PERSPECTIVE

TTV viral load as a predictor of antibody response to SARS COV-2 vaccination

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The measure of torquetenovirus (TTV) viremia is widely recognized as an optimal biomarker of an individual immune status. In the context of COVID-19, the predictive role of TTV load with regard to vaccine response has also been demonstrated, suggesting other intriguing applications for this widespread anellovirus.
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Torquetenovirus (TTV), a widespread anellovirus recognized as the main component of the healthy human virome, displays viremia that is highly susceptible to variations in immune competence. In general, higher viremias are associated with poor immune competence (e.g., causing opportunistic infections), while lower viremias are associated with hyperactive immune system (e.g., causing allograft rejection). In COVID-19, the applications of TTV monitoring is dual.

The first aspect is the correlation between the TTV loads and prognosis, which is rather controversial. Querido et al reported a kidney transplant recipient who had a TTV load of 5.6 $\log_{10}$ copies/ml, which increased to 7.9 $\log_{10}$ copies/ml on day 43 after the diagnosis of SARS-CoV-2 infection, when the patient seroreverted.[1] Froque' et al reported that COVID-19 patients with detectable TTV DNA had an increased risk of subsequently developing infectious events (HR 9.28) and a trend ($p = 0.05$) toward higher TTV DNA area under a curve between days 7 and 17 after intensive care unit (ICU) admission in patients who died, as compared to survivors.[2] In line with the fact that the most severe

presentations of COVID-19 are due to an exaggerated immune response, Solis et al reported that the rate of severe cases was higher in patients with low TTV DNA load in plasma, considering a threshold of 700 copies/ml. In severe patients, SARS-CoV-2 viremia positivity rates were higher than those in mild-moderate cases at any time point. When combined, TTV DNA load and SARS-CoV-2 viremia allowed to predict the outcome of COVID-19 infection, with a higher risk (HR = 12.4) of ICU admission in patients with low TTV DNA load and positive SARS-CoV-2 viremia.[3] Stincarelli *et al* reported that serum TTV DNA seems unrelated to COVID-19 severity, while TTV miRNA tth8 seems related.[4] At the other end of the spectrum, Emmel et al found that the 100-day survival rate in cancer patients who died from COVID-19 was significantly lower in the TTV-positive group than in the TTV-negative group ($p = 0.0475$), and that in the cancer TTV-positive group, those who died also had a higher load of TTV than those who did not die ($p = 0.0097$).[5]

Saliva is an alternative (more easily accessible than blood) biological sample for PCR methods: Mendes-Correa et al reported that the saliva TTV and nasal-oropharyngeal SARS-CoV-2 loads were correlated ($p = 0.008$), and the TTV level decreased as symptoms resolved in the SARS-CoV-2 infected group ($p = 0.028$), but remained unchanged in the SARS-CoV-2 negative controls.[6]

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A second, more relevant, aspect is the predictive role of TTV load with regard to vaccine responses. Healthy individuals with a median baseline TTV load of 3.8 $\log_{10}$ copies/ml have an efficient immune response to the influenza vaccine 30 days after vaccination; more than 80% of healthy individuals with a median baseline TTV load of 4.1 $\log_{10}$ copies/ml have a response to hepatitis B vaccine when measured at day 90 after vaccination.[7] In lung transplantation, Hoek et al showed an odds ratio (OR) of 0.54 ($p < 0.0001$) for response to the first mRNA-1273 vaccine dose,[8] while Gallais et al showed an adjusted OR of 17.8 ($p = 0.001$) for pre-vaccine TTV viral load ≥ 6.2 $\log_{10}$ copies/ml and response to third BNT162b2 vaccine dose among 173 SARS-CoV-2-*naïve* recipients.[9] In kidney transplantation, Reindl-Schwaighofer et al showed OR = 0.92 for homologous (ChAdOx1) or heterologous third dose in 2-dose mRNA vaccine nonresponders.[10] No studies have been reported so far investigating TTV loads and COVID-19 vaccine responses in liver or hematopoietic stem cell transplantations. We have found that healthcare workers with a baseline TTV load equal to or below 3.4 $\log_{10}$ copies/ml of serum showed higher anti-Spike antibody levels when measured on day 30 after the first BNT162b2 vaccine dose ($p < 0.001$; data not shown).

Compared to other solid organ transplant recipients, lung transplant recipients receive higher levels of immunosuppression and accordingly have reduced COVID-19 vaccine responses.[11] These findings suggest a continuum where the higher the immunosuppression, the better the correlation between the basal TTV loads and vaccine-elicited antibody responses. Rezahosseini et al suggested that TTV load can be used to identify the optimal moment for vaccination in patients under maintenance immunosuppression,[12] and evidences published so far are strenghtening this intuition. Despite at this stage further and larger observational clinical trials are required to consolidate this hypothesis, TTV-driven vaccine boosts represent an intriguing opportunity to increase the response rate of immunocomprimised patients. In this regard, integration of a pilot trial within the Horizon2020-funded "TTV Guide Tx" project (https://www.ttv-guide.eu/) should be warranted, to assess utility in association with futher correlates of vaccine response. So far only advanced age,[8] mycophenolate use,[9,13] triple immunosuppression,[10] and more advanced stage of organ failure[13] are reliable predictors of vaccine responses, while there are discordant results for time since transplantation.[8,10]

Author contributions

D.F. searched the literature and wrote the first draft. A.B., L.A., and F.N. provided raw data for the HCW cohort. F.M. revised the manuscript.

Disclosure statement

The authors declare no conflict of interest related to this manuscript.

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