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## Early humoral response among lung transplant recipients vaccinated with BNT162b2 vaccine

Lung transplant recipients are given immunosuppressive therapy that might impair their ability to generate an adequate immune response to the BNT162b2 vaccine.[1] However, immunocompromised individuals were not included in the BNT162b2 vaccine clinical trials. We aimed to assess the immunogenicity response to the BNT162b2 vaccine in this population.

We did an observational prospective cohort study of lung transplant recipients who received the BNT162b2 vaccine between Dec 20, 2020, and Feb 8, 2021, at Rabin Medical Center, Petach Tikva, Israel. Patients were eligible if they were aged 18 years or older, had a lung or heart-lung transplant, were at least 30 days post-transplant, had no history of previous SARS-CoV-2 infection (as documented by positive nasal swab RT-PCR testing), and who had received two doses of BNT162b2 vaccine. Titres of IgG antibodies against the SARS-CoV-2 spike protein (S-IgG) were assessed at two clinic visits at days 1–7 and 14–21 after the second vaccine dose.[2] SARS-CoV-2 IgG II Quant assay (Abbott Ireland Diagnostic Division) was used for quantitative measurements of S-IgG antibodies. S-IgG titres of 50 AU/mL and greater in the immunoassay test were determined to be seropositive.[3] The primary outcome was the proportion of participants who were seropositive for S-IgG antibodies at days 14–21 after the second vaccine dose. Secondary outcomes were serious adverse events after vaccination and incidence of SARS-CoV-2 infection among symptomatic participants. Side-effects possibly related to SARS-CoV-2 vaccines were captured ad hoc by patients and specifically during clinic visits with the aid of a dedicated questionnaire. Relevant demographic and clinical data, including immunosuppressive drug regimens and trough levels, were recorded at the clinic visits or derived from hospital electronic medical records. We compared demographic and clinical baseline characteristics using the $\chi^2$ test for dichotomous variables and univariate logistic regression for continuous variables. Antibody levels are presented as geometric mean titres (GMTs) and SDs and were analysed using the Mann-Whitney *U* test. The calculated sample size for an estimated seropositivity rate of 60% in lung transplant recipients and 90% in healthy immunocompetent individuals was 76.

Between Jan 11 and Feb 10, 2021, 180 participants were enrolled, of whom 168 attended the second follow-up clinic visit and were included in the final analysis. Baseline demographic and clinical characteristics of participants in the final analysis cohort are shown in the table and appendix (p 2). Median time elapsed from the second vaccine dose to the second study visit was 16 days (IQR 15–18; range 11–21). Seropositive S-IgG antibody titres were detected in 31 (18%) of 168 analysable participants, and six (4%) had seropositive titres after the first vaccine dose (appendix p 2). The GMT of S-IgG antibodies in the seropositive group was 424·89 (SD 3·99) and in the seronegative group was 3·91 (3·48; p<0·0001; table; appendix p 1). In the seropositive group, the median age of participants was 57·0 years (IQR 36·0–63·0) and in the seronegative group was 61·0 years (51·0–68·5; p=0·0040). Participants in the seropositive group were less likely to be treated with a mammalian target of rapamycin (mTOR) inhibitor and antimetabolites (table). There were no reported serious adverse events after vaccination among the study participants. Minor adverse events were common, including fatigue (n=4 seropositive group, n=28 seronegative group) and localised tenderness at the injection site (n=21 seropositive group, n=87 seronegative group). No acute transplant rejection was documented in any participants during the study period. During the study follow-up period (median 68 days [IQR 65–73]), 12 (7%) of 168 participants, including three (10%) of 31 from the seropositive group, were tested after the second vaccine dose for SARS-CoV-2 infection due to symptoms suspicious of COVID-19 disease, with all testing negative for infection (data not shown).

We found a substantially reduced humoral immune response among lung transplant recipients after two doses of vaccine, with only 18% having positive S-IgG titre within 3 weeks after the second vaccine dose. To our knowledge, this is the first study to analyse the presence of S-IgG antibodies in lung transplant recipients after vaccination with two doses of BNT162b2. Immunogenicity data from solid organ transplant recipients after a single dose of either SARS-CoV-2 mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech) vaccines, detected antibodies in four (8%) of 49 lung transplant recipients included in the cohort at a median of 20 days after the first vaccine dose.[4] These results are consistent with our finding of 4% seropositivity at 20–28 days after the first vaccine dose. After the second vaccine dose, seropositivity increased in our study to 18%, suggesting an accretive, although moderate, effect of the second dose on antibody generation in lung transplant recipients. Nevertheless, our findings are in stark contrast with the 100% rate of antibody generation among 48 healthy immunocompetent adults 7 days after the second vaccine dose in the pivotal vaccine clinical trials.[5] Similarly, in a cohort study of 248 immunocompetent health-care workers, 247 (99·5%) participants had an adequate humoral response 7 days after the second BNT162b2 vaccine dose.[6]

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See Online for appendix

| | All participants (n=168) | Seropositive (n=31)* | Seronegative (n=137) | Odds ratio (95% CI) | p value |
|---|---|---|---|---|---|
| S-IgG titre first test, GMT | 3·12 (4·05) | 12·43 (6·42) | 2·24 (2·78) | .. | <0·0001 |
| S-IgG titre second test, GMT | 9·29 (9·22) | 424·89 (3·99) | 3·91 (3·48) | .. | <0·0001 |
| Age, years | 60·5 (49·25–67·75) | 57·0 (36·0–63·0) | 61·0 (51·0–68·5) | 0·95 (0·92–0·98)† | 0·004 |
| Gender | | | | | |
| Female | 56 (33%) | 10 (32%) | 46 (34%) | .. | .. |
| Male | 112 (67%) | 21 (68%) | 91 (66%) | 0·94 (0·41–2·16) | 0·88 |
| Time since transplantation, years | | | | | |
| <1 | 16 (10%) | 1 (3%) | 15 (11%) | 0·69 (0·31–1·52)‡ | 0·35 |
| 1–4 | 69 (41%) | 13 (42%) | 56 (41%) | .. | .. |
| 4–8 | 40 (24%) | 9 (29%) | 31 (23%) | .. | .. |
| >8 | 43 (26%) | 8 (26%) | 35 (26%) | .. | .. |
| Immunosuppression regimen | | | | | |
| Includes mTOR inhibitor | 29 (17%) | 1 (3%) | 28 (20%) | 0·13 (0·02–0·99)§ | 0·02 |
| Includes antimetabolite | 154 (92%) | 25 (81%) | 129 (94%) | 0·25 (0·08–0·80)¶ | 0·02 |
| Immunosuppression trough levels, IU‖ | 10·46 (9·17–11·90) | 9·46 (8·53–11·33) | 10·53 (9·31–12·06) | 0·90 (0·76–1·07)† | 0·24 |
| Prednisone dose, mg | 5·0 (5·0–10·0) | 5·0 (5·0–7·5) | 5·0 (5·0–10·0) | 0·94 (0·83–1·06)† | 0·33 |

Data are n (%), mean (SD), or median IQR. *Seropositivity was defined at 50 AU/mL (determined by the manufacturer). †Per 1 unit increase. ‡Comparison of time period from transplant; 4 years was chosen as a cutoff value because it was the median time from transplant. §Patients treated with combination therapy of CNI and everolimus. ¶Patients treated with mycophenolate mofetil, mycophenolic acid, or azathioprine. ‖Mean trough levels were calculated from the last three successive blood tests during clinical follow-up. The time period for values collection for each patient was between 1–5 months before vaccination and no missing values were registered. The variable was calculated as the sum of CNI and mTOR trough levels (when used). CNI=calcineurin inhibitors. mTOR=mammalian target of rapamycin.

***Table*: Demographic and clinical characteristics of study participants, stratified by seropositivity to anti-spike IgG antibodies after two vaccine doses**

Notably, in our study, lung transplant recipients who were younger were more likely to develop seropositive antibody titres. This finding is consistent with other studies that found an age-dependent immune response to mRNA vaccines.[4,7] Furthermore, participants in our study who were receiving either antimetabolites or mTOR inhibitors as part of their immunosuppressive drug regimens were less likely to develop seropositive antibody titres. A reduced immune response to vaccines among solid organ transplant recipients treated with antimetabolites has been observed in transplant recipients given mRNA and influenza vaccines.[4,8] However, the association between mTOR inhibitors and reduced immunogenicity has not been reported in previous studies. This association might be explained by a synergistic effect observed between calcineurin and mTOR inhibitors that, when simultaneously prescribed, can substantially inhibit lymphocyte proliferation and expression of interleukin 2 and transformation growth factor β (TGF-β).[9]

Limitations of our study include the absence of a control group of healthy vaccinated adults for comparison. Furthermore, we only assessed the humoral response of an IgG antibody against the virus spike protein, not neutralising antibody titres or memory T-cell response. However, S-IgG antibodies have a strong correlation with GMTs of neutralising antibodies and, as such, could be a valid surrogate for an adequate immune response.[5]

In summary, lung transplant recipients had reduced S-IgG antibody levels and consequently an absence of early humoral response after two doses of the BNT162b2 vaccine. Older age and immunosuppressive drug regimens, including antimetabolites and mTOR inhibitors, were associated with a reduced immune response. In light of the increase in seropositivity between the first and second vaccine doses, future research should assess the potential benefit of an additional booster dose on antibody generation among immunocompromised patients.

YS and NS contributed equally to this study and are joint first authors. MRK and BP contributed equally and are joint last authors. We declare no competing interests.

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