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Torque Teno Virus-Guided Immunosuppression in Kidney Transplantation: Expanding the Application

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Posttransplant care of kidney transplant recipients faces 2 major challenges that are associated with inadequate immunosuppression: alloimmune processes and infectious complications.[1] In contrast, no novel immunosuppressive drugs that were specifically developed for maintenance use in solid organ transplant recipients have been registered since the approval of belatacept and it is unlikely that novel compounds will enter clinical routine within the next years.[S1] Therefore, personalized medicine focusing on individual optimization of existing immunosuppressive regimens is a timely strategy.

Quantification of the highly prevalent and apathogenic torque teno virus (TTV) has been proposed as an "Immunometer" to assess the individual depth of immunosuppression in kidney transplantation.[2] In Supplementary Figure S1, we provide an overview on different aspects of TTV with relevance for the solid organ transplant setting. Almost all healthy individuals and kidney transplant recipients are infected with 1 to 20 species of these anelloviruses.[3] TTV load is detected by means of quantitative polymerase chain reaction; and since 2021, a commercial *in vitro* diagnostic regulatory conform assay is available for clinical use.[S2] Plasma TTV load is associated with the risk of graft rejection and infection in kidney, lung, liver, and heart transplant patients and it is hypothesized that TTV load indirectly reflects the immunocompetence of its host. A high TTV load indicates insufficient viral control because of more intense immunosuppression and a low TTV load likely indicates a more competent immune system because of low immunosuppression.[1] Differences in TTV loads between the 2 calcineurin inhibitors (CNIs), cyclosporine A and tacrolimus, were first described in lung transplant patients.[4] Cut-off values for risk stratification of graft rejection and infection for patients receiving CNI-based immunosuppression have been proposed, and are currently tested in 3 randomized controlled interventional trials recruiting over 500 kidney and lung transplant recipients in 7 European countries (TTVguideIT, VIGILung, and TAOIST).[S3]

In contrast, data on non-CNI-based immunosuppressive regimen are scarce and no TTV cut-off value has been defined for kidney transplant recipients in this setting. An earlier study in a cohort of long-term kidney transplant recipients has described a low TTV load in patients on mammalian target of rapamycin inhibitor (mTORi)-based immunosuppression and a high TTV load in patients on costimulation-blockade (belatacept)-based immunosuppression when compared to patients with CNI-based regimens.[5] With respect to these and other findings, direct actions of mTORi, costimulation blockade or lymphocyte-depleting agents on TTV replication influencing TTV load and its postulated replicative reservoir-independent from the grade of immunosuppression-have been hypothesized.[6,7] Thus, it has been suggested that CNI-based TTV cut-off values cannot be used for patients with mTORi-based and belatacept-based immunosuppression. With a substantial proportion of kidney transplant recipients treated with CNI-free immunosuppressive regimen, it is necessary to further analyze the TTV load kinetic in these patient cohorts.[8] In Figure 1, we illustrate a timeline of landmark studies that have shown the associations of TTV loads and kinetics with different immunosuppressants in SOT.

In this respect, the most recent study on this topic conducted by Cabezas *et al.*,[9] which was published in the current issue of Kidney International Reports, is highly appreciated. Their major finding was that, conversion from a CNI-based or mTORi-based dual or triple immunosuppressive regimen to

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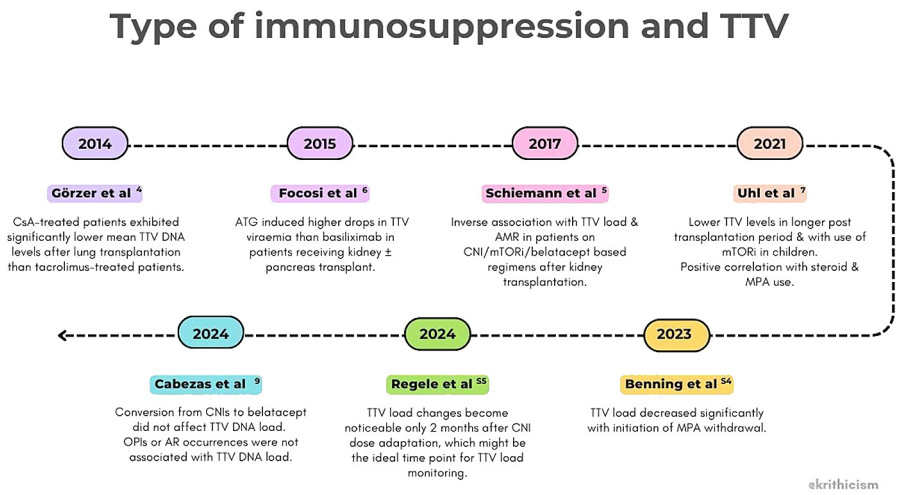

Figure 1. Type of immunosuppression and TTV. AMR, antibody-mediated rejection; AR, acute rejection; ATG, antithymocyte globulin; CNI, calcineurin inhibitor; CsA, cyclosporine A; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin inhibitor; OPI, opportunistic infection; TTV, torque teno virus.

a belatacept-based dual or triple regimen did not affect TTV load. In this well-designed retrospective, single-center study, tacrolimus (>80% of patients on tacrolimus, no patient on cyclosporine A) or mTORi conversion to belatacept was performed in motivation to limit CNI-toxicity in 68 patients, after a median time of 4 years after transplant. TTV was quantified by commercial polymerase chain reaction in whole blood at month 3, 6, and 12 after the conversion and TTV load remained stable at all 3 time-points. Tacrolimus was tapered until month 4 post switch and all other maintenance immunosuppressive medication were kept stable. In this context, it is important to note, that TTV load reflects immunosuppression of the last 3 months and TTV load changes are expected to mirror changes in immunosuppression only after 2 months.[S4,S5] Thus, because the conversion was carried out with an overlapping regimen of CNI and belatacept, the load at months 3 and 6 in the present study might not reflect the "pure" effect of belatacept conversion. However, the stable TTV load at month 12 following conversion is reassuring. Of note, absolute values of TTV load in the present study have to be interpreted with caution, because TTV was quantified in whole blood. TTV quantified in whole blood might generate up to 1 log level higher values compared to values detected in plasma or serum.[3]

How should we interpret the findings of the current study in the context of the existing literature? Until now, there is only 1 study published, in which TTV load was analyzed in a subset of patients on belatacept. Schiemann *et al.*[5] described higher TTV loads in patients on belatacept-based immunosuppression compared to patients with CNI-based immunosuppression. Patients had similar age and sex distribution and were analyzed at a similar time posttransplant compared to the present study; however, all of them were donor-specific antibody-positive at the time of TTV assessment. The authors hypothesized that costimulation blockade might lead to reduced TTV specific T cells, directly influencing viral control. In contrast to the study by Schiemann *et al.*,[5] the current study by Cabezas *et al.*[9] included more patients, followed the patients longitudinally, and was specifically designed to analyze TTV kinetics following conversion to belatacept. Taken together, the current literature does not support the hypothesis that TTV control is directly reduced due to costimulation blockade.

The association between TTV load and infection and rejection, respectively in solid organ recipients, is well-established.[1] The missing association in the present study can be explained by several factors. First, the study was neither designed nor powered to test for an association between TTV load and infection or rejection. Second, the events were mainly long after the TTV load assessment, and thus the selected TTV load might not represent immunosuppression at the time of the event. Third, the authors restricted their infectious events to cytomegalovirus disease, BK virus nephropathy, and hospitalization for any infectious cause. Of note, others have shown that TTV is associated with a broad range of infections including non-opportunistic pathogens and infections treated in an outpatient setting.[S6,S7] Therefore, relevant events could have been missed by the authors leading to reduced power and misclassification of event status. Taken together, the present study might not suffice to exclude an association between TTV load and infection and rejection in patients with belatacept-based immunosuppression, respectively. Until studies specifically designed to test for this association are available, it is reasonable to use TTV for risk stratification in kidney graft recipients with belatacept-based immunosuppression.

In conclusion, the present study supports the use of TTV load as a

marker of immunosuppression in kidney transplant recipients with belatacept-based immunosuppression. The findings of the present study have direct implications for the design of future interventional studies, which plan to recruit patients with CNI-based and belatacept-based immunosuppression.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplemental References.

Figure S1. Fact sheet on TTV and solid organ transplantation.

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