Letter to the Editor

Belatacept: the challenges with transformational drugs

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Dr. Westhoff's commentary on the recent article in the NEJM detailing the 7-year follow up study comparing the outcome of belatacept *vs.* cyclosporine in kidney transplantation is thoughtful, insightful and balanced (1) The pursuit of a CNI-free regimen that is effective, non-nephrotoxic and lacks the added cardiovascular risks inherent to the CNIs has been frustrating with multiple drugs having failed because of lack of efficacy or safety. The only agent to emerge from 2 decades of clinical trials is belatacept approved by the FDA in 2011. If belatacept offers all the advantages listed by Dr. Westhoff, why then the reluctance by transplant physicians to adopt it for wider use. With any transformative drug, there is a learning curve on how best to use the drug and who is most likely to benefit from it.

With belatacept however there were a number of challenges. Let's start with the acute rejection. Acute rejection was higher and more severe with belatacept than CSA treated patients. But this was in part due to the regimens utilized in the phase III trials that incorporated basiliximab, an anti-IL2 receptor antibody. Anti-IL2 mAb induction may not be a good pairing with belatacept, and several subsequent studies have shown a dramatic reduction in acute rejection with the use of depleting induction agents such as Thymoglobulin or alemtuzumab, which are not part of the FDA approved regimens for belatacept (2,3). Thus belatacept in a better regimen can be made more effective.

The antiproliferative used in the trial was mycophenolate mofetil (MMF) but data both experimental and from human trials suggest that mTor inhibitors are synergistic with co-stimulation blockade (4,5). The comparative arm was cyclosporine because at the initiation of the trials only CsA was approved for use with MMF. Would belatacept have fared as well if compared to a tacrolimus/MMF combination? Probably yes, although the differences in GFR may have been less dramatic as tacrolimus induces less vasoconstriction (but similar fibrosis) than CsA (6). A major advantage of belatacept therapy is also the remarkable decreased incidence of donor specific antibodies, which occur in approximately 20% of patients on CNIs and is an important cause of graft dysfunction.

The intravenous administration was considered an impediment but in fact it guarantees patient compliance with immunosuppression since non-adherence is an important cause of late graft loss.

The failure of belatacept to get appreciable traction in transplantation has sent a shiver through the industry and has discouraged pharma and biotechs from developing novel agents for transplantation. Yet many unmet needs in transplant therapeutics require innovation.

The lack of venues for open interactions and dissemination of different experiences with belatacept to educate physicians and allied healthcare personnel on the use of belatacept are also problematic: lack of support for educational activities, the Sunshine Act, conflicts of interest issues, the industry on the defensive have all contributed to this void.

Thus additional studies with belatacept are required to convince the transplant community at large of its benefit but the 7-year study provides reassuring data on both safety and long-term efficacy.

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Footnote

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