CORRESPONDENCE

Belatacept and Long-Term Outcomes in Kidney Transplantation

TO THE EDITOR: Vincenti and colleagues (Jan. 28 issue)[1] found that the risk of death or graft loss was lower with belatacept-based immunosuppression than with a cyclosporine-based regimen among kidney-transplant recipients during 7 years of follow-up. The results are notable, because data on long-term clinical outcomes are rare in the field. However, no data on the dosing of mycophenolate mofetil through the follow-up period were provided, which raises concern about the interpretation of the results. According to the trial protocol, patients initiated mycophenolate mofetil at a dose of 2 g per day, with dose adjustments at the investigator's discretion. Exposure to mycophenolic acid, the active immunosuppressant, is the best metric for the efficacy of mycophenolate mofetil.[2,3] Cyclosporine inhibits enterohepatic recirculation of mycophenolic acid, thereby reducing exposure by 30 to 40%.[2-5] Thus, even if the patients assigned to belatacept and those assigned to cyclosporine received similar doses of mycophenolate mofetil, the former may have been exposed to a substantially higher amount of active immunosuppressant. Because mycophenolate mofetil inhibits the proliferation of T and B lymphocytes, higher exposure in the belatacept-treated patients could account for the lower risk of death or graft loss through a reduction in donor-specific antibodies or other exposure-dependent mechanisms. Mycophenolate dosing and the exposure metrics over time are needed to compare the intervention and control groups properly.

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TO THE EDITOR: In the article by Vincenti et al., it is surprising that outcomes were best in the patient groups with the highest risk of acute rejection, under belatacept treatment. Given the clinically relevant distinction between T-cell–mediated

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rejection and antibody-mediated rejection[1-3] and the absence of information on the rejection subtype in the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT),[4] it is difficult to interpret the rejection data. The surprisingly low cumulative rates for the development of donor-specific antibodies in the belatacept-treated patients illustrate that episodes of acute rejection in these patients were mainly T-cell–mediated, not antibody-mediated.

The mean estimated glomerular filtration rate (eGFR) increased with belatacept but declined with cyclosporine, and the incidence of interstitial fibrosis and the cumulative rates for the development of donor-specific antibodies were significantly lower with belatacept than with cyclosporine.[4] Given that belatacept was associated with a lower rate of graft failure and a higher rate of unspecified acute rejection than cyclosporine, it's possible that the eGFR, interstitial fibrosis, and donor-specific antibodies are better surrogate markers for graft failure than unspecified acute rejection. The uncoupling of acute rejection from the overall risk of graft failure illustrates that it is time to rethink the use of acute rejection as a primary end point for clinical trials in kidney transplantation.

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TO THE EDITOR: Vincenti et al. report the benefit of belatacept as compared with cyclosporine on patient and graft survival after a 7-year follow-up. Although the long-term difference in the eGFR is assumed to be partly a consequence of cyclosporine-induced vascular and tubulointerstitial fibrosis,[1] renal vasoconstriction due to the calcineurin inhibitor may be both a major short-term and a long-term contributor.[2] That can be particularly relevant in older persons with a cardiovascular burden, who receive arteriosclerotic allografts more frequently than younger persons.

On the basis of this pathophysiological background, we replaced a calcineurin inhibitor with belatacept in 21 kidney-transplant recipients older than 65 years of age with predominant vascular lesions on allograft biopsy (eGFR [±SD], 17±10 ml per minute per 1.73 m^2 of body weight; donor age, 69±12 years). Graft function improved in 86% of the patients, and, importantly, 4 of the 5 dialysis-dependent patients were weaned after a 6-month follow-up.

Despite the negative results of the BENEFIT–Extended Criteria Donors (BENEFIT-EXT) trial reported by the authors, we believe that hemodynamic factors have to be taken into account in this particular context. Belatacept should be evaluated as a long-term rescue treatment in kidney-transplant recipients with a reduced eGFR that is attributed to allograft vascular lesions or heart failure.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Vincenti and colleagues report the 7-year outcomes of BENEFIT, one of the longest-term follow-up trials in transplantation. However, understanding its limitations will help define the role of belatacept in modern immunosuppressive regimens. First, the major limitation is the use of cyclosporine as the comparator. We think that tacrolimus is the standard of care on the basis of the results of the Efficacy Limiting Toxicity Elimination (ELITE)–Symphony trial, which showed its superiority over cyclosporine in graft survival

and function.[1] Second, the continuous rise of the eGFR throughout the trial in belatacept-treated patients may potentially reflect the shortcomings of creatinine in assessing renal function. Alternatively, a component of adaptive hyperfiltration could be present.[2] If available, measurements of direct renal function and proteinuria are vital in clarifying this issue. Third, although Vincenti et al. found low rates for the development of donor-specific antibodies in belatacept-treated patients, it is essential to note that cyclosporine reduces exposure to mycophenolate,[3] a known suppressor of B-cell maturation.[4] Fourth, belatacept was associated with a significantly higher rate of graft loss due to infections (24%) than was cyclosporine (0%). Enlightenment with regard to the details of infections leading to graft loss is necessary.

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THE AUTHOR REPLIES: We agree with Meaney's observation that in belatacept-treated patients, exposure to mycophenolate mofetil might be appreciably higher than in cyclosporine-treated patients. Though we can only speculate as to whether this difference in exposure affected efficacy outcomes, a review of the pivotal trials of cyclosporine and mycophenolate mofetil did not show an efficacy advantage of the dose of 3 g of mycophenolate mofetil per day as compared with the dose of 2 g per day.[1] Furthermore, conversion from a regimen of a calcineurin inhibitor and mycophenolate mofetil to a regimen of a mammalian target of rapamycin (mTOR) inhibitor and mycophenolate mofetil (which would also increase exposure to mycophenolate mofetil) resulted in a higher incidence of donor-specific antibodies.[2] The reduction of donor-specific antibodies with belatacept is supported by both experimental data and the increasing evidence that costimulation blockade inhibits activation of the follicular helper T cells required for germinal-center B-cell response.[3]

We completely agree with the argument proposed by Naesens and Lerut that the traditional end point in clinical trials — acute (mostly cellular) rejection, which is treatable and has little effect on long-term outcome — is no longer relevant.[4] Thus, antibody-mediated rejection, renal function as reflected by the glomerular filtration rate (GFR), and the development of donor-specific antibodies should be considered more relevant clinical end points in the present era of immunosuppression. To identify potential cases of antibody-mediated rejection, we searched for patients in whom donor-specific antibodies developed shortly before or during rejection or for whom C4d or humoral rejection was mentioned in the comment section on the clinical case-report form. In all, three patients who received the more-intensive belatacept regimen, none who received the less-intensive belatacept regimen, and seven who received cyclosporine met any of these criteria.

We agree with Bertrand et al. that the use of belatacept as rescue therapy in patients with persistent delayed graft function or a persistently reduced GFR should be more fully investigated, preferably in randomized, prospective trials.

Riella et al. make many valid points about the limitations of our study, especially the use of a cyclosporine-based control regimen rather than tacrolimus, but the regimen that we used was the only calcineurin inhibitor–mycophenolate mofetil regimen approved by the Food and Drug Administration when the trials were conducted. The best explanation of the persistent long-term increase in the GFR in belatacept-treated patients is that the compensatory hyperfiltration of a solitary kidney is unrestrained by the vasoconstriction of the calcineurin inhibitors, an observation also noted in kidney donors. Finally, infection was the adjudicated cause of graft loss in three patients treated with more-intensive belatacept, two patients treated with less-intensive belatacept, and no patients treated with cyclosporine; it is difficult to ascertain the clinical and safety relevance, but clearly there are no statistical implications.

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Since publication of his article, the author reports no further potential conflict of interest.

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Shared Genetic Predisposition in Peripartum and Dilated Cardiomyopathies

TO THE EDITOR: Ware et al. (Jan. 21 issue)[1] describe a very similar distribution of presumably causative genetic variants in *TTN* and other genes in women with peripartum cardiomyopathy and in persons with idiopathic dilated cardiomyopathy. The clinical outcome of peripartum cardiomyopathy is highly variable, ranging from full recovery to rapid progression to end-stage heart failure,[2] and the appropriate duration of therapy is controversial. I therefore wonder whether analysis of the data of Ware et al. can shed light on whether *TTN*-truncating variants are associated with late recovery or persistent left ventricular dysfunction in patients with peripartum cardiomyopathy.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Ware et al. report a striking similarity of the presumed genetic causes of peripartum and idiopathic dilated cardiomyopathies in a large series of women. In our recent analysis of data from a large administrative U.S. database (the Healthcare Cost and Utilization Project National Inpatient Sample), we found remarkable similarity between patients with dilated cardiomyopathy and those with peripartum cardiomyopathy in terms of demographic and clinical characteristics and patient outcomes in pregnancy during the hospitalization for delivery.[1] Approximately 30% of the women in each cohort were black, and the two cohorts had similarly elevated rates of death, heart failure, arrhythmias, and preeclampsia spectrum disorders. Perhaps some of the patients (mis)classified as having peripartum cardiomyopathy were women with an asymptomatic dilated cardiomyopathy before pregnancy, and the hemodynamic demands of pregnancy worsened the degree of left ventricular dysfunction, leading to clinical heart failure. Have the authors considered whether the overlap in the reported genetic variants is consequent to the same disease presenting differently owing to pregnancy?

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THE AUTHORS REPLY: In response to Biteker: we agree that there is an important need for prognostic indicators for women with peripartum cardiomyopathy. Our study was not powered to test whether genetic variants correlate with clinical outcomes, nor did we have information on clinical outcomes for all patients. We did, however, have information for 1 year after enrollment on the 83 women in the Investigations in Pregnancy Associated Cardiomyopathy (IPAC) study. We noted that women enrolled in that study who