

# Converting Maintenance Kidney-Transplant Patients From Belatacept to Another Immunosuppressive Regimen: A Cautionary Tale



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Despite being associated with higher rates of early acute rejection, immunosuppression with belatacept in *de novo* kidney-transplant recipients resulted in early and sustained superior renal graft function and a 43% reduction in the risk of death or graft loss at 7 years when compared with cyclosporine.<sup>1</sup> Avoidance of calcineurin inhibitor (CNI)-mediated nephrotoxicity<sup>2</sup> is likely to be the primary driver of the difference in renal function; the lower rate of *de novo* donor-specific antibody (DSA) development observed consistently in belatacept-treated patients<sup>1,3</sup> further raises the possibility that reduced chronic allograft rejection may be a contributor. Multiple groups have now shown that a significant improvement in renal function occurs when patients are switched from CNI to belatacept-based immunosuppression both early (in

patients with prolonged delayed graft function or CNI toxicity),<sup>4</sup> as well as later post-transplant.<sup>5</sup>

Belatacept may, however, be associated with more profound impairment of protective antiviral immunity when compared with a CNI-based regimen, resulting in increased rates and a higher burden of viremia, especially in virus-naïve patients.<sup>6</sup> Clinically, this is manifested by high risk of Epstein-Barr virus replication, and Epstein-Barr virus-induced post-transplant lymphoproliferative disorder observed in Epstein-Barr virus high-risk recipients as well as primary cytomegalovirus infection and prolonged viral replication in cytomegalovirus high-risk patients.<sup>7</sup> Such patients may need to be taken off belatacept and switched to alternative immunosuppression, including CNIs. Patients also may switch from belatacept to other immunosuppression for logistical reasons such as difficulty with i.v. access, change in health insurance coverage, or a supply shortage. There is a paucity of data, however, on the outcome in patients who are switched from

belatacept to a CNI-based immunosuppression regimen.

In this issue of *Kidney International Reports*, Gouin *et al.*<sup>8</sup> report the results of a retrospective, multicenter analysis of clinical outcomes in 44 kidney-transplant patients who were taken off belatacept for a variety of reasons. Overall, the effort to convert from belatacept to another regimen was undertaken with good intentions on the part of the clinician, with most patients (63.6%) being converted for cause. The clinical indications included cytomegalovirus infection (36%) and rejection (18%).<sup>8</sup> Of note, the population was markedly heterogeneous with respect to the duration of belatacept treatment (2–137 months) before conversion, as well as the timing of initiation of belatacept (only 32% had received *de novo* belatacept vs. 69% who were switched from a CNI-based regimen for poor renal function). Most (77%) were switched to a CNI-based regimen.

The most reliable finding in the entire cohort was a decrement in renal function after switching, even in the patients who were switched to a CNI-free regimen. Interestingly, there was no statistically significant difference in 13 patients who had stable graft function and no clear clinical indication for conversion before switching. However, in this group, there was a trend toward a reduction in the estimated glomerular filtration rate (eGFR). This contrasting finding between the conversion cohort for clinical indication and those who were stable suggests the potential danger of good intentions. As clinicians we want to act in the best interest of our patients, and this often leads to making multiple changes with the best of intentions

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to address unstable or worsening clinical scenarios. In this study, the unstable patients converted demonstrated a worse renal function outcome. It is possible that other interventions to address the underlying clinical scenario would have been more prudent, such as lowering other immunosuppression and/or using antiviral agents to treat a viral infection. For those patients who were converted due to rejection, it is also possible that the treatment of rejection with the continuation of belatacept may have yielded more stable allograft function. In the original phase 3 trials of belatacept, those patients who experienced rejection on belatacept maintained a superior eGFR compared with CNI-treated patients without rejection. Overall, this eGFR finding underscores the known nephrotoxic effects of CNIs and the previously observed benefits of belatacept with respect to preservation of renal allograft function.<sup>1</sup>

Three of 44 patients developed graft rejection after switching from belatacept. Two of these were antibody-mediated rejections, which aligns with the finding that belatacept-based regimens may be more effective at preventing and suppressing post-transplant DSA.<sup>1,3</sup> Although systematic graft histology and DSA data are not available for all participants, this may explain partially the decrement in eGFR seen in the group that was switched from belatacept to a CNI-free regimen. Given the data suggesting the reduction of DSA with belatacept treatment, it may be prudent to monitor for DSA development when stopping belatacept, particularly if converting to a mammalian target of Rapamycin inhibitor-based regimen.

A significant proportion of patients developed opportunistic infections (22%) and malignancy

(18%), with malignancy leading to death in 3 of 6 patients. Kidney-transplant recipients with poor graft function (the reason for belatacept treatment in most of the cohort) are especially vulnerable to infectious complications, and it is possible that the cumulative burden of immunosuppression (CNI, then belatacept, then CNI again) is particularly detrimental in this group.<sup>9</sup> Provision of anti-infectious prophylaxis when switching off belatacept with more intensive monitoring may help to mitigate this risk.

The study suffers from a number of limitations, including the retrospective nature, the lack of a contemporaneous control group, and the heterogeneity of the patient population. Nevertheless, the authors conclude from their experience, quite cautiously, that physicians should avoid converting from belatacept unless there is a strong clinical indication. It is unclear, however, that conversion even for cause is warranted or necessary. Validated strategies to prospectively identify and exclude patients at risk of belatacept-related complications, such as cytomegalovirus infection and rejection and strategies to stratify and mitigate the risk of eGFR decline, infection, and death following conversion from belatacept, are essential to reduce the need for conversion and improve safety. It is important to remember that any change in immunosuppression has a potential consequence and it is not clear from these data that the conversion from belatacept to another regimen yielded the intended outcome.

## DISCLOSURE

All the authors declared no competing interests.

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