Received: 28 November 2021 | Accepted: 29 November 2021

DOI: 10.1111/liv.15226

Liver INTERNATIONAL WILEY

EDITORIAL

Sars-Cov-2 vaccination in liver transplant recipients: The 'holy grail' in a hostile environment

In late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China as a serious threat to public health.[1] Since then, SARS-CoV-2 has become a devastating pandemic that has remarkably overwhelmed the healthcare systems around the world, resulting in almost 257 million infections with a death toll exceeding 5.1 million as of November 2021.[2]

Additionally, the collateral damage of the SARS-CoV-2 pandemic has been extensive, disrupting the management of acute and chronic diseases globally. In this regard, the hepatic consequences of SARS-CoV-2 infection are now recognized as an important component of coronavirus disease-19 (COVID-19).[3]

A recent international multi-society survey suggests that the first wave of pandemic impacted liver transplantation (LT) across the world differently, especially with detrimental effects on the hit countries.[4]

Within 17 months of the identification of SARS-CoV-2, COVID-19 vaccines were recommended for use by the World Health Organization (WHO), with a range of efficacy between 50% and 95% against symptomatic COVID-19 infections, using varying endpoint definitions.[5] For these reasons COVID-19 vaccines are crucial tools in the pandemic response and protect against severe disease and death. These vaccines have been demonstrated to be safe in the general population, however, no data regarding the effect of the vaccines on liver transplanted patients were originally reported.[6]

Reduced immune response to general vaccination has been reported in patients on the waiting list for end-stage liver disease[7] and those who received liver transplantation, thus, it is likely that transplanted patients might have attenuated immune responses to COVID-19 vaccination.[6] The recent Global Hepatology Society Statement advises however that patients with liver disease including liver transplant recipients should be vaccinated against SARS-CoV-2 with any authorized COVID-19 vaccine as the benefits outweigh the potential risks.[8–10]

In this issue of Liver International, D'Offizi et al.[11] present data characterizing the humoral and cellular responses after two doses of mRNA anti-SARS-CoV2 vaccine in a larger cohort of LT recipients (LTRs), compared with healthy controls, and investigated clinical features associated with non-response. The authors included 61 consecutive LTRs who received anti-SARS-CoV2 vaccination between March and April 2021 and analysed three time points: the first and second dose and 2 weeks after the second dose. Results were compared with a healthy control (HC) group of hospital employees with no major co-morbidities who underwent the same protocol. All subjects received either BNT162b2 or mRNA-1273 anti-SARS-CoV2 vaccine, the median time from transplant was 6 years (IQR 3–10, range 1–26), CNIs were used as immunosuppressive regimen backbone in 59 (96%) and 29 (47.5%) received mycophenolate mofetil (MMF) in combination with calcineurin inhibitors (CNIs). Amongst LTRs, diabetes was present in 15 patients (24.6%) and obesity in 14 (23%). Only 9 patients (14.5%) showed estimated glomerular filtration rate (eGFR) <51 ml/min. A significantly lower serological response was observed to the mRNA SARS-CoV2 vaccine amongst LTRs compared with HCs, with 77% developing anti-spike antibodies, and only 47.5% showing positive neutralizing-Ab (N-Ab) activity. Furthermore, in LTRs, the amount of interferon-γ (IFN-γ) released by S-specific T cells correlated with an anti-spike titre, N-Ab titre and IL-2 levels. Treatment with MMF was significantly associated with anti-receptor- binding domain (Anti-RBD) non-response, whilst time from transplant >6 years, age >55 years were associated with lower N-Ab and IFN- γ production, respectively. At least one comorbidity was not associated with humoral or T-cell non-response, although a trend was observed for obesity and GFR <51 ml/min. The authors conclude that, despite limitations related to small sample size and brief clinical follow-up, their study in LTRs demonstrated a blunted but coordinated humoral and T-cell-mediated response after two standard doses of mRNA anti-SARS-CoV2 vaccine compared with HCs.

The authors provide important insights into a variety of aspects regarding Sars-Cov-2 vaccination in LTRs. First of all, they confirmed a significantly lower serological response to the mRNA SARS-CoV2 vaccine amongst LTRs compared with HCs. As shown in Table 1, a few more real-life studies investigated the effectiveness of the approved vaccines in the liver transplant setting. Antibody responses ranged between 47.5% and 81%. (Table 1).[12–20] The most common factors related to reduced response rate are: age >65 years, shorter time from LT, immunosuppression regimens with multiple drugs, MMF, eGFR, type of vaccine and metabolic syndrome (higher Body Mass Index, obesity, arterial hypertension or diabetes).

Second, the authors analysed T cell response measuring peripheral blood mononuclear cell (PBMC) proliferation assay. It has

Abbreviations: Anti-RBD, anti-receptor- binding domain; CNIs, calcineurin inhibitors; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; HC, healthy control; IFN-γ, interferon-γ; IL-2, interleukin-2; LT, Liver Transplantation; LTRs, liver transplant recipients; MMF, mycophenolate mofetil; mRNA, messenger ribonucleic acid; N-Ab, Neutralizing antibody; PBMC, peripheral blood mononuclear cell; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

Handling editor: Alejandro Forner

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TABLE 1 Characteristics of LT recipients stratified according to the serologic response after 2 doses of the SARS-CoV-2 vaccines

Paper	Number of LT patients	Type of SARS-CoV-2 vaccine	Positive serological response rate	Antibody titre compared to the control group	Factors related to the reduced response rate
Guarino et al.	365	Pfizer- BioNTech BNT162b2	74.8%	214.79 ± 143 vs. 314.32 ± 94.1 AU/ml ($p < .0001$)	Age >65 years, higher BMI, shorter time from LT, immunos. Regimens with multiple drugs, antimetabolite T
Rabinowich et al.	80	Pfizer- BioNTech BNT162b2	47.5%	95.41 ± 92.4 vs. 200.5 ± 65.1) AU/ml ($p < .001$)	Age, lower eGFR, high dose predn. in the past 12, triple therapy immunos., MMF
Strauss et al.	161	Pfizer- BioNTech BNT162b2 Moderna mRNA-1273	81%	81.9–250 U/ml, no control	Antimetabolite ther., type of vaccine
Rashidi-Alavjeh et al.	43	Pfizer- BioNTech BNT162b2	79%	552.7 vs. >2080 BAU/ml ($p = .0001$)	MMF
Boyarsky et al.	129 (cohort of 658 SOT)	Pfizer- BioNTech BNT162b2 Moderna mRNA-1273	79.8%		SOT: age, type of organ, years since TR, antimetabolite therapy, type of vaccine
Marion et al.	58 (cohort of 367 SOT)	Pfizer- BioNTech BNT162b2 Moderna mRNA-1273	50%		No clinical data
Mazzola et al.	58 (cohort of 143 SOT)	Pfizer- BioNTech BNT162b2	37.5%		SOT: age >60, type of organ, treated with corticoids, triple- therapy immunosu., T <2 years, diabetic patients
Ruether et al.	141 (cohort of 194 pts, 53 cirr)	Pfizer- BioNTech BNT162b2 Moderna mRNA-1273 Astra Zeneca	Anti-S RBD 73.9% or the anti-S Trimer 63.0%	163 (12–1060) 154 (1–1723)	Age > 65 years and arterial hypertension, vaccination failure was less likely with CNI monotherapy
Fernandez Ruiz et al.	14 (cohort of 44 patients, 28 kidney transplant, and 2 double organ)	Moderna mRNA-1273	Anti-S 57.1% N-Ab activity 47.5%		MMF, Time from transplant >6 years, age >55 years
D'Offizi et al.	61	BNT162b2 or mRNA-1273	Anti-S 77% N-Ab activity 57.5%		

been suggested that the vaccine-induced T-cell response may have a protective effect even in the absence of a detectable vaccine-induced B-cell response by limiting the extent of viral replication and by supporting long-term immunological memory.[21] Therefore, LTRs with a strong T-cell response may be protected against a severe course of SARS-CoV-2 infection even in the absence of a seroconversion.[17] However this is not the case of this manuscript, where the authors found a correlation between the cellular and the humoral response.

But what is a real problem today? The long-term efficacy of vaccination also on the general population and, therefore, the risk to be infected despite two doses of vaccine. A recent study on longer-term follow-up of the participants in phase 2–3 randomized trial of the BNT162b2 vaccine showed a reduction in vaccine efficacy from 96% (in the period of 7 days to <2 months after receipt of the second dose) to 84% (in the period of 4 months to approximately 7 months after the receipt of the second dose), which indicated a decrease in protection by a factor of four. Preliminary reports of the waning effectiveness of the same vaccine have come from a health maintenance organization in Israel and the USA, and a decrease in vaccine-induced neutralization titers during the first 6 months after receipt of the second dose of vaccine has been reported.[22] These findings supported the choice to make a third dose available to immunocompromised people. The first study included 30 patients with suboptimal response, a third dose increased antibody titers in one-third of patients who had negative antibody titers and in all patients. In another study with 59 non-responders to two doses of vaccine, a third dose achieved a serological response in 26 (44%) and an increase in antibodies titers amongst those with previous responses were seropositive at 4 weeks after the third dose.[23]

The present study, however, has some limitations. First of all, no data regarding the indication for liver transplantation and more importantly, the stage of liver disease in the LTRs are reported. Then, the small sample size does not permit to make final considerations, even if we consider the total number of patients enrolled in the published manuscripts so far overcome a thousand patients.

In addition, the hypothesis of modification of immunosuppressive therapy in the immediate pre and post vaccination period to increase the number of recipients who can benefit from anti-SARS-CoV-2 vaccination has been speculated from previous studies mainly dealing with withdrawing of MMF. Finally, a longer follow-up of the humoral and cellular response will allow us to define the immune correlate of protection in this group of patients.

The manuscript has also some important clinical implications, such as the suggestion of a possible role of the antibody research in this category of frail patients, and the support of the third and maybe other boosters in the future.

CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose.

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