JIM Research Letter

doi: 10.1111/joim.13361

Immunogenicity of SARS-CoV-2 mRNA vaccine in solid organ transplant recipients

Dear Editor,

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike messenger RNA (mRNA) vaccines are reported to prevent Covid-19 in 94%–95% of adults after a two-dose regimen [1,2]. However, the immunogenicity in solid organ transplant (SOT) recipients is currently unknown.

As a result of lifelong immunosuppressive treatment, SOT recipients are at a higher risk of severe infections, including Covid-19 [3,4].

The immunosuppressive treatment affects both the humoral and cellular immune responses with an expected reduced immune response to the Covid-19 vaccine in SOT recipients, as has been previously observed following influenza and pneumococcal vaccination [5,6]. Previous studies have shown that SOT recipients have a decreased or no immune response following Covid-19 infection [3,7,8]. In addition, less than 17% had detectable SARS-CoV-2 antibodies after the first dose of the mRNA vaccine was administrated, which increased to 54%, weeks following the second vaccine dose [9–11]. It is currently not well described whether a two-dose regimen of a Covid-19 vaccine is sufficient to elicit an immune response in SOT recipients.

Our aim was to investigate the cellular and humoral immune responses in SOT recipients following a two-dose regimen of Covid-19 vaccination.

All SOT recipients (≥18 years of age) from the Region of Southern Denmark were invited to participate in the study since 29 January 2021 (Danish Ethical Committee, record No. 77786). All the participants received vaccination as part of the national Covid-19 vaccination program, and the SOT recipients were identified as a prioritized target group.

Blood samples were drawn 6 weeks following the second vaccination. The SARS-CoV-2 spike S1 IgG response was measured by a semiquantitative EUROIMMUN SARS-COV-2 ELISA assay (FDA approved). Test results were interpreted according to the manufacturer; ratios ≤0.8 were interpreted as negative, 0.8 to <1.1 as borderline, and ≥1.1 as positive. For this study, values >0.8 were reported as positive. T-cell response was measured by the interferon-γ enzyme-linked immunospot Qiagen QuantiFERON SARS-CoV-2 assay (research use only), which includes specific SARS-CoV-2 peptides pool from spike antigen (S1 and S2 subunits). The cut-off for a positive response was set at 0.15 (personal communication with Qiagen).

Categorical data were described by total and percentages. Data comparisons were made using the chi-square test or Fisher's exact test as appropriate. Continuous variables were described as medians with interquartile ranges (IQRs) and compared using Wilcoxon rank sum test. A p-value of less than 0.05 (5%) was considered statistically significant.

A total of 663 SOT recipients were identified and 423 consented to be included in the study. We report the preliminary results of the humoral and cellular immune responses in our ongoing study including the first 80 SOT recipients, who completed the two-dose vaccine regimen. All but one SOT recipient received the BNT162b2 (Pfizer) vaccine ($n = 79$).

The median age was 58.9 years (IQR: 47.9–66.8) with 55% (44/80) being male. The majority of SOT recipients were kidney transplant recipients (65%).

The median time from second vaccination to antibody testing was 5.6 weeks (IQR 5.1–6.3). The median IgG antibody response was 0.3 (IQR 0.2–2.7). The QuantiFERON SARS-CoV-2 assay was positive in five (6.3%) SOT recipients.

Table 1 shows the baseline characteristics stratified by SARS-CoV-2 spike IgG immune response. Only 35% ($n = 28$) were able to mount a positive IgG immune response 6 weeks after the second dose of vaccine (Fig. 1). Vaccine responders were significantly younger than non-responders ($p <$

Table 1. *Characteristics of solid organ transplant recipients after two-dose regimen with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) messenger RNA vaccine*

Characteristics	Responders	Non-responders	*p*-value
N	28 (35.0%)	52 (65.0%)	
Age (mean)	52.9 (IQR 44.9–61.5)	60.2 (IQR 51.7–68.6)	<0.01
Sex (male)	14 (50%)	30 (57.7%)	0.64
BMI	27.6 (IQR 23.5–31.5)	26.0 (IQR 22.5–28.3)	0.18
Organ transplant			0.70
Kidney	16 (57.1%)	36 (69.2%)	
Liver	5 (17.9%)	8 (15.4%)	
Heart	4 (14.3%)	5 (9.6%)	
Lung	1 (3.6%)	2 (3.9%)	
Combined[a]	2 (7.1%)	1 (1.9%)	
Time from Tx[b] to vaccine (months)	114.6 (IQR 57.1–191.8)	80.4 (IQR 37.8–168.4)	0.26
Immunosuppressive treatment			
Prednisolone	8 (28.6%)	13 (25.0%)	0.8
CNI[c]	28 (100%)	47 (90.4%)	0.16
Proliferation inhibitor[d]	23 (82.1%)	52 (100%)	<0.01
mTOR inhibitor[e]	1 (1.9%)	1 (3.6%)	0.58

Note: Thirty-seven (97.4%) SOT recipients received a combination of at least two immunosuppressive drugs.
Abbreviation: IQR, interquartile range.
[a]Kidney/liver, kidney/heart, and heart/lung.
[b]Transplantation.
[c]Calcineurin inhibitor (CNI): tacrolimus and cyclosporine.
[d]Proliferation inhibitor: mycophenolate mofetil, mycophenolic acid, and azathioprine.
[e]Mammalian target of rapamycin inhibitor (mTORi): everolimus and sirolimus.

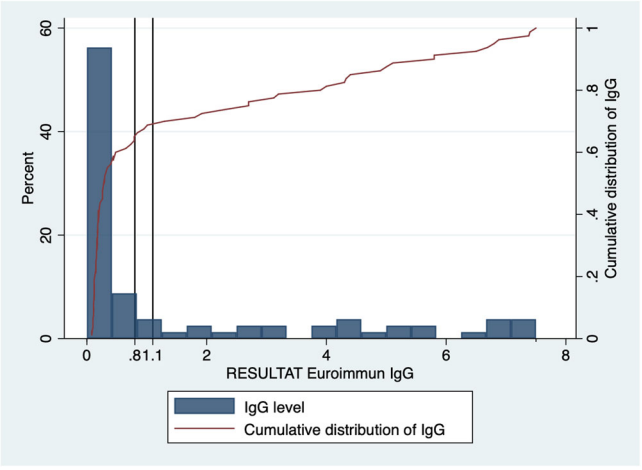

Fig. 1 *Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike S1 IgG response 6 weeks after the second vaccine.*

0.01). All SOT recipients were treated with a combination of at least two immunosuppressive drugs. A total of 61 SOT recipients received proliferation inhibitors and the proportion of non-responders was significantly higher in this group ($p < 0.01$). Covid-19 infection was not diagnosed in any of the SOT recipients before or after vaccination.

This study provides insights into the limitations of immunization following a two-dose regimen of Covid-19 mRNA vaccine in SOT recipients. The key finding was a reduced antibody response 6 weeks after the second vaccination, with only 35% of SOT recipients having IgG levels interpreted as positive, which is considerably lower than recently

reported by Boyarsky et al. [11]. Younger SOT recipients were more likely to develop an IgG antibody response following vaccination. The number of SOT recipients in this preliminary study was limited, and whether the level of immunosuppression is correlated to the immune response following vaccination cannot yet be determined. Finally, it is unknown whether even a minimal antibody response or a cellular response following vaccination can protect from developing severe Covid-19 infection.

There are limited data on T-cell responses after vaccination and its protective effect compared to humoral responses. Additionally, there are no standardized assays for the measurement of T-cell vaccine responses. The T-cell response rate in our population was extremely low, also when compared to a previous study [12]. This could be caused by the assay's performance, or the fact that SOT recipients are heavily treated with T-cell immunosuppressants—especially calcineurin inhibitors [13]. The true T-cell response might be underestimated, and our results need to be further studied in a larger cohort.

Our study was limited by a small sample size, the fact that all patients except one received the Pfizer vaccine and that the IgG antibody response was not measured between vaccinations.

Protective levels of SARS-CoV-2 IgG antibodies after infection or vaccination have not yet been established, nevertheless, the majority of SOT recipients in this preliminary study had a poor response to the mRNA Covid-19 vaccines. Our findings highlight that SOT recipients require continuous use of personal protective measurements even after vaccination and call for further studies to determine strategies to achieve effective immune responses in SOT recipients.

Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

Isik S. Johansen and Ulrik S. Justesen are responsible for the conception and design. Claus Bistrup, Rozeta Abazi, Jesper R. Davidsen and Mikael K. Poulsen collected the data. Anna C. Nilsson and Ulrik S. Justesen are responsible for the laboratory data. Isik S. Johansen and Susan O. Lindvig are responsible for the project administration. Janne F. Hansen and Inge K. Holden are responsible for the analysis. Inge K. Holden and Isik S. Johansen are responsible for the interpretation and the writing. All authors are responsible for the review and revision of the manuscript. All authors read and approved the final manuscript.

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