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BNT162b2 vaccination in heart transplant recipients: Clinical experience and antibody response

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KEYWORDS:
BNT162b2 vaccine; heart transplantation; antibody response

BACKGROUND: Data on the safety and efficacy of SARS-CoV-2 vaccines in immunocompromised populations are sparse.
METHODS: We conducted a prospective study of 77 heart transplant (HT) recipients vaccinated with two doses of BNT162b2 vaccine and monitored for adverse events following both doses, the receptor-binding domain (RBD) IgG response, and neutralizing antibodies.
RESULTS: BNT162b2 vaccination was associated with a low rate of adverse events, characterized mostly by pain at the injection site. By a mean 41 days post second dose there were no clinical episodes of rejection, as suggested by a troponin leak or allograft dysfunction. At a mean 21 days following the second dose, IgG anti-RBD antibodies were detectable in 14 (18%) HT recipients. Immune sera neutralized SARS-CoV-2 pseudo-virus in 8 (57%) of those with IgG anti-RBD antibodies. Immunosuppressive regimen containing mycophenolic acid was associated with lower odds of an antibody response (OR = 0.12, $p = 0.042$).
CONCLUSIONS: Whether a longer time-frame for observation of an antibody response is required after vaccination in immunosuppressed individuals remains unknown.
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Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has significantly challenged the clinical management of heart transplant (HT) recipients. The current efficacy data for mRNA coronavirus disease 2019 (COVID-19) vaccines are >90% for the general population, with a favourable safety profile,[1,2] but data for immunocompromised patients, in whom immunogenicity could potentially be reduced, are sparse and only now emerging.[3,4] The Pfizer BNT162b2 COVID-19 vaccine was approved in December 2020 by the Israel Government, and a national immunization campaign was set in motion. In accordance with the dedicated recommendations, we have taken a proactive stance in promoting vaccination of the HT patients in our care.[5] Here, we describe our experience with the BNT162b2 vaccination, with emphasis on identifying and characterizing the safety and early antibody response to this vaccine.

Seventy-seven stable adult HT patients received two doses of the BNT162b2 vaccine (Pfizer, New York, USA and BioNTech, Mainz, Germany) and were followed prospectively. Patients were actively screened for adverse

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events[1] within the seven days after each dose, and for the vaccine-induced antibody response of the receptor-binding domain (RBD) IgG and neutralizing antibodies at three weeks after the second vaccine. The study was approved by our institutional review board (7982-20-SMC). Samples from vaccinated HT patients were evaluated with an "in-house" enzyme-linked immunosorbent assay that detects IgG antibodies against SARS-CoV-2 RBD. A SARS-CoV-2 pseudo-virus (psSARS-2) neutralization assay was performed to detect SARS-CoV-2 neutralizing antibodies using a propagation-competent VSV-spike similar to the one previously published (kindly provided by Gert Zimmer, University of Bern, Switzerland).[6] Statistical analyses were conducted using R (version 4.0.3).

The patients were evaluated at a mean 21 (±10) days following the second dose of the vaccine (Table 1). Median age was 62.0 (49.0-68.0) years; 64% were male; and median time after HT was 7.4 (3.3-15.1) years. Comorbidities were frequent, with hypertension (74%), diabetes mellitus (35%), chronic kidney disease (38%), and dyslipidemia (88%) being the most common. Immunosuppression with a calcineurin inhibitor, a mycophenolate, and prednisone, was the most frequently followed protocol (48%). Nineteen (25%) patients had already been weaned off chronic steroids.

Among the vaccine recipients, 60% and 53% reported at least one adverse event after the first and second doses, respectively. By age group, 77% and 69% in the younger group (aged < 55 years) and 51% and 45% in the older group (aged >55 years) reported at least one adverse event after the first and second doses, respectively. Among the vaccine recipients, 56% and 49% reported at least one local injection site reaction (Table S1) after the first and second doses, respectively. By age group, 80% and 72% in the younger group and 44% and 38% in the older group reported at least one local reaction after the first and second doses, respectively. Pain at the injection site was the most frequent local reaction, and was more frequently reported by the younger age group. At least one systemic reaction (mainly fatigue or headache) after the first and second doses was reported by 37% and 49% of the recipients, respectively (Table S2). The frequency of systemic adverse events was higher in the younger than the older age group, being 72% vs 20% and 100% vs 22% after the first and second doses, respectively. The majority of systemic events were mild or moderate, and no emergency room visits or hospitalizations for adverse events were reported. Patients who produced antibodies did not demonstrate higher rates of adverse events (Table S3). Clinical episodes of rejection as suggested by a troponin leak or allograft dysfunction did not occur at a mean time of 41(±8) days post second dose (Table 1).

At a mean 21 days following the second dose, IgG anti-RBD antibodies were detectable in 14 (18%) of the HT recipients. Immune sera neutralized psSARS-2 in 8 (57%) of those with IgG anti-RBD antibodies. Immunosuppression characteristics of patients by antibody responses are presented in Table 1. Values for lymphocytes, creatinine, C-reactive protein, and neutrophil/lymphocyte ratio were similar for the antibody positive and negative groups. A significantly lower use of mycophenolate and a higher use of everolimus were demonstrated for patients with a positive antibody response. In an adjusted logistic regression analysis, mycophenolate use was associated with a reduced odd of achieving a positive antibody response (OR = 0.12, 95% CI 0.01-0.82, p = .042) (Table S4).

A healthy control group of 136 subjects was evaluated at a mean of 13.3 (±1.4) days following the second dose of the BNT162b2 vaccine. Mean age was 63 (±13) years, and 63% were female. IgG anti-RBD antibodies were detectable in 134 (98.5%) of the healthy controls. Immune sera neutralized psSARS-2 in 94.8% of those with IgG anti-RBD antibodies.

Our results confirm the predicted estimations for the safety of vaccinating the HT population, thereby encouraging immunization when vaccine is locally available.[5] Rates of adverse events reported were significantly lower than those reported for the non-transplant population, for which 84.7% reported at least one local injection site reaction and 77.4% reported at least one systemic reaction.[1]

In the nontransplant population, the BNT162b2 vaccine elicits antibody responses against the RBD, and plasma binding and neutralizing activity of the vaccine against SARS-CoV-2 has been demonstrated.[7] However, for immunosuppressed populations, it remains to be confirmed whether vaccine-induced antibody responses confer immunity to SARS-CoV-2 infection. The presence of antibodies in the transplant recipients in our cohort probably suggests some degree of protection from infection (supported by the presence of neutralizing antibodies), although the exact titers needed to prevent infection, timing, and duration, have not yet been established, thus warranting adopting a careful approach.[5]

As vaccine-induced protective immunity against viral infection is mediated by both humoral immunity and cell-mediated immunity, the role of T-cell responses in coronavirus-vaccinated transplant populations should be addressed. It has been suggested that in addition to a strong anti-SARS-CoV-2 antibody response, a coronavirus vaccine should also optimally induce virus-specific T-cell responses.[8] Thus, defining the T-cell responses and the resulting protective immunity in response to SARS-CoV-2 vaccines is essential,[8] particularly for transplant patients with chronically low T cell counts.

Our preliminary results suggest that the type of immunosuppression impacts the ability to mount an immune response; notably, mycophenolate use was independently associated with a reduced likelihood of generating an antibody response. Previous studies have reported the association of mycophenolate treatment with a reduced likelihood of achieving seroprotection for the influenza vaccine in solid organ transplant recipients.[9] Similarly, low immunogenicity of the first dose of the mRNA SARS-CoV-2 vaccine and an association with anti-metabolite treatment were recently reported.[3] The inhibition of both T-cell and B-cell proliferation by mycophenolate might contribute to differences in antibody responses, and a potent suppressive effect of mycophenolate on the humoral immune response has

Table 1 Recipients Characteristics, Stratified by Antibody Response

Variable	Total cohort n = 77	Antibody positive n = 14	Antibody negative n = 63	*p* value
Recipient characteristics				
Age, years, median (IQR)	62.0 (49.0- 68.0)	61.5 (47.8- 68.0)	62.0 (49.5-68.5)	.648
Female sex, n (%)	27 (35.5)	5 (35.7)	22 (35.5)	1.000
BMI, kg/m^2, (mean±SD)	26.4 ± 5.4	28.4 ± 6.6	26.1 ± 5.1	.214
Diabetes mellitus, n (%)	23 (35.4)	4 (36.4)	19 (35.2)	1.000
Hypertension, n (%)	48 (73.8)	9 (81.8)	39 (72.2)	.777
Dyslipidemia, n (%)	57 (87.7)	9 (81.8)	48 (88.9)	.883
Chronic kidney disease, n (%)[a]	29 (37.7)	6 (42.9)	23 (36.5)	.890
Blood type, n (%)				.996
A	24 (42.1)	4 (40)	20 (42.6)	
AB	6 (10.5)	1 (10)	5 (10.6)	
B	10 (17.5)	2 (20)	8 (17)	
0	17 (29.8)	3 (30)	14 (29.8)	
Cardiac allograft vasculopathy, n (%)	14 (23.3)	1 (9.1)	13 (26.5)	.400
Immunosuppression data[b]				
Mycophenolic acid therapy, n (%)	58 (75.3)	5 (35.7)	53 (84.1)	.001
Mycophenolate sodium, n (%)	41 (53.2)	3 (21.4)	38 (60.3)	.019
Mycophenolate mofetil, n (%)	17 (22.1)	2 (14.3)	15 (23.8)	.674
Mycophenolate sodium dose, mg, (mean±SD)	1225.4 ± 385.4	1386.7 ± 641.7	1212.6 ± 368.8	.458
Mycophenolate mofetil dose, mg, (mean±SD)	1441.2 ± 496.3	1500 ± 707.1	1433.3 ± 495.2	.865
Everolimus therapy, n (%)	20 (26.0)	9 (64.3)	11 (17.5)	.001
Immunosuppression protocol				<.001
Tacrolimus + Mycophenolate + Prednisone, n (%)	32 (41.6)	3 (21.4)	29 (46)	
Cyclosporine +Mycophenolate + Prednisone n (%)	5 (6.4)	1 (7.1)	4 (6.3)	
Tacrolimus + Mycophenolate, n (%)	13 (16.8)	0 (0)	13 (20.6)	
Cyclosporine + Mycophenolate, n (%)	2 (2.6)	0 (0)	2 (3.2)	
Cyclosporine + Everolimus + Prednisone, n (%)	3 (3.9)	3 (21.4)	0 (0)	
Tacrolimus + Everolimus + Prednisone, n (%)	9 (11.7)	3 (21.4)	6 (9.5)	
Mycophenolate + Everolimus + Prednisone, n (%)	3 (3.9)	0 (0)	3 (4.8)	
Everolimus + Cyclosporine, n (%)	2 (2.6)	2 (14.3)	0 (0)	
Everolimus + Mycophenolate, n (%)	2 (2.6)	0 (0)	2 (3.2)	
Cyclosporine+ Prednisone, n (%)	4 (5.2)	1 (7.1)	3 (4.8)	
Tacrolimus + Prednisone, n (%)	1 (1.3)	0 (0)	1 (1.6)	
Tacrolimus + Everolimus + Mycophenolate + Prednisone, n (%)	1 (1.3)	1 (7.1)	0 (0)	
Chronic prednisone, n (%)	58 (75.3)	12 (85.7)	46 (73.0)	.513
Prednisone dose, mg, median (IQR)	2.50 (1.5- 2.5)	2.50 (2.1, 2.9)	2.5 (0- 2.5)	.408
Tacrolimus trough level, μg/L, (mean±SD)[c]	8.1 ± 3.7	6.6 ± 4.4	8.4 ± 3.5	.191
Tacrolimus trough level, μg/L, median (IQR)[c]	9.00 (5.4, 10.5)	5.00 (4.2, 6.7)	9.6 (5.7, 10.7)	.063
Cyclosporine trough level, μg/L, (mean±SD)[c]	91.1 ± 49.3	80.5 ± 50.9	96.4 ± 50.0	.535
Cyclosporine trough level, μg/L, median (IQR)[c]	102.5 (54.0, 118.0)	58.0 (47.8, 92.3)	112.5 (89.3, 122.5)	.261
Laboratory data*				
Lymphocyte absolute, K/μL, n (%)	1.4 ± 0.7	1.5 ± 0.6	1.4 ± 0.7	.575
White blood cell, K/μL, n (%)	6.8 ± 2.3	6.9 ± 2.6	6.8 ± 2.3	.895
Neutrophil absolute, K/μL, n (%)	4.6 ± 2.0	4.9 ± 2.7	4.5 ± 1.8	.546
Neutrophil/lymphocyte ratio, n (%)	4.2 ± 4.6	3.4 ± 1.8	4.4 ± 5.0	.480
Creatinine, mg/dL, n (%)	1.2 ± 0.6	1.2 ± 0.5	1.2 ± 0.6	.963
C-reactive protein, mg/L, n (%)	7.3 ± 10.8	10.6 ± 15.0	6.6 ± 9.7	.234
Low-density lipoprotein, mg/dL, n (%)	85.5 ± 34.1	99.1 ± 36.3	82.7 ± 33.2	.116
Triglycerides, mg/dL, n (%)	172.6 ± 69.2	181.9 ± 74.1	170.7 ± 68.6	.599
Donor specific antibody, n (%)	5 (7.0)	2 (15.4)	3 (5.2)	.483
Troponin I HS baseline, ng/L, baseline, median (IQR)	4.2 (3.0-6.9)	4.4 (3.9-6.8)	4.1 (3.0-6.8)	0.307
Troponin I HS post second vaccine, ng/L, median (IQR)	4.3 (3.1-7.3)	4.3 (3.6-9.3)	4.4 (3.0-6.6)	.172
Δ Troponin, ng/L, median (IQR)	0.0 (-0.2- 0.3)	0.0 (-0.3, 0.6)	0.0 (-0.2- 0.3)	.537
Time-table				
HT to second vaccine, years, median (IQR)	7.4 (3.3-15.1)	9.8 (4.1-17.3)	7.4 (3.2-14.8)	.615
Second vaccine to antibody testing, days (mean±SD)	20.6 ± 10.0	20.5 ± 10.4	20.7 ± 10.0	.955
Follow-up from second vaccine, days (mean±SD)	40.8 ± 7.6	40.3 ± 4.1	40.9 ± 8.2	.781

(*continued on next page*)

Table 1 (*Continued*)

Variable	Total cohort n = 77	Antibody positive n = 14	Antibody negative n = 63	*p* value
Echocardiography				
Ejection fraction, baseline, % (mean±SD)	58.9 (3.2)	57.9 (4.7)	59.2 (2.7)	.148
Ejection fraction, post second vaccine, % (mean±SD)	59.1 (3.0)	57.5 (5.0)	59.4 (2.3)	.057
Δ Ejection fraction, % (mean±SD)	0.03 (0.72)	0.00 (0.00)	0.04 (0.79)	.875

BMI, Body mass index; HT, heart transplantation; SD, standard deviation.

[a]Defined as estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 using the CKD-EPI formula.

[b]On day of antibody testing.

[c]Whole blood trough levels were measured on the day of antibody testing (at least 4 half-lives on fixed-dose regimen).A chi-square test was used for comparison of categorical variables between the groups. Student's *t*-test was performed for comparison of normally distributed continuous variables, and the Mann-Whitney U test was used for non-normal distribution.

indeed been described.[10] The results of our study should be carefully interpreted before any recommendations can be made: while immunosuppressive therapies decrease the ability of the transplant recipient to mount an antibody response to COVID-19, the risk of rejection may be greater with a significant reduction in immunosuppression.[5]

Our results should be taken in the context of several limitations. The number of participants in our study was relatively low, and no randomization with a control group was done. While this study suggests a favorable safety profile, it was not designed to establish the vaccine's clinical efficacy in this population or the role of T cell response. Finally, whether the RBD antibody is best suited to evaluate the immunogenicity in transplant recipients should be further assessed.

In conclusion, given the preliminary nature of our study, it is still too early to draw conclusions about the effectiveness of the BNT162b2 mRNA vaccine in HT patients. Further study is needed to define and optimize the vaccine immunization protocol, with emphasis on vaccination timing, immunosuppression protocols, formulation and dosing. In addition, correlations of clinical outcomes with laboratory-determined antibody responses combined with markers of cell-mediated immunity would make an invaluable contribution to establishing vaccination recommendations.[8]

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2021.04.003.

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