KI REPORTS
KIReports.org

Walking the Line Between Antidonor and Antiviral Immunity: A Potential Role for Belatacept

Deepthi Gunasekaran[1], John Pell[1] and Madhav C. Menon[1]

[1]Division of Nephrology, Department of Medicine, Yale University School of Medicine, New Haven, Connecticut, USA

Kidney Int Rep (2023) **8,** 1–3; https://doi.org/10.1016/j.ekir.2022.11.005

See Clinical Research on Page 126

Belatacept, a selective T-cell costimulation blocker, was introduced as a promising change from the nephrotoxic and metabolic side effects of calcineurin (CNI) based maintenance immunosuppression. Seven-year follow up of the belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study) trial showed superior patient and graft survival along with higher mean estimated glomerular filtration rate with the use of belatacept as compared to cyclosporine.[1] However, following its Food and Drug Administration approval in 2011, reportedly only 3% of transplant centers in the United States use belatacept as *de novo* or first line immunosuppression,[2] although a larger proportion of patients may likely convert to belatacept from CNI in later months posttransplantation. Logistic barriers to regular intravenous administration, the increased rate of acute cellular rejection, and increased risk of opportunistic infections are the major barriers to its widespread adoption.

A study by Schaenmen *et al.*[3] published in this issue of *KI Reports* attempts to investigate the latter 2 issues in a prospective transplant cohort by assaying peripheral blood mononuclear cells (PBMCs) to study the immunologic impact of switching to belatacept maintenance immunosuppression. Specifically, the authors here investigated belatacept's impact on T-cell phenotype in the context of donor-specific immunity (alloimmunity) and antiviral immunity. They studied 19 first time kidney transplant recipients with CNI toxicities (renal or others) who were switched to belatacept within 3 months of transplant and followed-up with for at least 6 months. At baseline and follow-up, the authors used a multiparameter panel to gate CD4+ and CD8+ T-cell populations for maturation subtypes i.e., naïve (CCR7+/CD45RA+), effector memory (CCR7+/CD45RA−) and terminally differentiated effector memory (CCR7−/CD45RA+ i.e., terminally differentiated effector memory) cells. In addition, exhaustion, senescence, and activation subsets were evaluated using the surface markers KLRG1, CD57, CD38, CD28, and PD-1. A 1-way mixed lymphocyte reaction (MLR), where inactivated donor cells were incubated with recipient PBMCs for 15 hours was used to study alloimmunity. To evaluate the impact on antiviral immunity, isolated PBMCs were incubated overnight with peptide pools representing cytomegalovirus (CMV) or Epstein-Barr virus (EBV) antigens, and surface markers and intracellular cytokine staining of responder T cells were assayed. Donor-specific antibody was meas ured in sera. All clinical and flow parameters were then compared to age-matched and transplant-mat ched controls on CNI therapy, as well as within-group analyses of slope using serial time points.

Clinically, the authors identified no significant differences in rates of acute rejection, or infectious complications between study groups. In serial analyses, the authors report a consistent trend of reduced naïve T-cell- with increased terminally differentiated effector memory proportions with time from transplantation, regardless of belatacept or CNI. In donor-specific MLRs, the proportions of single-cytokine or double-cytokine (interferon gamma/tumor necrosis factor alfa) positive T cells were also similar between belatacept and CNI patients, suggesting similar donor-specific T-cell responses with both regimens. However, as reported in several series, rates of detectable donor-specific antibodies were significantly lower with belatacept. Interestingly, CMV-specific, single-cytokine or double-cytokine positive CD28+ CD8+, CD28+CD4+ T-cell

Correspondence: Division of Nephrology, Department of Medicine, 300 Cedar street, TAC S255A, Yale University School of Medicine, New Haven, Connecticut, USA. E-mail: madhav.menon@yale.edu

proportions tended to increase with time after conversion among belatacept patients, but not with CNI. The authors discuss that tjough there was an inhibition of donor-specific T-cell immune response with belatacept (similar to CNI) as expected, this occurred in tandem with preservation of antiviral immunity among the belatacept cohort.

Despite the small sample size, *ex vivo* studies on PBMC collected from patients receiving belatacept with a matched CNI comparator group are important data adding to prior *in vitro* studies with belatacept, and raise intriguing points. For example, in a prior systematic review,[4] belatacept was associated with a higher rate of rejection compared with CNI, most of which occurred within 1 year of transplant or switch. Contrary to this, no differences in alloreactivity as measured by T-cell cytokine responses in MLR was seen between groups, whereas an increased rate of donor-specific antibodies was observed in the CNI group. In this context, the study also identified an association of belatacept treatment with enrichment of CD57+CD28− T cells, antigen-experienced T-cells which have been previously linked to belatacept-resistant rejection.[5] Furthermore, in the current data set the authors encountered overall low event rates for rejection in both study groups. Therefore, whether the levels of MLR donor-reactivity identified here will correlate with actual episodes of acute rejection needs further analyses pairing donor-specific MLRs with longer term rejection outcomes.

The interesting positive correlation between frequency of CD28-negative, CMV-specific cytokine producing T-cells among belatacept patients over time identified by the authors here, may allude to a cellular mechanism of belatacept "escape" where antigen-experienced T-cells that downregulate CD28 are resistant to costimulatory blockade, thus preserving anti-CMV T-cell responses. Though CD28-CD8+ and CD28-CD4+ cells have been reported to be specifically important for anti-CMV responses,[6] the authors did not include this gating strategy during the antidonor MLRs. Whether this mechanism represents an adaptive global response in belatacept-exposed T cells regardless of antigen remains unanswered from this data. Furthermore, despite the similar CMV-specific T-cell cytokine responses, nearly 37% of belatacept patients developed CMV viremia within the first year versus only 10% in CNI limb. Therefore, the relevance of these findings for clinical CMV disease when on belatacept, still needs to be evaluated in larger clinical data, especially in light of conflicting prior reports.[4,7] The authors also identified a differential impact of belatacept on EBV as compared to CMV. In their predominantly EBV seropositive adult recipients, EBV-specific double-positive and triple-positive CD4+ cells (interferon gamma+ tumor necrosis factor alfa+ interleukin-2+) declined significantly with CNI but not with belatacept, findings that may partly conflict with previously reported increased rates of EBV reactivation.[4] It must also be noted that the authors performed several analyses in a relatively small data set, although they adjusted for multiple comparisons.

Overall, these flow cytometric analyses advance our understanding of belatacept's impact on T-cell subsets and their antigen-respon siveness, especially in the context of antiviral immunity. A clear strength of these data is the serial evaluation of T-cell phenotype in the *in vivo* context of belatacept administration, as opposed to *in vitro* addition of belatacept to PBMCs. Considering previous studies on belatacept's impact on B-cell phenotype,[8] and role in immunomodulation of dendritic cells,[9] future studies must include serial investigation of other cell types to explore immune cell crosstalk under belatacept versus CNIs. Ultimately, these observations move toward reconciling 2 somewhat opposing phenotypes that are highly relevant to immunosuppressants, i.e., effects on donor-reactivity (a correlate of rejection) on the one hand, and effects on antiviral immunity on the other. The authors provocatively discuss that in the case of belatacept, the former may be inhibited as *de novo* donor-antigen recognition mostly occurs by naïve CD28+ T cells, whereas *apriori* viral antigen-experienced CD28-negative T-cells that mediate antiviral responses would escape belatacept inhibition. Though this important pilot study offers new insights, walking this fine line between alloimmunity and antiviral immunity remains an elusive goal in transplantation.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENT

MCM acknowledges research funding from NIH/NIDDK DK122164.

REFERENCES

1. Vincenti F, Rostaing L, Grinyo J, et al. Belatacept and long-term outcomes in kidney transplantation. *N Engl J Med*. 2016;374:333–343. https://doi.org/10.1056/NEJMoa1506027
2. Karadkhele G, Duneton C, Garro R, et al. Temporal trends and current use of de novo Belatacept in kidney transplant recipients in the United States. *Clin Transpl*. 2022;36:e14531. https://doi.org/10.1111/ctr.14531
3. Schaenman J, Rossetti M, Pickering H, et al. Preservation of antiviral

immunologic efficacy without alloimmunity after switch to Belatacept in CNI-intolerant patients. *Kidney Int Rep*. 2023;8:126–140.

4. Lombardi Y, François H. Belatacept in kidney transplantation: what are the true benefits? A systematic review. *Front Med (Lausanne)*. 2022;9:942665. https://doi.org/10.3389/fmed.2022.942665
5. Espinosa J, Herr F, Tharp G, et al. CD57(+) CD4 T cells underlie Belatacept-resistant allograft rejection. *Am J Transplant*. 2016;16:1102–1112. https://doi.org/10.1111/ajt.13613
6. van Leeuwen EM, Remmerswaal EB, Heemskerk MH, ten Berge IJ, van Lier RA. Strong selection of virus-specific cytotoxic CD4+ T-cell clones during primary human cytomegalovirus infection. *Blood*. 2006;108:3121–3127. https://doi.org/10.1182/blood-2006-03-006809
7. Chavarot N, Divard G, Scemla A, et al. Increased incidence and unusual presentations of CMV disease in kidney transplant recipients after conversion to Belatacept. *Am J Transplant*. 2021;21:2448–2458. https://doi.org/10.1111/ajt.16430
8. Leibler C, Matignon M, Pilon C, et al. Kidney transplant recipients treated with Belatacept exhibit increased naïve and transitional B cells. *Am J Transplant*. 2014;14:1173–1182. https://doi.org/10.1111/ajt.12721
9. Bahri R, Naji A, Menier C, et al. Dendritic cells secrete the immunosuppressive HLA-G molecule upon CTLA4-Ig treatment: implication in human renal transplant acceptance. *J Immunol*. 2009;183:7054–7062. https://doi.org/10.4049/jimmunol.0803054