

Torque teno virus in liver diseases and after liver transplantation

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Abstract

Torque teno virus (TTV) has been proposed as a surrogate biomarker for immune monitoring in different patient cohorts. Historically, TTV has been associated with different liver diseases such as post-transfusion hepatitis, hepatitis B, and hepatitis C, but the virus's pathogenicity is controversial. TTV is a ubiquitous DNA virus, highly prevalent and mostly indolent in the general population. Thus, TTV viral load is more relevant than prevalence to understand TTV infection. In the context of liver transplantation, TTV viral load is modulated by the immune, viral, and inflammatory status. After liver transplantation, the TTV viral load positively correlates with the intensity of immunosuppression (IS), and low TTV viral burden is a predictor of acute rejection episodes, making it an attractive marker for the efficacy of IS. However, the TTV role as a single or a panel biomarker needs to be evaluated in further independent prospective trials.

Key Words: Torque teno virus; Solid-organ transplantation; Biomarker; Liver disease; Liver transplant; Immune system

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Core Tip: Torque teno virus (TTV) is a ubiquitous, highly prevalent, and mostly indolent DNA virus in the general population. Historically, it has been associated with different liver diseases, but the virus's pathogenicity is controversial. TTV viral load is modulated by immune, viral, and inflammatory status. TTV viral load positively correlates with the intensity of immunosuppression, making it an attractive surrogate biomarker for immune monitoring in different patient cohorts, including liver transplant recipients. However, the TTV role as a single or a panel biomarker needs to be evaluated in further trials.

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INTRODUCTION

The presence of torque teno virus (TTV) DNA has been proposed as a novel and attractive surrogate biomarker for the efficacy of immunosuppression in different patient cohorts^[1-3]. In solid-organ transplant recipients, immunosuppressive therapy is aimed to prevent rejection and increase organ and patient survival. Usually, a combination of drugs with different action mechanisms is used to control the immune system and prevent/treat the rejection^[4,5]. However, the immune monitoring strategies are still based on rough surrogates such as the immunosuppressive drug levels, liver function tests, and biopsies. Other currently available tools are still suboptimal or impractical for the assessment of personalized immune system control^[6-8]. In an attempt to optimize the immune system's control, a search for an optimal monitoring tool (*e.g.*, a biomarker) is an ongoing challenge.

TTV

TTV is a non-enveloped, circular single-strand deoxyribonucleic acid (DNA) virus, first identified in Japanese patients with acute post-transfusion hepatitis in 1997^[9]. TTV is a member of the Anellovirus family, together with two additional viruses, torque teno mini virus and torque teno midi virus, thus named because of their smaller genomes^[10]. Its biological significance is still unknown and evolving. TTV has a high genetic diversity with five genogroups and 29 genotypes identified so far^[11]. TTV is ubiquitous, present in water, air, soil, and different human samples^[12,13]. The virus's replication has been demonstrated in hematopoietic cells, mononuclear cells and granulocytes, lymphocytes, hepatocytes, and lungs^[14-19], reaching far beyond the initially assumed viral hepatotropism. There is no generally standardized diagnostic algorithm for TTV. Polymerase chain reaction (PCR) methods that target TTV can be distinguished as universal, which amplifies most, if not all, the human TTVs, and species-specific, which permits grouping of the virus in one of the 29 TTV genotypes. The diagnosis is focused on the possible pathologic consequence of TTV infection and is performed to measure the kinetics of TTV viremia in selected populations, such as patients treated with immunosuppressive therapy^[12].

TTV AND LIVER DISEASES

The first reports on TTV showed low prevalence rates in the general population and patients with liver diseases, most likely due to the use of inappropriate PCR primers^[20]. More recent reports demonstrate significantly higher prevalence rates in various liver patients: 77% hepatitis C virus (HCV), 77.7 % hepatitis A virus, 87.6% hepatitis E virus (HEV) and 92% non-A-E hepatitis patients^[21]. Historically TTV, has been associated with different liver diseases from post-transfusion hepatitis, HCV, and hepatitis B virus (HBV); however, the pathogenicity of the virus is controversial^[13]. The fast-growing evidence shows that the virus infects a great majority of people without causing overt disease. More recent epidemiological studies showed that TTV viremia prevalence rates are over 80%-90% in some populations^[22-25], with higher viral load in immunosuppressed patients compared to a healthy population^[26]. In addition, the results of one Italian study suggested TTV's role in immune senescence and the prediction of all-cause mortality risk in the elderly. Three-year survival differed significantly by TTV load in a cohort of 379 elderly subjects. The proportion of patients that died after 3 years was estimated to be 21.9% for patients with TTV DNA copies \geq 4.0 log and 5.4% for patients with TTV copies $<$ 4.0 log. These results indicated that TTV may represent an additional virus that establishes latency after primary infection and reactivates in aging when the immune system is compromised^[27].

TTV AND LIVER TRANSPLANTATION

Regardless of the high prevalence and mostly indolent role in the general population, the TTV role in immunocompromised populations needs to be further elucidated. Given the high global prevalence, TTV viral load is more relevant than the prevalence itself to understand the TTV infection^[28]. In patients with compromised immune response, TTV viral load increases as the replication of the virus is inversely correlated with the number and function of T lymphocytes^[26,29-31]. A substantial body of evidence supports that TTV is more an associated co-factor, but not a major pathogen itself, in the development of post-transplant outcomes. In immunocompromised patients, the low TTV viral burden has been associated with the development of acute rejection episodes in populations after different organ transplantations^[32-34]. In addition, higher TTV levels, isolated from the post-transplant lymphoproliferative disease (PTLD) tissues, are shown to predict independently predict death within 5 years of PTLD diagnosis^[35]. Studies show that TTV viral load is modulated by immune, viral, and inflammatory status after liver transplantation (LT). Studies evaluating TTV viral load in pediatric^[28] and adult LT^[3,26,30,36-39] provided evidence that in the early post-LT period, the viral load is higher than before the transplant. Accordingly, the TTV viral load positively correlates with the intensity of immunosuppression^[3,26,37]. It progressively increases and peaks around 3 mo post-transplant^[3,26,30,37]. After that, the viral load declines, reflecting the progressive reduction of immunosuppressive drugs, to reach a baseline level, on average, after the 1st year of transplant^[3]. The viral load is lower in patients with post-LT chronic hepatitis and HEV immunoglobulin M/immunoglobulin G positive patients^[28], possibly because the liver is one of the sites of TTV replication. The TTV viral load, however, is not associated with the level of liver enzymes^[28]. The pre-transplant TTV status inversely correlates with the acute cellular rejection (ACR) episodes, suggesting that higher immunocompetence in TTV negative patients before the transplant could be responsible for the higher incidence of ACR within 1 year post-LT^[36]. Moreover, as confirmed in other transplant populations, lower TTV viral load is associated with the ACR in LT recipients. TTV DNA shows high sensitivity and negative predictive value in the diagnosis of ACR and therefore could be regarded as a non-invasive tool to rule out moderate ACR episodes^[3]. Besides, TTV viral loads are associated with the recipient cytomegalovirus (CMV) status; lower levels are present in CMV negative patients^[3,30], and early TTV viral load (0-10 d post-LT) is a predictor of CMV reactivation within first 4 mo post-LT^[30]. In the context of HBV reactivation in immunocompromised patients including LT recipients, TTV viral load in addition to HBV viral load and HBV genotype are not associated with the development of acute liver/graft failure^[40]. Multiple genogroups are frequently found in a single individual infected with TTV. Their distribution differs before and after transplantation, yet it does not affect LT outcomes^[28]. Major key points of the LT studies are presented in [Table 1](#).

CONCLUSION

Sophisticated and non-invasive tools to define and/or predict properly the immune-related events in the post-transplant period are still lacking. The currently available instruments are based on the occurrence of robust clinical events such as rejection or infection episodes. The development and implementation of non-invasive and reliable biomarkers to personalize the immune system's control after transplant remain a challenge. In a search for such a biomarker, collaborative effort over the past decade has brought TTV to the frontline of the medical literature as a promising marker of immune status. The TTV association with the immune status in the immunocompromised transplant population is indisputable. However, we are still looking to understand the impact and the mechanisms behind this interplay. The TTV role as a single or a panel biomarker needs to be evaluated in further independent prospective trials.

Table 1 Torque teno virus in the context of liver transplantation: Major key points

Population, <i>n</i>	TTV prevalence	Study key points	Ref.
German, adult, 104	17.3% pre-LT; 24% post-LT	TTV DNA prevalence not associated with the number of transfused blood products	Schroter <i>et al</i> ^[36] , 1998
British, adult, 37	16% pre-LT; 46% post-LT	prevalence and TTV viral load increased after LT; no correlation of TTV viral load with liver enzyme levels	Shang <i>et al</i> ^[39] , 2000
Italian, adult, 25	100% pre-LT	TTV viral load increased significantly after LT ($P < 0.001$); TTV viral load was higher in patients on CNI + AZA/MMF <i>vs</i> CNI alone ($P = 0.04$) at 3 mo after LT; no differences in viral load in regard to the etiology of liver disease; no correlation of viral load and TTV genotype with ALT or histological liver damage	Burra <i>et al</i> ^[37] , 2008
Canadian, pediatric, 80	68% healthy control; 71% pre-LT; 98%-99% post-LT	TTV viral load post-LT was higher than in pre-LT ($P < 0.001$) and healthy controls ($P < 0.0001$); TTV viral load was lower in post-LT chronic hepatitis; TTV viral load decreased during the post-LT follow-up; no correlation between TTV viral load and ALT or number of transfusions; TTV viral load was lower in anti-HEV IgM/IgG positive patients	Béland <i>et al</i> ^[28] , 2014
Italian, adult, 46	100% pre-LT	TTV viral load increased after LT; low CNI + ECP protocol was associated with the lowest increase in TTV viral load compared to CNI only protocol ($P < 0.01$) or CNI + AZA/MMF protocol ($P < 0.01$)	Focosi <i>et al</i> ^[26] , 2014
Swiss, adult, 39	74% pre-LT	TTV viral load increased significantly 6 mo post-LT <i>vs</i> pre-LT ($P < 0.0001$) and decreased 12 mo post-LT <i>vs</i> 6 mo post-LT; 1-yr cumulative incidence of rejection was lower (21%) in TTV positive <i>vs</i> 70% in TTV negative patients ($P = 0.0042$)	Simonetta <i>et al</i> ^[37] , 2017
German, adult, 136	84.6% post-LT (serum); 66.6% post-LT (urine)	TTV viral load negatively correlated with the BKV viral load ($P = 0.038$), but had no impact on renal impairment	Herrmann <i>et al</i> ^[1] , 2018
Italian, adult, 134	92% pre-LT	TTV viral load progressively increased to a maximum at day 80 post-LT; TTV viral load was higher on Cyc <i>vs</i> on Tac ($P = 0.016$); TTV viral load did differ between different Tac levels (within or beyond the therapeutic range); TTV viral load was lower in CMV DNA negative <i>vs</i> positive patients ($P = 0.001$); TTV viral load at day 0-10 post-LT predicts CMV reactivation (OR: 1.5, 95%CI: 1.0-2.3)	Maggi <i>et al</i> ^[30] , 2018
Spanish, adult, 63	93.7% pre-LT; 100% post-LT	TTV viral load progressively increased peaking at month 3 and then decreased during months 6-12 post-LT; patients on triple IS had higher viremia <i>vs</i> on double IS ($P < 0.001$); no differences in TTV viremia according to the type of CNI; TTV viral load was lower during ACR (4.41 <i>vs</i> 5.95 log ₁₀ copies/mL; $P = 0.002$) and higher during CMV infections (5.79 <i>vs</i> 6.59 log ₁₀ copies/mL; $P = 0.009$); the area under the ROC curve of TTV viral load for moderate ACR was 0.869, with a sensitivity and negative predictive value of 100%, respectively, for a cut-off point of 4.75 log ₁₀ copies/mL; TTV viral load did not differ in long-term or tolerant patients and healthy controls	Ruiz <i>et al</i> ^[3] , 2019
German, immunosuppressed patients with HBV reactivation, 87 (20 LT recipients)		TTV viral load did not differ between patients with ALF <i>vs</i> non-ALF; no differences in TTV viral loads diagnosed during <i>vs</i> after IS ($P = 0.740$), nor after HBV resolution <i>vs</i> chronic HBV ($P = 0.727$)	Anastasiou <i>et al</i> ^[40] , 2019

ACR: Acute cellular rejection; ALF: Acute liver failure; ALT: Alanine aminotransferase; AZA: Azathioprine; BKV: BK virus; CI: Confidence interval; CMV: Cytomegalovirus; CNI: Calcineurin inhibitor; Cyc: Cyclosporine; DNA: Deoxyribonucleic acid; ECP: Extracorporeal photopheresis; HBV: Hepatitis B virus; Ig: Immunoglobulin; IS: Immunosuppression; LT: Liver transplant; MMF: Mycophenolate-mofetil; OR: Odds ratio; Tac: Tacrolimus; TTV: Torque teno virus.

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