Correspondence

Torque Teno Virus Viremia Correlates With Intensity of Maintenance Immunosuppression in Adult Orthotopic Liver Transplant

To the Editor—We read with interest the recent article by Béland et al, detailing torque teno virus (TTV) kinetics in pediatric orthotopic liver transplant (OLT) recipients [1]. Interestingly, the authors show that TTV load increased with the number of immunosuppressive agents received.

TTV viremia, which is normally at about 2 log10 in healthy subjects, has been shown to increase (up to 4 log10) in almost every condition of chronic immunosuppression (congenital, acquired, or iatrogenic); our group and others have reported high TTV viremia in congenital mannose-binding lectin deficiencies [2], HIV infection [3], cancer [4], heart and lung transplant [5], and high-dose chemotherapy for lymphomas and myelomas. High TTV viremia correlates with high CD27- dysfunctional B-lymphocyte [3] and high CD8+CD57+ dysfunctional T-lymphocyte [6] counts in peripheral blood.

In the setting of solid organ transplant, De Vlaminck et al have recently reported that TTV viremia correlates with intensity of maintenance immunosuppression in heart and lung transplant recipients [5]. In OLT, we and others previously reported that TTV DNA load increased significantly after transplant (P < .001) and that, in accordance with the report by Béland et al, TTV DNA was significantly higher in patients on calcineurin inhibitors plus azathioprine or mycophenolate mofetil (CNI + AZA/MMF) than in patients on CNI alone (P = .04) at 3 months after OLT [7]. Because CNIs have severe toxicities in liver transplant recipients and strong iatrogenic immunosuppression may cause hepatitis B virus (HBV) and hepatitis C virus (HCV) reactivation in OLT recipients, some centers have introduced protocols combining low-dose CNIs and extracorporeal photopheresis (low-CNI + ECP) [8, 9], with positive clinical results (reduced numbers of HCV reactivations [8]). We investigated here whether such improved hepatitis control throughout the first year after transplant could be due to better immune competence (reduced iatrogenic immunosuppression), using TTV viremia as a surrogate marker.

Forty-six adult patients with HBV/HCV-related cirrhosis undergoing consecutive OLT at the Liver Transplant Centre of the Azienda Ospedaliero-Universitaria Pisana in 2009–2011 were enrolled in the low-CNI + ECP study. Pre- and posttransplant peripheral blood serum samples were obtained from these patients after they provided written informed consent during ECP visits at 3, 6, and 12 months after transplant. Retrospective pre- and posttransplant samples from historical controls treated with standard immunosuppression in 1996–2001, namely, CNI monotherapy (n = 19) or CNI + AZA/MMF (n = 6), were provided by the University of Padua Transplant Centre, as previously published [7]. Cyclosporine A C2 levels were maintained at 800–1200 ng/mL for the first 3 months, then at 600–800 ng/mL up to 6 months and 400–600 ng/mL up to 12 months after liver transplant. Tacrolimus trough levels were kept at 10–15 ng/mL for the first 6 months, then at 8–12 ng/mL up to 12 months after OLT. Azathioprine (1.5 mg/kg) up until the year 2000 and mycophenolate mofetil (1.5–2 g) thereafter were added when the patient’s serum creatinine level was >200 μmol/L, to minimize the cyclosporine or tacrolimus dosage. In all 3 treatment arms, 70% of all patients received induction immunosuppression.

Figure 1. Kinetics of TTV viremia according to different maintenance immunosuppression regimens and compared to healthy donors. Abbreviations: AZA, azathioprine; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; OLT, orthotopic liver transplant; TTV, torque teno virus.
with anti-CD25 monoclonal antibody basiliximab 20 mg intravenously on post-transplant days 1 and 4. In HCV-infected patients, antiviral therapy with pegylated interferon and ribavirin for 6–12 months was given for fibrosis stage 2 or higher; in HBV-infected patients, anti-HBV immunoglobulins plus lamivudine 100 mg/day was administered. Forty healthy blood donors served as a control group. DNA extracted from 200 μL of plasma samples was examined for TTV presence and loads by using single-step universal TaqMan real-time polymerase chain reaction with a sensitivity of 2.0 log_{10} DNA copies/mL of plasma, as previously described [7].

No statistically significant difference was found in mean recipient or donor age, sex, or baseline liver disorder across the 3 experimental groups. All recipients tested positive for TTV viremia on the pretransplant serum sample. Figure 1 summarizes the kinetics of TTV viremia in the 4 experimental arms (1 prospective and 3 retrospective). The low-CNI + ECP protocol was associated with the lowest increase in TTV viremia compared with the other 2 different immunosuppressive protocols used in the historical arms of the study throughout the first posttransplant year (CNI vs low-CNI + ECP, \( P < .01 \); CNI + AZA/MMF vs low-CNI + ECP, \( P < .01 \)), thus establishing a continuous direct relationship between intensity of iatrogenic maintenance immunosuppression and increases in TTV viremia.

These findings are not entirely unexpected, as it was already known from studies in hematological patients treated with high-dose chemotherapy that TTV viremia has a fast and sustained dose-response effect [10] that might eventually be exploited to tailor iatrogenic immunosuppression. Because there is a growing need for tailor-made maintenance immunosuppressant dosing to minimize side effects (opportunistic infections, viral reactivations, and secondary cancers) while maximizing graft survival, we propose that TTV could be a cheap surrogate marker of functional immune competence. Larger prospective studies with a longer follow-up will be needed to confirm this, including in other kinds of solid organ transplants.

**Notes**

**Author contributions.** D. F. designed the study and wrote the manuscript. L. M. performed laboratory testing for TTV titers. F. M. analyzed the data and wrote the manuscript. M. P. provided scientific supervision of the entire project and manuscript.

**Potential conflicts of interest.** All authors: No reported conflicts.

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**Torque Teno Virus Load as a Biomarker of Immunosuppression? New Hopes and Insights**

To the Editor—We thank Focosi and colleagues for their comments [1] concerning our article [2]. The results presented in their letter are of major interest and the conclusions are attractive.

We want to emphasize that, similar to studies in adults, our results confirmed that a clear correlation between torque teno virus (TTV) load and the intensity of immunosuppression was shown in pediatric liver transplant recipients. This was related to the number of immunosuppressive drugs. As it has been clearly established that TTV is ubiquitous but has a variable prevalence [3], we also believe that TTV infection should be evaluated mainly on the basis of the viral load, and not on the prevalence, in healthy individuals as well as in patients with chronic conditions.

Focosi et al [1] suggested that a continuous relationship can be established between intensity of iatrogenic maintenance immunosuppression and increase in TTV viremia in hepatitis B virus.

**Author contributions.** D. F. designed the study and wrote the manuscript. L. M. performed laboratory testing for TTV titers. F. M. analyzed the data and wrote the manuscript. M. P. provided scientific supervision of the entire project and manuscript.

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