

Chronic-active Antibody-mediated Rejection: To Belatacept or Not, That Is the HOT Question

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The BENEFIT and BENEFIT-EXT studies in which belatacept-based immunosuppression was compared to a standard cyclosporine A-based regimen brought hope to kidney transplant recipients (KTRs).^{1,2} The use of belatacept was shown to result in superior renal function and in higher patient and allograft survival.^{1,2}

Interestingly, the blockage of crosstalk between T and B cells by belatacept may lead to a new use of this drug.³ The blockage prevents B cell proliferation and differentiation into plasmablast secreting antibodies. Therefore, treating KTRs with belatacept may possibly lower the incidence of chronic-active antibody-mediated rejection (caAMR) or slow its progression. KTRs who received belatacept maintenance therapy had reduced formation of de novo donor-specific anti-HLA antibodies (DSAs) as compared with the patients treated with standard cyclosporine A.² In a smaller retrospective study by the group of Gupta et al,⁴ no development of DSA was reported in 6 immunized KTRs (panel reactive antibody >80%, or positive flow cytometry crossmatch) who were converted from tacrolimus to belatacept because of presumed acute calcineurin inhibitor nephrotoxicity and chronic injury (median 4 mo after transplantation).

In the current edition of *Transplantation*, Kumar et al⁵ describe 19 patients who were converted from tacrolimus-based maintenance therapy to a belatacept-based immunosuppressive regimen because of caAMR. caAMR was

diagnosed by means of Banff 2017 revised criteria, in which the authors combined both histologic and molecular assessment. The authors judged that in all patients, there was a relative contraindication for salvage immunosuppressive therapy because of the patients' clinical condition or a high degree of chronicity in the renal transplant biopsy. Kumar et al not only describe the clinical and histologic effects of the conversion to belatacept but also the molecular profile of renal biopsies before and after this intervention. The authors' main findings are that conversion to belatacept of patients with caAMR may stabilize renal function and that this conversion reduces inflammation as evidenced by molecular profiling of follow-up biopsies, although conventional histology of the biopsy showed no difference in the degree of inflammation. Two aspects of this article are of interest: first, the clinical effects of conversion to belatacept in patients with caAMR and second, the use of molecular profiling to assess the impact of conversion.

There is no proven effective therapy for caAMR. Neither bortezomib, eculizumab, rituximab, plasma exchange, nor combinations thereof has convincingly demonstrated benefit for KTRs with caAMR.^{6,7} Importantly, these treatments are associated with considerable toxicity and healthcare costs. Tocilizumab, a monoclonal antibody directed against the interleukin-6 receptor, has shown promise as rescue therapy for caAMR.⁸ A major problem when studying the effectiveness of a therapy for caAMR is the definition of endpoints for clinical trials. Hard endpoints, such as graft survival, require large numbers of patients and long-term follow-up. DSA levels tend to fluctuate and can be considered surrogate endpoints at best.

The patients described Kumar et al⁵ were 44 months after transplantation when they were converted to belatacept. Rather than switching these patients overnight, tacrolimus was tapered over the course of 90 days. The mycophenolate mofetil and prednisolone dose was 1g/d and 5 mg/d, respectively. With the use of this protocol, no acute T cell-mediated rejection episodes occurred. This is in marked contrast to KTRs who received belatacept maintenance therapy in a de novo setting.^{9,10} This suggests that conversion to belatacept in the setting of caAMR is relatively safe in the initial phase, despite the occurrence of (infectious) complications.

The use of gene expression analysis by Kumar et al is novel in assessing the response to therapy in the setting of caAMR. The authors used the microarray-based molecular microscope diagnostic system platform using Affymetrix

Received 20 March 2020. Revision received 31 March 2020.

Accepted 2 April 2020.

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D.A.H. has received lecture and consulting fees from Astellas Pharma, Chiesi Farmaceutici S.p.A., and Hikma Pharma, as well as grant support from Astellas Pharma, Bristol Myers-Squibb, and Chiesi Farmaceutici S.p.A. (paid to the Erasmus MC). M.C.C.-v.G. received grant support from Astellas Pharma (paid to the Erasmus MC). The other authors declare no conflicts of interest.

M.v.d.Z., D.A.H., C.C.B., and M.C.C.-v.G. participated in writing of the commentary and provided intellectual content of critical importance to the work.

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ISSN: 0041-1337/21/1053-478

DOI: 10.1097/TP.0000000000003279

U133 2.0 microarrays to obtain a molecular classifying score.¹¹ In this platform, transcription levels in a biopsy are measured, which are subsequently placed in an algorithm consisting of a reference set of samples to which the biopsy is compared. A molecular classifying score is then generated indicating the rejection and injury risk.¹¹ A limitation of this platform is that it requires an extra biopsy on which no histology is performed, as the sample has to be placed immediately in RNAlater for optimal preservation of mRNA. Unfortunately, the molecular microscope diagnostic system classifying score is platform specific and requires central assessment.

During the last Banff meeting in September 2019 in Pittsburgh, United States, the NanoString Banff-Human Organ Transplant (B-HOT) panel was introduced. This panel includes genes related to graft rejection, drug toxicity, tolerance, and viral infection. Its main advantage is that this is an on-location platform in which sections of the renal biopsy, which has first been formalin-fixed and paraffin-embedded for histologic assessment, are used for molecular analysis. The utility of this panel still has to be validated in a clinical multicenter setting. Nonetheless, it would be interesting to see how this commercially available molecular profiling panel performs in research settings, such as the one described here and, subsequently, in everyday clinical practice.

Molecular profiling has the potential to identify changes in inflammation and injury before it is visible by conventional light-microscopic examination of a renal transplant biopsy. Molecular analysis on renal transplant biopsies with acute rejection allowed us to identify a case with a molecular profile of nonrejection in a biopsy showing acute vascular T cell-mediated rejection.¹² More research is needed to investigate the additive value of molecular profiling in renal transplant pathology and its clinical performance in establishing more accurate diagnoses and predicting the outcomes of therapeutic interventions such as the one described by Kumar et al.⁵ Collaboration of the members of the Banff Molecular Diagnostics Working Group will hopefully answer these questions in the near future. Molecular profiling does not only have the potential for a more precise diagnosis, but it could also lead to a superior and tailored therapeutic approach in transplant patients.¹³

The promising results of the pilot study by Kumar et al require proper confirmation in an adequately powered,

preferably multicenter, randomized controlled trial. It is our belief that incorporation of molecular profiling in trials, such as these, is of vital importance, as it will increase our understanding of the pathophysiological mechanisms underlying novel therapeutic interventions for caAMR. Only then, with this knowledge, may we be able to improve the prognosis of this condition, which is now bleak.

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