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ORIGINAL ARTICLE

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Improved immunogenicity following the third dose of BNT162b2 mRNA vaccine in heart transplant recipients

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Key question

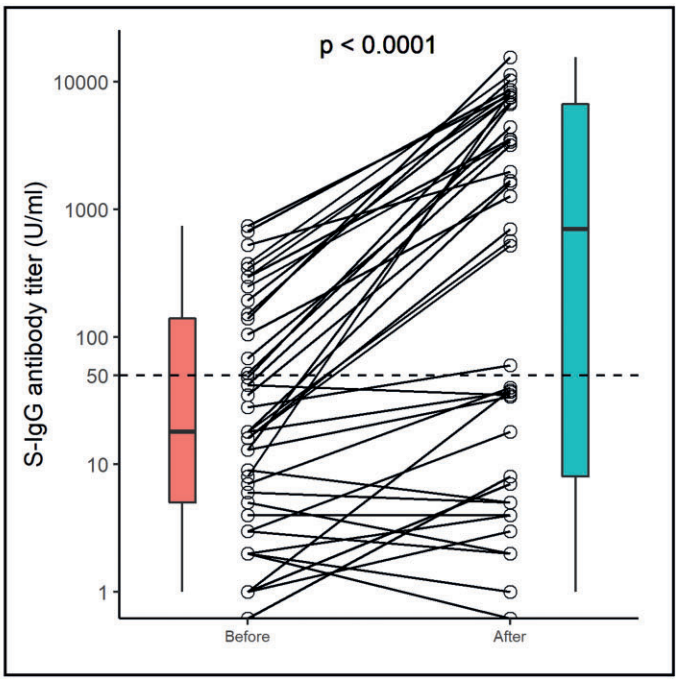
What is the immunogenicity of a third-dose booster SARS-CoV-2 vaccine in heart transplant recipients?

Key finding(s)

The proportion of S-IgG seropositive patients increased from 33% to 57% and median titer increased from 18 U/mL to 633 U/mL.

Take-home message

The third-dose booster of SARS-CoV-2 BNT162b2 vaccine is safe and significantly increased immunogenicity among heart transplant recipients.



Abstract

OBJECTIVES: The immunogenicity of two-dose severe acute respiratory syndrome coronavirus 2 vaccine is lower among heart transplant (HTx) recipients, compared with the general population. Our aim was to assess the immunogenicity of a third-dose vaccine in HTx recipients.

METHODS: This is a prospective cohort study of HTx recipients who received a third dose of the BNT162b2 vaccine. Immunogenicity was assessed by serum levels of anti-spike immunoglobulin G (S-IgG), taken at baseline and 14–28 days after the third dose. Titres above 50 U/ml were interpreted positive.

RESULTS: We Included 42 HTx recipients at a median age of 65 years [interquartile range (IQR) 58–70]. At baseline, the median of 27 days (IQR 13–42) before the third dose and the median titre of the whole group was 18 U/ml (IQR 4–130). Only 14 patients (33%) were S-IgG seropositive. After the third dose, the proportion of seropositive patients increased significantly to 57% ($P = 0.05$) and the median titre increased significantly to 633 U/ml (IQR 7–6104, $P < 0.0001$). Younger age at HTx (OR per 1-year decrease 1.07, $P = 0.05$), low tacrolimus serum level (OR per 1-unit decrease 2.28, $P = 0.02$), mammalian target of rapamycin use (OR 13.3, $P = 0.003$), lack of oral steroids use (OR 4.17, $P = 0.04$) and lack of calcineurin inhibitor use (71% of responders vs 100% non-responders received calcineurin inhibitors, $P = 0.01$) were predictors of seropositive result after the third dose. However, no significant association was detected following adjustment for baseline S-IgG titre.

CONCLUSIONS: Third-dose booster of BNT162b2 vaccine significantly increased immunogenicity among HTx recipients who previously received a two-dose vaccine.

Keywords: Severe acute respiratory syndrome coronavirus 2 • COVID-19 • Heart transplantation • BNT162b2 vaccine • Third dose

ABBREVIATIONS

CNI	Calcineurin inhibitors
HTx	Heart transplant
IQR	Interquartile range
mTOR	Mammalian target of rapamycin
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
S-IgG	Anti-spike immunoglobulin G

INTRODUCTION

Heart transplant (HTx) recipients, as other solid organ transplant recipients, are at increased risk for poor outcome following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1, 2]. The SARS-CoV-2 vaccine proved to be highly efficacious among the general population [3–5] and therefore was implemented for solid organ transplant recipients as well. However, emerging data regarding vaccine-based immune response among solid organ transplant recipients were concerning, with only about half of recipients seropositive for SARS-CoV-2 antibodies after vaccination in 1 trial [6], and even less in other trials [7]. As previously reported by our group, HTx recipients do not differ in this respect, with only 49% of HTx recipients induced antibodies after the vaccine [8]. Similar results were observed in another trial of HTx recipients [9]. The suboptimal immunogenicity after the SARS-CoV-2 vaccine [7] has raised the need for a third booster dose. Recently, preliminary trials among solid organ transplant recipients have shown that a third booster dose is safe and significantly improves SARS-CoV-2 immunogenicity, evaluated as anti-spike antibody titre [10–12]. The number of HTx recipients included in these trials was low; thus, it is currently unknown whether this unique population may benefit from a third dose, as do solid organ transplant recipients in general. In this study, we aimed to assess the safety and immunogenicity of a third-dose SARS-CoV-2 vaccine in a population of HTx recipients.

PATIENTS AND METHODS

Ethical statement

The study protocol was approved by the institutional review board of Rabin Medical Center (approval 1069-20-RMC, given on 4 January 2021) and patients' written informed consent was obtained.

We conducted a prospective cohort study of HTx recipients at the Rabin Medical Center, a tertiary referral centre that coordinates the management of approximately half of HTx recipients in Israel. We included HTx recipients who have previously received a 2-dose SARS-CoV-2 mRNA vaccine (BNT162b2; Pfizer-BioNTech, Mainz, Germany, prime-boost regimen on days 0 and 21, respectively, at a dose of 30 μg each) between December 2020 and January 2021, and in July 2021 received a third dose, as part of the recommendation of the Israeli Ministry of Health to vaccinate all immunosuppressed patients with a third booster dose. Patients received the vaccination either at our institution or at their hometown outpatient clinic. Major exclusion criteria were age below 18 years, HTx within 30 days prior to the first vaccine, patient's refusal to get the previous two-dose or current third-dose vaccine and a known prior SARS-CoV-2 infection, either before or after vaccinations, documented by positive polymerase chain reaction nasal swab.

Blood samples for the quantification of anti-spike immunoglobulin G (S-IgG) antibodies were drawn at 2 time points: at baseline (3–6 months after the first dose) and 14–28 days after the third dose. Serum was separated by centrifugation, aliquoted and stored at -20°C. Antibody quantitative testing was performed using the Abbott architect analyzer i2000sr platform in accordance with the manufacturer's package insert [13]. The assay detects antibodies against the receptor-binding protein of the S1 subunit of the spike protein of SARS-CoV-2. S-IgG value of above 50 U/ml was interpreted as seropositive [13, 14]. The study population was divided into 2 groups with respect to their S-IgG immunogenicity after the third dose: responders' group (HTx recipients who had seropositive antibody response) and non-responders' group (HTx recipients who had seronegative antibody response).

Clinical and pharmacological data were extracted from patients' electronic medical records. All patients were under standard immunosuppressive therapy protocols that included a combination of either calcineurin inhibitors (CNI, tacrolimus or cyclosporine), antimetabolites (mycophenolate mofetil or mycophenolic acid), mammalian target of rapamycin (mTOR, everolimus) and oral steroids (prednisone).

The statistical analysis was generated using SAS Software, Version 9.4 (SAS Institute Inc., Cary, NC, USA). All plots were constructed using R: A language and environment for statistical computing, Version 4.0.0 (R foundation, Vienna, Austria). Continuous variables were presented as median and interquartile 25th, 75th range. Categorical variables were presented as percentages. The clinical characteristics of study patients by serologic response were compared using the Chi-square test and the Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for

continuous variables. The Wilcoxson signed-rank test was used for the paired comparison of the S-IgG titre before and after the third dose following natural log transformation.

Potential predictors of seropositive response were evaluated using the univariable logistic regression analysis. We examined the logistic model calibration with the Hosmer and Lemeshow goodness of fit test and the model discrimination ability by *C*-statistic, corresponding to the area under-a-receiver operating characteristics curve. Hosmer & Lemeshow test $P < 0.3$ for the majority of the univariate models and *C*-statistic ranged between 0.6 and 0.9. The analysis was repeated with adjustment for natural log-transformed baseline S-IgG titer. Lack of collinearity was ascertained by examination of the correlation between each predictor and baseline titer (Spearman correlation <0.7 for all models) and the variance inflation factor in linear regression predicting S-IgG titer (natural log transformed) following a third vaccine dose (variance inflation factor <2 for all models). *P* for Hosmer and Lemeshow goodness of fit test ranged between 0.59 and 0.99 (1 exception: $P = 0.39$ for model with CNI reduced as predictor), and *C*-statistic >0.9 for all models. *P*-Value of <0.05 was considered statistically significant.

RESULTS

The study included 42 HTx recipients who completed all 3 doses of SARS-CoV-2 BNT162b2 mRNA vaccine and for whom serologic data before ('baseline') and after the third dose were available. We excluded patients with documented previous SARS-CoV-2 infection ($n = 5$), those who underwent HTx within the last month ($n = 2$) and those who did not complete all 3 doses of the vaccine or refused for the serology testing after the third dose.

Baseline characteristics, including immunosuppressive regimens and vaccination-related adverse events, are shown in Table 1. The median age was 65 years [interquartile range (IQR) 58–70] and 76% were males. Time from HTx to the third dose was 9.7 years (IQR 3.4–14.2) and age at HTx was 57 years (IQR 47–61). Immunosuppressive drugs used were CNI (83%), mTOR inhibitors (40%), oral steroids (60%) and antimetabolites (71%), with all patients using 2 or 3 drugs, in accordance with common protocols as presented in Table 1. The most common adverse event after the third-dose vaccination was local pain at the injection site ($n = 18$, 43%) with only 2 patients suffering from systemic fever, myalgia, headache, diarrhoea or cough each. There were no clinical overt episodes of allograft rejection, as assessed by routine outpatient clinic visits.

Baseline serology was taken at a median of 27 days (IQR 13–42) before the third dose. At baseline, the median titre of the whole group was 18 U/ml (IQR 4–130). Only 33% ($n = 14$) of patients were S-IgG seropositive. Of those who were seronegative before the third dose ($n = 28$), there were only 2 patients that were seropositive earlier, after the second dose. Both had borderline titres of 100–150 U/ml, that dropped below 50 U/ml before the third dose.

After the third dose, the proportion of seropositive patients increased significantly to 57% ($n = 24$, $P = 0.05$), and the median titre level increased significantly to 633 U/ml (IQR 7 to 6104, $P < 0.0001$) (Central image). Among the 28 patients found seronegative before the third dose, 12 patients had converted to seropositive, giving a conversion rate of 43%. As of this writing, none of the patients had developed clinical SARS-CoV-2 infection.

To evaluate the predictors for seropositivity after the third dose, we performed an analysis of responders' versus non-responders' groups. Baseline characteristics are shown in Table 2. Predictors for a seropositive result after the third dose were younger age at HTx (OR per 1-year decrease 1.07, 95% CI 1.00–1.14, $P = 0.05$), low tacrolimus serum level (OR per 1-unit decrease 2.28, 95% CI 1.12–4.65, $P = 0.02$), mTOR use (OR 13.3, 95% CI 2.5–72.0, $P = 0.003$), lack of oral steroids use (OR 4.17, 95% CI 1.05–16.39, $P = 0.04$) and lack of CNI use (71% of responders vs 100% non-responders received CNI, $P = 0.01$). In view of the strong correlation between baseline S-IgG titre and seropositivity after the third dose, we repeated the analysis with adjustment for the natural log-transformed value of baseline S-IgG titre and found that it was accounted for most of the association with seropositive result following the third dose. Following an adjustment to the baseline S-IgG titre, none of these predictors were significantly associated with a seropositive result (Supplementary Material Table S1).

Table 1: Baseline characteristics of heart transplant recipients who received the third-dose BNT162b2 mRNA vaccine

Patients (*n*)	42
Age, years	65 (58–70)
Male gender, *n* (%)	23 (76)
Time from HTx, years	9.7 (3.4–14.2)
Age at HTx, years	57 (47–61)
Immunosuppressive drugs, *n* (%)	
Calcineurin inhibitors	35 (83)
mTOR inhibitors	17 (40)
Oral steroids	25 (60)
Antimetabolites[a]	30 (71)
Immunosuppressive protocol, *n* (%)[b]	
CNI based	25 (59)
CNI reduced	10 (24)
CNI free	7 (17)
Immunosuppression drug levels, ng/ml	
Tacrolimus	5.6 (4.1–6.6)
Cyclosporine	64 (54–127)
Everolimus	3.7 (3.2–4.4)
Adverse response to vaccine, *n* (%)	
Pain at the injection site	18 (43)
Swelling or redness at the injection site	0 (0)
Fatigue	3 (7)
Myalgia	2 (5)
Headache	2 (5)
Diarrhoea	2 (5)
Cough	2 (5)
Systemic fever	2 (5)

Data are presented as percentages or as median (25th–75th quartiles), as appropriate.

[a]Antimetabolites immunosuppression refer to mycophenolate mofetil and mycophenolic acid.

[b]CNI-based immunosuppression protocol includes CNI with (mostly) or without antimetabolites, CNI-reduced protocol includes CNI and mTOR inhibitors and CNI-free protocol includes mTOR inhibitors and antimetabolites.

CNI: calcineurin inhibitors; HTx: heart transplant; mTOR: mammalian target of rapamycin.

DISCUSSION

We report here the immunogenicity profile among HTx recipients following the third dose of SARS-CoV-2 vaccine. Our findings demonstrate that the third dose of BNT162b2 vaccine was safe and significantly improved immunogenicity, as assessed with both S-IgG seropositivity rates and titre levels.

Table 2: Baseline characteristics of heart transplant recipients stratified by anti-spike immunoglobulin G immunogenicity after the third-dose BNT162b2 mRNA vaccine

	Responders ($n = 24$)	Non-responders ($n = 18$)	*P*-Value
Age, years	63 (47–70)	68 (61–71)	0.16
Male gender, *n* (%)	16 (67)	16 (89)	0.094
Time from HTx, years	13.2 (4.1–15.2)	6.0 (1.9–12.1)	0.058
Age at HTx, years	48 (42–59)	61 (57–63)	0.005
S-IgG titre >10 U/ml at baseline, *n* (%)	23 (96)	3 (17)	<0.001
Immunosuppressive drugs, *n* (%)			
Calcineurin inhibitors	17 (71)	18 (100)	0.012
mTOR inhibitors	15 (63)	2 (11)	<0.001
Oral steroids	11 (46)	14 (78)	0.037
Anti-metabolites[a]	15 (63)	15 (83)	0.14
Immunosuppressive protocol, *n* (%)[b]			
CNI based	9 (38)	16 (89)	<0.001
CNI reduced	8 (33)	2 (11)	0.094
CNI free	7 (29)	0 (0)	0.012
Immunosuppression drug levels, ng/ml			
Tacrolimus	4.2 (3.7–5.2)	6.1 (5.7–8.9)	0.004
Cyclosporine	54 (53–54)	127 (105–141)	0.032
Everolimus	3.6 (3.1–4.0)	5.7 (5.2–6.2)	0.068

Data are presented as percentages or as median (25th–75th quartiles), as appropriate.

[a]Antimetabolites immunosuppression refer to mycophenolate mofetil and mycophenolic acid.

[b]CNI-based immunosuppression protocol includes CNI with (mostly) or without antimetabolites, CNI-reduced protocol includes CNI and mTOR inhibitors and CNI-free protocol includes mTOR inhibitors and antimetabolites.

CNI: calcineurin inhibitors; HTx: heart transplant; mTOR: mammalian target of rapamycin; S-IgG: anti-spike immunoglobulin G.

Three recently published studies investigated the humoral immune response following the third dose of SARS-CoV-2 vaccine in the overall population of solid organ transplant recipients, with HTx recipients accounting for only 7–15% of patients. The first report, by Werbel *et al.* [12], included 30 patients who received one of 3 vaccines: Ad26.COV2.S (Johnson & Johnson/Janssen), mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech). Of the 24 patients with negative antibody titres before the third dose, only 6 (25%) had high-positive titres after the third dose, 2 (8%) had low-positive titres and 16 (67%) remained negative. This translates to a rise in the prevalence of seropositive results from 20% before to 47% after the third dose. The second report, by Kamar *et al.* [11], included 101 solid organ transplant recipients and showed seropositive results of 40% before and 68% after the third dose of BNT162b2 vaccine. These 2 reports were followed by a randomized control trial by Hall *et al.* [10] that enrolled 120 solid organ transplant recipients to receive either a third dose of mRNA-1273 vaccine or placebo. After the third dose, 55% of patients in the vaccine group were seropositive compared with only 18% in the placebo group. Our findings are consistent with these studies in solid organ transplant recipients and demonstrate improved third-dose immunogenicity in HTx recipients.

We found that high-intensity immunosuppression (higher use of CNI and oral steroids and higher tacrolimus serum levels) and lower use of mTOR-based immunosuppression protocol were predictors of low immunogenicity after the third dose; however, no significant association was detected following adjustment for baseline S-IgG titre.

Importantly, the safety profile of the third dose in HTx recipients was favourable. Except for pain at the injection site, which was reported by 43% ($n = 18$) of patients, there was a very low rate of any other adverse events after the vaccination. Moreover, no clinical events of allograft rejection were documented, an important consideration in this complex subset of patients.

These findings should guide the vaccination strategy and clinical management of HTx recipients. First, all precautions should be rigorously maintained for low immunogenicity HTx recipients, including barrier measures and vaccination of household members. Second, immunosuppression regimens may be individually adjusted, with a low threshold for changing to mTOR-based protocols when otherwise indicated. Decreasing the intensity of immunosuppression is currently not recommended [15], since it is yet unknown whether this strategy would improve immunogenicity, while it may predispose to the development of donor-specific antibodies and allograft rejection. In addition, in selected cases, if exposure has occurred, prophylactic administration of novel monoclonal antibodies (REGEN-COV) should be considered [16].

Limitations

This study has several limitations. First, this is a single-centre study with a small sample size. Second, neither polymerase chain reaction test nor anti-N protein for SARS-CoV-2 infection was taken routinely before and during the study; therefore, a prior SARS-CoV-2 infection cannot be completely ruled out. However, all HTx recipients at our centre were closely followed with a low threshold for SARS-CoV-2 screening, so that infected patients were most likely to be diagnosed and thus excluded from the study. Third, we assessed S-IgG antibody titre response to the vaccine, and not neutralizing antibody activity. We were unable to measure CD4 and C8 T-cell responses to the vaccine. Nevertheless, S-IgG antibodies were found to correlate with neutralizing antibodies either after vaccination [17] or infection [18] and also related to lower infectivity [19]. Moreover, a recent work by Levin *et al.* [20] has clearly showed that S-IgG antibody levels were

highly correlated with neutralizing antibodies' activity after BNT162b2 vaccine. Thus, S-IgG antibodies may represent a surrogate for an adequate immune response and protection from SARS-CoV-2 infection.

Although the long-term effects of the SARS-CoV-2 BNT162b2 vaccine are yet unknown, at close follow-up of the vaccinated group, no major adverse events have occurred. Patients are screened for any adverse events prospectively.

CONCLUSION

The third-dose booster of SARS-CoV-2 BNT162b2 vaccine among HTx recipients is safe and significantly increases immunogenicity. We believe that these data strongly support the continuing campaign of third-dose booster vaccination in Israel and should prompt other countries to launch similar vaccination programs.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Aviv Avraham Shaul: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing—original draft; Writing—review & editing. **Osnat Itzhaki Ben Zadok:** Conceptualization; Data curation; Investigation; Methodology; Resources; Validation; Writing—review & editing. **Binyamin Ben-Avraham:** Investigation; Resources; Supervision. **Vicky Yaari:** Data curation; Investigation; Methodology; Project administration; Resources; Validation. **Alon Barsheshet:** Formal analysis; Methodology; Writing—review & editing. **Amos Levi:** Formal analysis; Methodology; Writing—review & editing. **Haim Ben Zvi:** Investigation; Resources. **Noa Eliakim Raz:** Investigation; Supervision. **Galia Abed:** Investigation; Resources. **Miriam Abuhazira:** Investigation; Resources. **Mahmood Abu Akel:** Investigation; Resources. **Israel Mats:** Investigation; Resources. **Yaron D. Barac:** Investigation; Resources; Supervision. **Dan Aravot:** Investigation; Resources; Supervision. **Ran Kornowski:** Conceptualization; Supervision; Writing—review & editing. **Tuvia Ben-Gal:** Conceptualization; Data curation; Methodology; Resources; Supervision; Writing—review & editing.

Reviewer information

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