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BRIEF REPORT

Third dose of SARS-CoV2 mRNA vaccination produces robust persistent cellular and humoral immune responses in liver transplant recipients

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Abstract

Weaker responses have been described after two doses of anti-SARS-CoV2 vaccination in liver transplant recipients (LTRs). At the Italian National Institute for Infectious Diseases, 122 LTRs (84% males, median age 64 years) were tested for humoral and cell-mediated immune response after a third doses of anti-SARS-CoV2 mRNA vaccines. Humoral response was measured by quantifying anti-receptor binding domain and neutralizing antibodies; cell-mediated response was measured by quantifying IFN-γ after stimulation of T cells with SARS-CoV-2-specific peptides. Humoral and cellular responses improved significantly compared to the second vaccine dose; 86.4% of previous non-responders to the first 2 vaccine doses ($N = 22$) became responders. Mycophenolate mofetil-containing regimens were not associated with lower response rates to a third vaccine; shorter time since transplantation (<6 years) was associated with lower humoral and cellular responses to third vaccine. Protective antibodies against Omicron variant were detected in 60% of patients 12 weeks after third vaccine dose.

KEYWORDS
anti-RBD titre, interferon-γ, liver transplant, SARS-CoV2 vaccination

1 | INTRODUCTION

Solid organ transplant recipients (SOTRs) have an increased risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection[1] and of developing severe coronavirus disease-2019 (COVID-19).[2] Although liver transplant recipients (LTRs) show a better immune response to vaccine than other SOTRs,[3,4] many studies suggested a poorer antibody response to SARS-CoV2 vaccination in

Abbreviations: Anti-RBD, anti-receptor binding domain; BAU, binding arbitrary units; CNIs, calcineurin inhibitors; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; IFN-γ, interferon-γ; IQR, interquartile range; LTRs, liver transplant recipients; MMF, mycophenolate mofetil; MNA, micro-neutralization assay; N-Ab, neutralizing antibody; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; SOTRs, solid organ transplant recipients.

LTRs.[5,6] Efficacy of antibody protection induced by anti-SARS-CoV2 vaccine in LTRs is not well defined.

Our previous study assessed humoral and cell-mediated immune response after a 2-dose regimen of mRNA anti-SARS-CoV2 vaccine in LTRs.[7,8] We confirmed significantly lower serological and cellular responses to the mRNA SARS-CoV2 vaccine among LTRs than in healthy controls, with 77% developing anti-receptor binding domain (RBD) antibody, 47.5% showing positive neutralizing antibody, and 72.1% obtaining specific T-cell response 2 weeks after second dose. We also found a negative effect of mycophenolate mofetil and calcieurin inhibitor (MMF/CNI) combination on both antibody and cytokine production.

Given the low seroconversion rates after a 2-dose vaccine regimen in immunocompromised patients, an additional (third) vaccine dose is standard practice in Italy.[9] Several studies assessed immunological response after 3 doses in SOTRs[10]; however, immunosuppressive regimens in non-liver SOTRs differ significantly in terms of dose and drug combination, therefore, these results cannot be translated directly to LTRs. A recent study from Italy performed in LTRs confirmed a higher rate of serological response after a third vaccine.[11]

As of December 2021, the variant of concern (VoC) B.1.1.529 (Omicron) with over 30 mutations in spike protein was identified globally.[12] Several studies have assessed neutralization capacity of a 3-dose vaccine regimen against VoCs, including Omicron,[13] although the efficacy of anti-SARS CoV2 vaccines against omicron is unclear.[14]

The objective of our study was assessment of humoral and cellular responses after a third dose of mRNA anti-SARS-CoV2 vaccine in LTRs, compared to the previous 2-dose vaccine regimen; furthermore, we evaluated of N-Ab activity against Omicron variant in a subgroup of patients and investigated clinical features associated with non-response.

Key points

- In December 2020, the first vaccine against COVID-19 became available in Italy, and the National Health System implemented a nationwide program to start vaccinating the highest risk subjects: the elderly and those with weakened immune systems, such as people who had received an organ transplant.
- However, after the first two doses of vaccine, protection in organ transplant recipients was found to be lower than in the general population; a third dose of vaccine was, therefore, administered to boost response rates.
- In this study, we describe how the third vaccine dose greatly improved immune response against COVID-19 in subjects who had received a liver transplant, even if their response to the first two doses of vaccine had been unsatisfactory.

2 | PATIENTS AND METHODS

Consecutive 122 LTRs (84% males, median age 64 years [IQR 60–70, range 22–79]) who received a third dose of anti-SARS-CoV2 vaccine (mRNA-1273) between September and October 2021 were enrolled. All patients underwent testing for both humoral and cell-mediated immune response at four time points: two weeks after 2nd dose (T2), before 3rd dose (T3), one month after 3rd dose (T4), and 3 months after 3rd dose (T5). All patients had completed two doses of either BNT162b2 or mRNA-1273 vaccines 5–6 months earlier. Patients with documented SARS-CoV2 infection at any time point before receiving the third dose were excluded. The study was approved by INMI L. Spallanzani Ethical Committee 3580 (March 17, 2021 and further amendments), and all participants signed a written informed consent.

2.1 | Antibody evaluation

Two commercial chemiluminescence microparticle antibody assays (ARCHITECT SARS-CoV-2 IgG, and ARCHITECT SARS-CoV-2 IgG II Quantitative, Abbott Laboratories, Wiesbaden, Germany) were performed on ARCHITECT® i2000sr (Abbott Diagnostics, Chicago, IL, USA) and used according to manufacturer's instruction to detect anti-RBD IgG. Positive anti-RBD response was defined as ≥7.1 Binding Antibody Units (BAU)/mL.

2.2 | Micro-neutralization assay

Micro-neutralization assay (MNA) based on live virus was performed using either Wuhan-D614G strain (GISAID accession ID EPI_ISL_568579) or Omicron BA.1 strain (GISAID accession ID EPI_ISL_7716384), as challenging virus. MNA was performed as previously described.[15] The highest serum dilution inhibiting at least 90% of the CPE was indicated as the neutralization titre. To standardize inter-assay procedures, positive control samples showing a high (1:160) and low (1:40) neutralizing activity were included in each assay session. Serum from the National Institute for Biological Standards and Control, UK (NIBSC) with a known neutralization titre (research reagent for anti-SARS-CoV-2 Ab NIBSC code 20/136) was used as the reference in MNA. The standardized cut-off MNA90 ≥ 1:10 was used to define neutralization activity; only for computational and statistical purposes, samples resulted ≥ 1:640 were arbitrarily considered = 1:1280.

2.3 | T-cell immune response

Peripheral blood was collected in heparin tubes and stimulated with a pool of peptides spanning the Spike antigen (S-peptides, Miltenyi Biotech, Bergisch Gladbach, Germany) at 37°C (5% CO_2). A superantigen was used as positive control. Cultured plasma was harvested after 16–20 h of stimulation and stored at −80°C. Th1 cytokine production of interferon-γ (IFN-γ) was quantified in plasma using an automatic

ELISA (ELLA, Protein Simple). Detection limit of the assay was .17 pg/mL, and positive IFN-γ response was defined as ≥12 pg/mL.[16,17]

2.4 | Clinical variables

LTRs were evaluated for obesity (BMI ≥ 30 kg/m^2), diabetes mellitus, chronic renal disease with estimated glomerular filtration rate (eGFR), years from transplantation. Immunosuppressive regimens were defined as containing CNIs, MMF, everolimus or steroids.

2.5 | Statistical analysis

Continuous variables including anti-RBD and N-Ab titres, and IFN-γ levels were and reported as median and interquartile range (IQR). Comparisons of medians across different groups were evaluated using Mann–Whitney *U* test. Correlation analyses were performed by non-parametric Spearman's rank test. Categorical variables including dichotomous anti-RBD, N-Ab, IFN-γ were summarized as counts and percentages and compared with Chi-square test or Fisher's Exact test. A multivariate regression analysis model was constructed including gender, age, years, since transplant, immunosuppression and comorbidities. Statistical analysis was performed by using R statistical software (version 4.1.0). A 2-sided *p* value <.05 was considered to be statistically significant.

3 | RESULTS

122 LTRs received a third dose of either BNT162b2 or mRNA-1273 vaccine at a median of 158 days (IQR 146–170, range 108–238) after the second dose. Median time from transplant was 8 years (IQR 5–13, range 1–26). CNIs were used as immunosuppressive regimen backbone in 115 (94%) and 64 (52.5%) received MMF in combination with CNIs. Type 2 diabetes mellitus was present in 33 patients (27%) and obesity in 17 (14%); 15 patients (12.3%) had chronic renal insufficiency with eGFR<51 mL/min. Baseline characteristics overall and based on MMF treatment groups are shown in Table 1.

3.1 | Clinical variables

No significant differences were observed in humoral and cellular responses after third vaccine dose (T4 and T5) based on treatment with MMF, age ≥55 years, diabetes mellitus, obesity and chronic renal insufficiency.

Time from transplant <6 years was associated with reduced humoral response at T4 (median anti-RBD 1031 vs. 3383 BAU/mL, $p < .001$; median N-Ab 80 vs. 320 MNA, $p = .03$) and at T5 (median anti-RBD 333 vs. 1848 BAU/mL, $p < .001$; median N-Ab 40 vs. 160 MNA, $p < .001$; Figure 1A,B).

Time from transplant <6 years was associated with reduced cellular response at T4 (median IFN-γ 57 vs. 147 pg/mL, $p = .03$); the difference was not statistically significant at T5 (median IFN-γ 33 vs. 60 pg/mL, $p = .07$, Figure 1C).

At univariate analysis, shorter time from transplant was significantly associated with anti-RBD non-response at T4, but not with IFN-γ non response (Table S1).

At linear regression, longer time from transplant showed a positive correlation with anti-RBD and IFN-γ levels at T4 and T5 ($r^2 = .05$, $p < .001$).

Eighteen patients (14.7%) developed SARS-CoV-2 infection after receiving third vaccine dose. Median time from vaccination to infection was 132 days (range 77–180). None developed serious disease requiring hospital admission.

TABLE 1 Clinical characteristics of liver transplant recipients who received 3rd dose of mRNA anti-SARS CoV2 vaccine, grouped by immunosuppressive treatment with mycophenolate mofetil.

	Overall	No MMF	MMF	*p*
N	122	58	64	
Males	102 (83.6%)	47 (81%)	55 (86%)	.46
Median age (years)	64.1 (IQR 59.8–69.7)	64.7 (IQR 60.6–69.7)	63.7 (IQR 57.5–70)	.51
Median time from LT (years)	8.1 (IQR 4.9–13)	8.7 (IQR 5.9–13)	6.2 (IQR 3.4–13.2)	.13
Time from LT ≥6 years	85 (69.7%)	46 (79.3%)	39 (60.9%)	.02
Diabetes mellitus	33 (27%)	16 (27.6%)	17 (26.6%)	.89
Obesity	17 (14%)	8 (13.8%)	9 (14.1%)	.96
Chronic renal insufficiency	15 (12.3%)	3 (5.2%)	12 (18.7%)	.02
Responder to 2nd dose vaccine	93 (80.2%)	51 (94.4%)	42 (67.7%)	.0003
Positive anti-RBD after 3rd dose	119 (97.5%)	57 (98.3%)	62 (96.9%)	.6
Positive N-Ab after 3rd dose	113 (92.6%)	55 (94.8%)	58 (90.6%)	.37
Positive IFN-γ after 3rd dose	101 (90.9%)	50 (92.6%)	51 (89.5%)	.5

Abbreviations: IFN-γ, interferon-γ; LT, liver transplant; MMF, mycophenolate mofetil; N-Ab, Neutralizing antibody; RBD, anti-receptor binding domain.

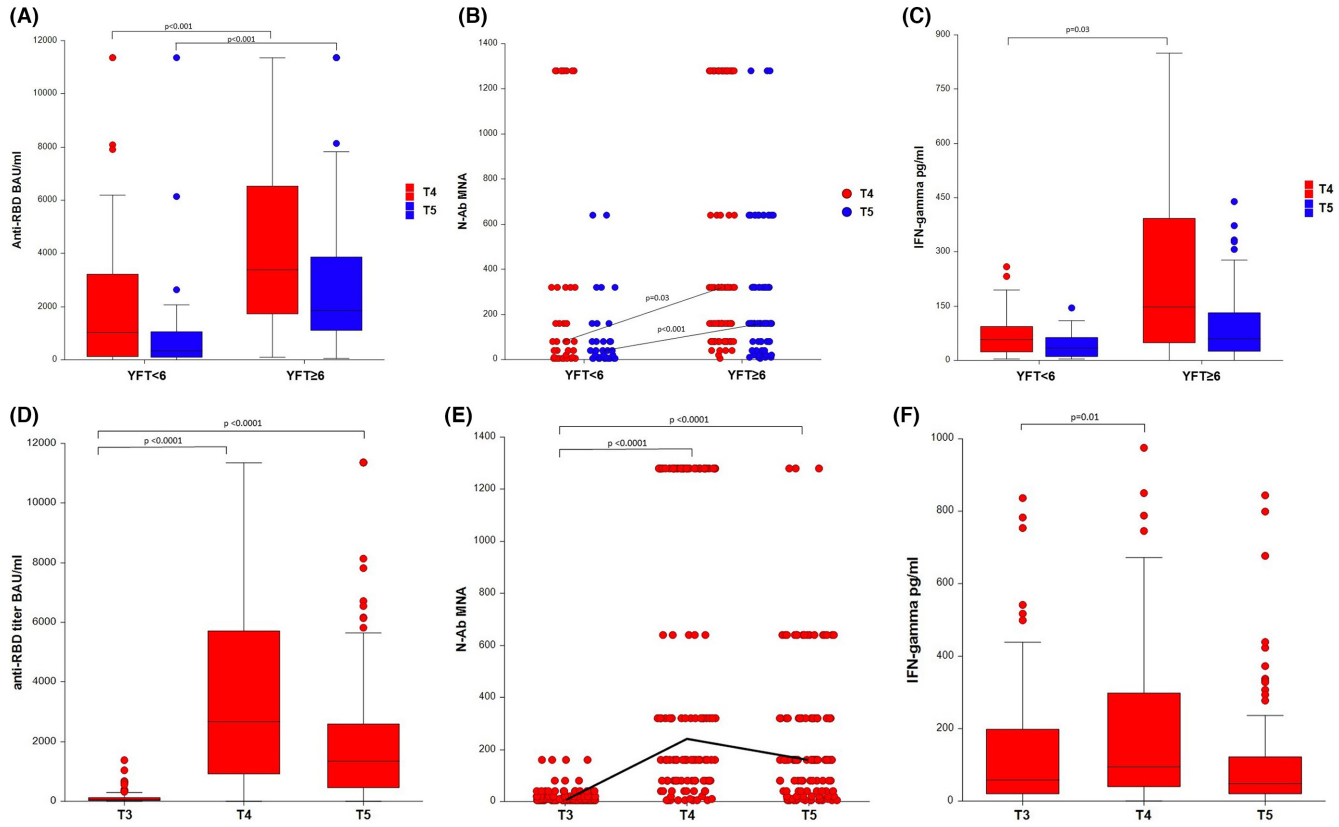

FIGURE 1 Serological and cellular response to 3rd dose of mRNA anti-SARS CoV2 vaccine in 122 liver transplant recipients. T3: before 3rd dose; T4: 4 weeks after 3rd dose; T5 12 weeks after 3rd dose. Panel (A) Anti-receptor binding domain titres based on time from transplant. Panel (B) Neutralizing Ab titres based on time from transplant. Panel (C) Interferon-γ production based on time from transplant. Panel D) Anti-receptor binding domain titres. Panel (E) Neutralizing Ab titres. Panel (F) Interferon-γ production. anti-RBD, anti-receptor binding domain; BAU, binding arbitrary units; IFN-γ, interferon-γ, MNA, micro-neutralization assay; N-Ab, neutralizing antibody; YFT, years from transplant.

3.2 | Humoral response

Before third vaccine dose (T3) median anti-RBD titre was 47.4 BAU/mL (IQR 13–131); after third vaccination median anti-RBD titre increased significantly to 2665 BAU/mL (IQR 902–5716) at T4 and 1352 BAU/mL (IQR 457–2599) at T5 (Figure 1D, $p < .001$). Positive anti-RBD response was observed in 97.5% at T4 and 97.2% at T5; 86.4% of previous non-responders to the first 2 vaccine doses ($N = 22$) obtained a positive anti-RBD response.

Before third vaccine dose (T3) median N-Ab titre was 5 MNA (IQR 5–20); after third vaccination median N-Ab titre increased significantly to 240 MNA (IQR 80–1280) at T4 and 160 MNA (IQR 40–320) at T5 (Figure 1E, $p < .001$).

Positive N-Ab response was observed in 92.6% at T4 and in 91% at T5; 77% of previous non-responders to the first 2 vaccine doses ($N = 48$) obtained a positive N-Ab response.

A total of 63 patients were tested for Omicron N-Ab at T3, and all were negative. However, after third vaccination 68% showed a positive response at T4 (median MNA 20, IQR 5–80). A total of 37 patients were tested for omicron N-Ab at T5 and 62% maintained a positive neutralization titre (MNA 20, IQR 5–40).

3.3 | Cellular response

Specific T-cell response to S-peptides was measured by evaluating IFN-γ-specific production after in vitro stimulation.

Before third vaccination, 86% of LTRs maintained detectable levels of IFN-γ. Median IFN-γ level was 59 pg/mL (IQR 20–198) before third dose (T3), 93.3 pg/mL (IQR 40–98) at T4, and fell to 49 pg/mL (IQR 19–121) at T5 (T3 vs. T4, $p = .01$; Figure 1F). Positive IFN-γ response was observed in 91% at T4 and in 86.7% at T5.

4 | DISCUSSION

Previous studies have shown that LTRs mount a blunted humoral and T-cell-mediated response after two standard doses of mRNA anti-SARS-CoV2 vaccine.[5,6]

Our study assessed both humoral and cell-mediated response 4 and 12 weeks after third vaccination dose in 122 LTRs; 12 weeks after vaccination we observed a humoral response rate of 97% and 91% for anti-RBD and N-Ab, respectively, while IFN-γ response rate was 86%. These response rates are higher than reported in

previous studies (58% to 73%),[3,10] which were conducted in a mixed cohort of SOTRs; in fact other transplant categories, such as kidney recipients, have shown lower responses to vaccines.[4] Nevertheless, our response rate was higher than reported in a recent study including only LTRs.[11] These differences may be explained by differences in study population, including immunosuppressive regimen and time since transplant. Furthermore, differences in type of serological test and cellular assays may account for differences in results.

Type of immunosuppressant therapy and use of MMF has been shown to impact the response to vaccines.[11,18] In our study, use of MMF did not impact response after a third dose of anti-SARS CoV2 vaccine, with over 90% overall obtaining positive anti-RBD and N-Ab titres. This result differs from the literature and is challenging to explain. Our immunosuppressive protocol includes decreasing MMF dose over time, with a median dose of 500 mg bid after 6–12 months and 250 mg bid between 36 and 48 months from transplant. As median time from LT was 8 years, the majority of patients were receiving a low dose of MMF. Furthermore, in 60% of patients who did not achieve a response to the first two-dose vaccine regimen, MMF dose was further reduced ahead of third vaccination. The relationship between MMF dose and response to vaccine requires further study.

As already widely reported, time from transplantation represented an independent predictor of humoral response to vaccine.[3,11,18] In our study population, almost 70% of patients had been transplanted over 6 years before vaccination, accounting for the previously mentioned differences in immunosuppression regimen.

Regarding cell-mediated response, a significant increase in IFN-γ-specific T cell response 4 weeks after third vaccination was followed by a decrease over the subsequent 8 weeks. Furian et al. demonstrated a correlation between humoral and cellular responses in the short-term after a booster dose of vaccine,[4] however, to the best of our knowledge, there are no studies investigating cytokine response in the medium or long term. It is unknown whether a decrease in IFN-γ levels may impact the possibility of acquiring symptomatic infection; however, it is likely that an asymptomatic infection be associated with stronger specific T-cell production of IFN-γ compared to a symptomatic one.[19]

Since November 2021, the SARS CoV2 VoC Omicron (B.1.1.529) became predominant in Europe.[12] A total of 37 patients in our study group were tested for Omicron N-Ab after the booster dose and a positive response over 60% was observed. The response was maintained at 12 weeks at median semi-quantitative titre of 20 MNA. These data show that early versions of m-RNA vaccines can elicit a response against Omicron variant, although with a lower rates than for wild type virus in LTRs. Saharia et al. reported similar data in a cohort of SOTRs.[20] The small subset ($N = 18$) of patients who developed SARS-CoV2 infection after the third vaccine dose were not tested for SARS CoV2 variants; however, all cases occurred when Omicron was the predominant circulating variant in our region. None of the infected patients had severe disease requiring hospitalization, confirming the reduced clinical aggressiveness of the Omicron variant even in this extremely fragile population.

In conclusion, LTRs who received a third dose of mRNA anti-SARS CoV2 obtained strong persistent humoral responses for anti-RBD and N-ab, which persisted up to 12 weeks after vaccination. T cell-mediated response measured via IFN-γ production decreased at three months; however, a positive response was maintained in over 85% of patients. These results confirm the stronger and prolonged effect of the booster dose compare to the standard 2-dose vaccine regimen in immunosuppressed transplant recipients. Shorter from transplantation (<6 years) was confirmed to be a predictor of poor response, while the negative effect of MMF was voided by the booster.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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