OBSERVATIONS: CASE REPORTS

Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series

Background: The antibody response after 2 doses of an mRNA vaccine against SARS-CoV-2 is excellent in the general population (1), but the response is different in recipients of solid organ transplants. For example, we have found markedly attenuated antibody responses in transplant recipients after 2 doses of an mRNA vaccine against SARS-CoV-2 (2). In addition, reports of COVID-19 breakthrough infections in vaccinated transplant recipients (3) have prompted interest in administering additional doses of vaccine.

Objective: To describe antibody responses and vaccine reactions in recipients of solid organ transplants who had a suboptimal response to standard vaccination and subsequently received a third dose of vaccine between 20 March 2021 and 10 May 2021.

Case Series: This study was approved by the Johns Hopkins institutional review board, and participants provided informed consent.

Thirty patients reported receiving a third dose of vaccine (Table 1). Their median age was 57 years (interquartile range [IQR], 44 to 62 years), 17 were women, and 1 identified as non-White. None of the patients reported an illness before vaccination that was consistent with COVID-19 or a positive result on polymerase chain reaction (PCR) assay. In 25 patients, maintenance immunosuppression included tacrolimus or cyclosporine plus mycophenolate. In addition, corticosteroids were used for 24 patients, sirolimus for 1, and belatacept for 1. The median time between transplantation and initial vaccination was 4.5 years (IQR, 2.3 to 10.5 years). During the initial vaccination, 57% of the 30 patients received 2 doses of the 162b2 vaccine (Pfizer/BioNTech), and 43% received 2 doses of the mRNA-1273 vaccine (Moderna).

We tested all patients for antibodies against the spike protein at a median of 9 days (IQR, 2 to 33 days) before they received their third dose of vaccine; 24 patients had

Table 1. Vaccines Administered, Antibody Responses, Patient Characteristics, and Organs Transplanted

Patient	Initial Vaccine Series	Third Vaccine Dose	Antibody Titer Before Dose 3*	Antibody Titer After Dose 3*	Days Between Dose 2 and Dose 3	Patient Age, *y*	Patient Sex	Organ Transplanted	Years Since Transplant†
1	Pfizer/BioNTech	J&J/Janssen	<0.4‡	0.04	39	40–49	Male	Kidney	3.5
2	Pfizer/BioNTech	J&J/Janssen	<0.4‡	0.11	81	40–49	Male	Kidney	1.5
3	Pfizer/BioNTech	J&J/Janssen	0.33	0.37	41	50–59	Female	Kidney	5.5
4	Pfizer/BioNTech	J&J/Janssen	<0.4‡	1.13‡§	54	70–79	Male	Kidney	13
5	Pfizer/BioNTech	J&J/Janssen	0.00	1.77§	68	60–69	Female	Kidney	22.5
6	Pfizer/BioNTech	J&J/Janssen	0.66	2.87§	61	50–59	Male	Kidney	1.5
7	Pfizer/BioNTech	J&J/Janssen	2.75‡§	>250‡§	66	60–69	Male	Heart	2.5
8	Pfizer/BioNTech	Moderna	0.05	0.08	52	30–39	Female	Heart‖	6.5
9	Pfizer/BioNTech	Moderna	0.13	0.32	74	40–49	Male	Kidney	2
10	Pfizer/BioNTech	Moderna	<0.4‡	2.75§	81	60–69	Female	Kidney	8.5
11	Pfizer/BioNTech	Moderna	0.82‡	4.45§	81	70–79	Female	Liver	18.5
12	Pfizer/BioNTech	Moderna	1.26§	4.58§	75	60–69	Female	Liver	3
13	Pfizer/BioNTech	Moderna	0.25	4.72§	85	40–49	Female	Pancreas	1.5
14	Pfizer/BioNTech	Moderna	10.35‡§	5.31§	64	50–59	Male	Liver	1
15	Pfizer/BioNTech	Pfizer/BioNTech	<0.4‡	0.09	96	40–49	Male	Kidney	3
16	Pfizer/BioNTech	Pfizer/BioNTech	<0.4‡	0.43	93	40–49	Male	Kidney	3
17	Pfizer/BioNTech	Pfizer/BioNTech	0.55	3.67§	71	40–49	Male	Kidney	3
18	Moderna	J&J/Janssen	0.04	0.01	24	50–59	Female	Kidney	2
19	Moderna	J&J/Janssen	<0.4‡	0.1	57	40–49	Female	Kidney	15
20	Moderna	J&J/Janssen	0.09	0.11	36	50–59	Male	Kidney	6
21	Moderna	J&J/Janssen	0.06	0.13	51	40–49	Female	Kidney and pancreas	8.5
22	Moderna	J&J/Janssen	<0.4‡	0.23	48	60–69	Female	Kidney	1
23	Moderna	J&J/Janssen	0.05	0.33	70	60–69	Male	Kidney	7
24	Moderna	J&J/Janssen	0.06	0.37	84	70–79	Female	Lung	4.5
25	Moderna	J&J/Janssen	0.88	3.42§	70	70–79	Female	Kidney	10.5
26	Moderna	Moderna	0.15	0.32	101	20–29	Female	Kidney	13.5
27	Moderna	Moderna	3.84§	6.93§	60	50–59	Male	Kidney	3
28	Moderna	Moderna	1.53	8.26§	86	50–59	Female	Kidney	19.5
29	Moderna	Pfizer/BioNTech	0.03	0.06	55	40–49	Female	Kidney	4.5
30	Moderna	Pfizer/BioNTech	1.8§	9.11§	57	60–69	Female	Kidney	10.5

J&J = Johnson & Johnson; RBD = receptor-binding domain.
* EUROIMMUN anti-S1 IgG assay or Roche Elecsys anti-RBD pan-Ig assay. A negative result was defined by manufacturer data as EUROIMMUN anti-S1 IgG <1.1 arbitrary units or Roche anti-RBD pan-Ig <0.8 units/mL. A low-positive result was defined as anti-S1 IgG of 1.1 to 4 arbitrary units or anti-RBD pan-Ig of 0.8 to 50 units/mL. A high-positive result was defined as anti-S1 IgG >4 arbitrary units or anti-RBD pan-Ig >50 units/mL.
† Rounded to the nearest half-year.
‡ Roche assay.
§ Positive result.
‖ This recipient experienced antibody-mediated rejection in the transplanted organ after dose 3 of vaccine.

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Table 2. Self-Reported Reactions After a Third Dose of Vaccine

Reaction and Severity*	Johnson & Johnson/ Janssen Vaccine Recipients (*n* = 11‡), *n* (%)	mRNA Vaccine† Recipients (*n* = 12‡), *n* (%)
Local symptoms		
Pain		
None	5 (45)	0 (0)
Mild	5 (45)	6 (50)
Moderate	1 (9)	5 (42)
Severe	0 (0)	1 (8)
Redness		
None	9 (82)	8 (67)
Mild	1 (9)	3 (25)
Moderate	1 (9)	1 (8)
Swelling		
None	9 (90)	8 (67)
Mild	0 (0)	2 (17)
Moderate	1 (10)	2 (17)
Systemic symptoms		
Fever (none)	11 (100)	11 (100)
Chills		
None	9 (82)	11 (92)
Mild	1 (9)	0 (0)
Moderate	1 (9)	1 (8)
Headache		
None	6 (55)	6 (50)
Mild	3 (27)	3 (25)
Moderate	2 (18)	2 (17)
Severe	0 (0)	1 (8)
Fatigue		
None	3 (27)	6 (50)
Mild	5 (45)	3 (25)
Moderate	3 (27)	3 (25)
Myalgia		
None	7 (64)	8 (67)
Mild	2 (18)	4 (33)
Moderate	1 (9)	0 (0)
Severe	1 (9)	0 (0)
Diarrhea		
None	10 (91)	10 (83)
Mild	1 (9)	2 (17)

* Symptoms were defined as mild if they did not interfere with daily activities, moderate if they produced some interference with daily activity, and severe if they prevented daily activity.
† Pfizer/BioNTech or Moderna.
‡ Questionnaires were not reported for 4 Johnson & Johnson/Janssen vaccine recipients and 3 mRNA vaccine recipients.

negative antibody titers, and 6 patients had low-positive antibody titers. Patients received the third dose of vaccine a median of 67 days (IQR, 54 to 81 days) after the second dose of their initial vaccine series; 15 patients received the Ad26.COV2.S vaccine (Johnson & Johnson/Janssen), 9 received the mRNA-1273 vaccine (Moderna), and 6 received the 162b2 vaccine (Pfizer/BioNTech).

We repeated antibody testing a median of 14 days (IQR, 14 to 17 days) after the third dose of vaccine. Of the 6 patients with low-positive antibody titers before the third dose, all had high-positive antibody titers after the third dose. In contrast, of the 24 patients with negative antibody titers before the third dose, only 6 (25%) had high-positive antibody titers after the third dose. Two (8%) had low-positive antibody titers, and 16 (67%) remained negative.

Twenty-three patients completed a questionnaire 7 days after receiving their third dose that asked about specific vaccine reactions (Table 2). Fifteen patients reported mild or moderate local reactions, and 1 reported severe arm pain. The most frequent systemic reaction was mild or moderate fatigue in 14 participants; 1 patient reported severe headache, and 1 patient reported severe myalgia. No patient reported fever, and we did not observe any anaphylactoid reactions or neurologic complications. One heart transplant recipient had biopsy-proven, antibody-mediated rejection 7 days after her third dose of vaccine in the setting of acute volume overload. She did not experience an increase in her titer of antibodies against the spike protein, heart function remained normal, and immunosuppressive intensification was not initiated. In addition, no patient reported PCR-confirmed COVID-19 during additional follow-up, although the duration of this follow-up was limited.

Discussion: To our knowledge, this is the first report of patients with solid organ transplants receiving a third dose of vaccine directed against SARS-CoV-2. It is encouraging that antibody titers increased after the third dose in one third of patients who had negative antibody titers and in all patients who had low-positive antibody titers. In addition, the vaccine reactions seem acceptable, given the benefits that these vaccines can confer. Antibody responses, however, appear to vary, and potential risks, such as organ rejection, should be evaluated on an individual basis.

Limitations of this study include a small and heterogeneous convenience sample and the absence of assays for neutralizing antibody, B-cell memory, and T-cell responses.

We believe that these observations support the use of clinical trials to determine whether booster doses to prevent COVID-19 in transplant patients can be incorporated into clinical practice, as they have been for hepatitis B and influenza vaccination (4).

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