Belatacept: Where the BENEFITS Outweigh the Risk

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It is often challenging to explain to potential transplant recipients that the mainstay of their immunosuppressive regimen is lifelong therapy with a calcineurin inhibitor (CNI). Despite careful monitoring of drug levels, these agents are nephrotoxic, reduce kidney transplant function, and for a small number of nonkidney transplant recipients, may even lead to kidney failure requiring dialysis or transplantation. Moreover, the available CNIs have a range of other side effects (hypertension, new-onset diabetes mellitus, dyslipidemia, neurotoxicity, and cosmetic effects) and may contribute to the increased risk for cardiovascular (CV) disease following transplantation. These factors may lead to nonadherence, which is a leading contributor to transplant failure, particularly in young people. As a consequence, we combine classes of immunosuppressive agents to minimize the side effect of each, and although CNI therapy has made solid-organ transplantation routine, the development of new agents that allow minimization of CNI or even CNI-free immunosuppression has become a priority.[1]

In this issue of AJKD, Grinyo and colleagues[2] provide further evidence that the costimulation blocker belatacept offers a viable alternative to CNI-based immunosuppression, raising the question as to why it has not been more widely adopted in kidney transplantation. Belatacept is given by injection every few weeks, circumventing adherence issues, and has no effect on the development of posttransplantation diabetes mellitus, dyslipidemia, or hypertension.[3; 4; 5] The pivotal trials of de novo use, the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) and BENEFIT-Extended Criteria Donors (BENEFIT-EXT),[3; 4] demonstrated greatly improved kidney function at 1 year in recipients of standard and extended criteria donor kidneys.[3; 4] Using mathematical modeling, we used the 1-year data to predict long-term CV outcomes and survival over a 7-year horizon, predicting that the CV benefits of lower blood pressure, less dyslipidemia, and improved transplant function would be substantial, lead to improved survival, and as a consequence, be cost-effective despite the higher cost of treatment.[5]

Although the early use of belatacept identified an increased risk for cerebral lymphoma, a severe challenge due to the limited treatment options, subsequent avoidance of belatacept treatment in patients with prior Epstein-Barr virus infection in both clinical trials and clinical use negated this safety concern. Follow-up of BENEFIT and BENEFIT-EXT to 7 years has confirmed the long-term safety and efficacy (specifically with respect to kidney function) of belatacept versus CNI-based therapy. In particular, the long-term follow-up of BENEFIT[6] confirmed not only improved transplant function, but a substantial reduction in transplant loss and mortality, and despite the increased risk

for acute rejection, there was no increase in the development of donor-specific antibodies. Overall, the longer term follow-up studies have confirmed the predicted outcomes based on 1-year outcomes5 and lend credence to the use of mathematical modeling strategies to predict long-term outcomes in kidney transplantation studies. However, most importantly, they make an extremely strong case of the use of belatacept as primary immunosuppression.

An alternative strategy is to start with CNI-based therapy (with which patients and clinicians are experienced and comfortable)[7] and to switch at either a predefined time or in reaction to the development of CNI toxicity. In clinical practice, the former strategy is difficult to implement because neither the patient nor the physician is inclined to "rock the boat" when transplant function is stable. However, the reactive strategy, although more easily accepted, is often ineffective due to established pathology. Switch strategies have been extensively studied over the last decade, following the introduction of the mTOR (mammalian target of rapamycin) inhibitors sirolimus and everolimus. A series of studies investigated predetermined switches from CNI- to mTOR inhibitor–based immunosuppression at time points from 7 days to many months after kidney transplantation, and others, the effect of later switches in patients with decreased kidney function.[8; 9] The results can be summarized briefly as follows. In studies with follow-up of about 1 year, early switches are effective; the earlier the better. Switching to an mTOR inhibitor–based CNI-free regimen is typically associated with better transplant function and lower blood pressure at the expense of a slightly higher acute rejection rate, with persistent benefits reported at later time points in patients who remain on treatment. In contrast, reactive switches are not effective. In particular, patients with heavy proteinuria appear to have poor kidney outcomes, with increased proteinuria and accelerated transplant loss, although there may be some modest benefits in the subset of patients without proteinuria or with good transplant function.[8; 9] However, the most important issue is tolerability. Side effects, including gastrointestinal symptoms, oral ulceration, skin rashes, dyslipidemia, and edema, limit mTOR inhibitor use in 30% to 50% of patients and have deterred clinicians from adopting these drugs more widely. Instead, their use is limited to patients intolerant of other agents or those with a past or current history of malignancy, particularly skin malignancy, for which the incidence and recurrence rates are reduced by mTOR inhibitors.[10; 11]

In the current issue, Grinyo and colleagues report a study of a late switch from CNI-based immunosuppression to belatacept. The study population included 173 kidney transplant recipients with stable kidney function (mean estimated glomerular filtration rate, 53 mL/min/1.73 m2), half of whom were recipients of kidneys from live donors. Of these patients, 89 were randomly assigned to continue on CNI-based immunosuppression, and 84, to switch to belatacept 6 to 36 months after transplantation. Belatacept was started at a dose of 5 mg/kg given fortnightly, increasing to 4-weekly by 2 months. The main trial reported outcomes at 24 months after transplantation, after which patients initially randomly assigned to CNI treatment were offered the opportunity to convert to belatacept (at the investigator's discretion) in a long-term extension study. Sixteen patients switched to belatacept therapy. The analyses took into account the varying exposure to belatacept in the 2 groups with the primary aim of assessing long-term safety and efficacy.

A total of 74 of 84 patients assigned initially to belatacept and 72 of 89 (including 16 who switched to belatacept after 2 years) assigned initially to CNI completed 36 months of follow-up. In the

primary report, after 2 years of follow-up, patients randomly assigned to belatacept had improved transplant function.12 The current report confirms sustained improvement in kidney function despite the dilution of CNI exposure due to the inclusion of the 16 patients who converted. The study has other strengths. The CNI control arm included patients on tacrolimus and cyclosporine therapy, allowing comparison against the current standard therapy (rather than only cyclosporine), and there was a low incidence of donor-specific antibodies, in contrast to what is seen when switching to an mTOR inhibitor, further good news for long-term transplant function.[13]

There are weaknesses. The small size and failure to include patients with poor or deteriorating kidney function or proteinuria means that the findings are not necessarily generalizable, specifically not to the setting in which CNI minimization or withdrawal is usually considered, although a recent report[14] suggests similar benefits from belatacept conversion in kidney transplant recipients from extended criteria donors with poor transplant function (estimated glomerular filtration rate circa 20 mL/min/1.73 m2).

The new report from Grinyo et al is a confirmation of the 1- and 2-year follow-up of the original population described previously and needs to be viewed in that context. By itself, it is a rather small extension study that adds to available evidence on the tolerability and safety of prolonged use of belatacept. It confirms that belatacept-based CNI-free immunosuppression is associated with improved transplant function over 3 years with (unlike mTOR inhibitors) comparable safety and tolerability, as well as similar transplant and patient survival, to CNI. Like the mTOR inhibitor studies, switching was associated with an increased incidence of acute rejection, but without the expected effects on transplant function. This is likely to reflect the tendency to attribute increases in serum creatinine levels to the “experimental arm” of therapeutic trials, leading to a lower threshold for indication biopsies and thus more readily detecting low-grade rejection. However, it may reflect a change in the pathophysiology of acute rejection, uncoupling the established link between acute rejections and adverse transplant outcomes. Regardless, viewed in a broader context, the study is supportive of the strongly positive outcomes in the 7-year follow-up of de novo belatacept use in BENEFIT.[6] Compared with other agents and late switch strategies, belatacept appears to be effective and well tolerated, with an improvement in kidney function likely to translate into long-term CV and mortality benefits.[5]

To many, this study will appear to add to the body of evidence that belatacept should be the agent of choice in kidney transplantation and raises the question of its limited use. Although initially the risk for lymphoma deterred many and overall long-term outcome data are scarce compared with established agents, the hard truth is that the limits may be financial. Belatacept treatment is expensive and at least initially requires the infrastructure to administer outpatient infusions. Our modeling of its use suggested that prolonged transplant and patient survival, reduced monitoring, and lesser need for CV medications would reduce costs in the long term.5 The benefits to transplants and patients have been established, to which the present study contributes additional evidence; only the health economics of widespread use remains to be proved. However, the take home message in the current funding environment is that a switch from a CNI to belatacept in patients with reasonably preserved kidney function is safe, well tolerated, and associated with improved transplant function.

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