementioned studies, data are insufficient to draw conclusions as to which alternative de novo regimen is best. The optimal induction agent and number of induction doses, mTORi blood levels, and dose, duration, and use of corticosteroids have yet to be determined. Based on the available (albeit limited) data, T cell–depleting induction followed by a steroid-sparing belatacept-based regimen containing an mTORi seems to be the most promising regimen, as it has been shown to yield AR rates on par with tacrolimus-based

immunosuppression.[49] However, the positive metabolic attributes associated with belatacept may be negated by long-term mTORi use; thus, a larger prospective study over a prolonged time period is needed. Because the majority of belatacept-treated patients will likely not require an mTORi beyond the early posttransplantation period, the discovery of a robust and reliable biomarker that identifies individuals at high AR risk would allow for more targeted mTORi prescription. In addition to biomarker studies, future clinical trials of alternative belatacept-based regimens should seek to hone patient selection criteria (e.g., based on viral serostatus), explore the use of co-stimulation blockade with IL-6 or CD40/CD40-ligand inhibitors, and establish the optimal timing of conversion from CNI-based to belatacept-based immunosuppression. Moreover, since CNI-based immunosuppression is used in other transplant settings, there may be clinical benefit in evaluating the efficacy and safety of belatacept in nonrenal transplant recipients.

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