RESEARCH LETTER

Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients

In contrast to immunocompetent participants in vaccine trials,[1,2] a low proportion (17%) of solid organ transplant recipients mounted a positive antibody response to the first dose of SARS-CoV-2 messenger RNA (mRNA) vaccines, with those receiving anti-metabolite maintenance immunosuppression less likely to respond.[3] In this study, we assessed antibody response after the second dose.

Methods | Transplant recipients without prior polymerase chain reaction–confirmed COVID-19 were recruited from across the US to participate in this prospective cohort through a digital campaign. Those who completed the 2-dose SARS-CoV-2 mRNA vaccine series between December 16, 2020, and March 13, 2021, were included and followed up through April 13, 2021. As described previously,[3] semiquantitative antispike serologic testing was undertaken with the Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay, positive cutoff of at least 0.8 U/mL, which tests for the receptor-binding domain of the SARS-CoV-2 spike protein,

Table. Demographic and Clinical Characteristics of Study Participants, Stratified by Immune Response to the 2 Doses of SARS-CoV-2 mRNA Vaccine

	No. (%) by postvaccination antibody response			
	Dose 1− Dose 2−	Dose 1− Dose 2+	Dose 1+ Dose 2+	*P* value
No.	301 (46)	259 (39)	98 (15)	
Age category, y[a]				
18-39	46 (41)	35 (31)	32 (28)	.002[b]
40-59	86 (42)	94 (46)	26 (13)	
≥60	169 (50)	129 (38)	40 (12)	
Sex[c]				
Female	170 (45)	152 (40)	58 (15)	.92[d]
Male	124 (46)	103 (39)	40 (15)	
Race[e]				
White	261 (45)	228 (40)	85 (15)	.74[d]
Black or African American	11 (55)	7 (35)	2 (10)	
Asian or Pacific Islander	13 (39)	12 (36)	8 (24)	
Other	10 (48)	8 (38)	3 (14)	
Organ[f]				
Kidney	168 (52)	118 (37)	36 (11)	<.001[d]
Liver	26 (20)	62 (48)	41 (32)	
Heart	42 (43)	45 (46)	10 (10)	
Lung	43 (61)	22 (31)	6 (8)	
Pancreas	4 (80)	1 (20)	0	
Other multiorgan	15 (58)	7 (27)	4 (15)	
Years since transplant[g]				
<3	114 (63)	54 (30)	13 (7)	.001[b]
3-6	69 (50)	53 (39)	15 (11)	
7-11	54 (38)	61 (43)	26 (18)	
≥12	62 (33)	85 (45)	43 (23)	
Maintenance immunosuppression regimen				
Includes antimetabolite[h]	268 (57)	167 (35)	38 (8)	<.001[d]
Does not include antimetabolite[i]	33 (18)	92 (50)	60 (32)	
Vaccine[j]				
mRNA-1273 (Moderna)	124 (40)	116 (38)	67 (22)	<.001[d]
BNT162b2 (Pfizer-BioNTech)	175 (51)	138 (40)	29 (8)	
Enzyme immunossay[k]				
Roche Elecsys	206 (44)	188 (40)	76 (16)	.19
EUROIMMUN	95 (51)	71 (38)	22 (12)	

[a] Missing in 1 (column 3).

[b] Kruskal-Wallis test, treating variables (age and years since transplant) as continuous.

[c] Missing in 11 (7 in column 2, 4 in column 3).

[d] Fisher exact test P value.

[e] Missing in 10 (6 in column 2, 4 in column 3). Race/ethnicity options were defined by the investigators and classified by the participants. Race/ethnicity was assessed to evaluate potential race/ethnicity differences in immune response. "Other" includes American Indian or Alaska Native, Arabic or Middle Eastern, multiracial, or chose not to answer.

[f] Missing in 8 (3 in column 2, 4 in column 3, 1 in column 4).

[g] Missing in 9 (2 in column 2, 6 in column 3, 1 in column 4).

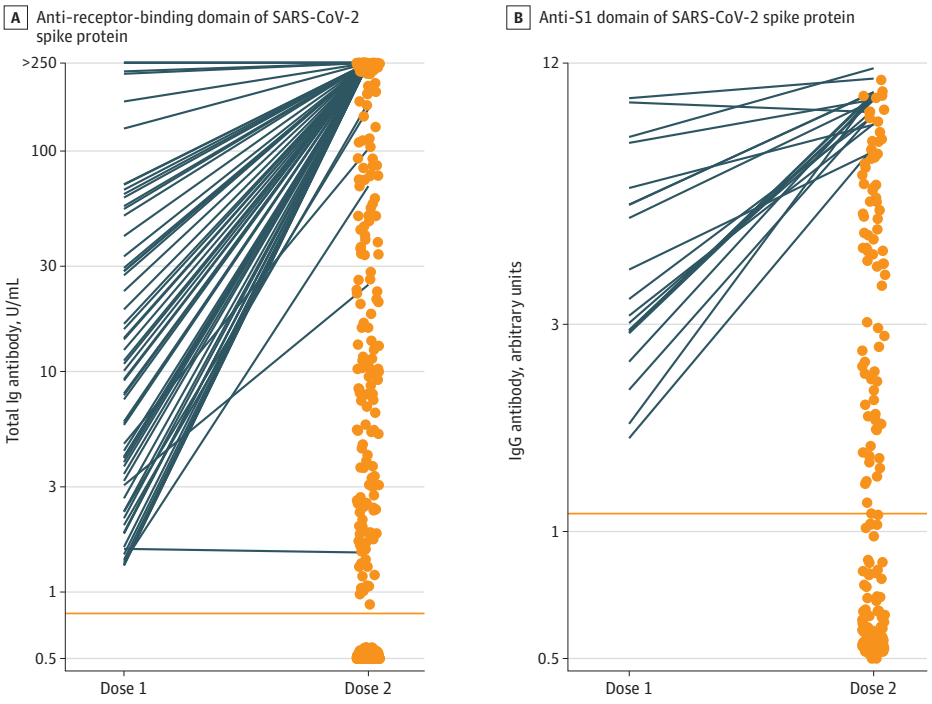
[h] Includes mycophenolate mofetil, mycophenolic acid, or azathioprine.

[i] Includes corticosteroids, tacrolimus, cyclosporine, sirolimus, everolimus, or belatacept, but not antimetabolites.

[j] Missing in 9 (2 in column 2, 5 in column 3, 2 in column 4).

[k] Manufacturer cutoffs; positive ≥0.80 U/mL (Roche); positive ≥1.1 arbitrary units (EUROIMMUN).

Figure. Antibody Levels of Study Participants After 2-Dose Series of SARS-CoV-2 mRNA Vaccine



A, Roche Elecsys anti–SARS-CoV-2 S enzyme immunoassay (n = 470) tests for total antibody against the receptor-binding domain of the SARS-CoV-2 spike protein. The manufacturer cutoff for detectable antibody is 0.80 U/mL (shown as a horizontal orange line). The lowest value reported by the assay is <0.4 U/mL; the highest value is >250. B, EUROIMMUN enzyme immunoassay (n = 188) tests for IgG to the S1 domain of SARS-CoV-2 spike protein. The manufacturer cutoff for detectable antibody is 1.1 arbitrary units (shown as a horizontal red line). The lines beginning at dose 1 reflect the antibody trajectory of participants who had detectable antibody after dose 1. Orange dots represent the antibody levels of participants who had undetectable antibody after dose 1.

or the EUROIMMUN enzyme immunoassay, positive cutoff of at least 1.1 arbitrary units, which tests for the S1 domain of SARS-CoV-2 spike protein, both key measures of humoral immune response.[4,5] This study was approved by the Johns Hopkins institutional review board; participants provided informed consent electronically.

The proportion of patients who developed a positive antibody response was assessed with an exact binomial confidence interval. The Fisher exact test was used to compare categorical variables, such as antimetabolite immunosuppression, and the Kruskal-Wallis test for continuous variables. All tests were 2-sided with α = .05. Analyses were performed using Stata 16.1/Windows.

Results | We studied 658 transplant recipients who received 2 doses of SARS-CoV-2 mRNA vaccine (**Table**); the first-dose results of 396 of these recipients were previously reported.[3] At a median (IQR) of 21 (18-25) days after dose 1, antibody was detectable in 98 participants (15%) (95% CI, 12%-18%). At a median (IQR) of 29 (28-31) days after dose 2, antibody was detectable in 357 participants (54%) (95% CI, 50%-58%).

Overall, of the 658 participants, 98 (15%) had measurable antibody response after dose 1 and dose 2; 301 (46%) had no antibody response after dose 1 or dose 2; and 259 (39%) had no antibody response after dose 1 but subsequent antibody response after dose 2 (**Figure**).

Among all 658 participants, median (IQR) antibody levels after dose 2 were 2.14 U/mL (<0.4-245.8) (Roche) and 1.23 arbitrary units (0.13-6.38) (EUROIMMUN). Among the 357 with detectable antibody after dose 2, median (IQR) antibody levels were 142.1 U/mL (9.44->250) (Roche) and 6.48 arbitrary units (3.75-8.72) (EUROIMMUN) overall; 34.7 U/mL (5.38->250) (Roche) and 5.05 arbitrary units (2.33-7.02) (EUROIMMUN) in the 259 with no antibody response after dose 1; and >250 U/mL (>250->250) (Roche) and 9.23 arbitrary units (8.62-9.73) (EUROIMMUN) in the 98 with antibody response after dose 1.

Among the 473 receiving antimetabolites, 38 participants (8%) had antibody response after dose 1 and dose 2; 268 (57%) had no antibody response after dose 1 or dose 2; and 167 (35%) had no antibody response after dose 1 but subsequent antibody after dose 2. Among the 185 participants not receiving antimetabolites, 60 (32%) had antibody response after dose 1 and dose 2; 33 (18%) had no antibody response after dose 1 or dose 2; and 92 (50%) had no antibody response after dose 1 but subsequent antibody after dose 2.

Discussion | In this study of the humoral response to 2 doses of mRNA SARS-CoV-2 vaccine among solid organ transplant recipients, the majority had detectable antibody responses after the second dose, although participants without a response after dose 1 had generally low antibody levels. Poor humoral response was persistently associated with use of antimetabolite immunosuppression.

Although no threshold has been established for protective immunity, antibody levels were well below that which has been observed in immunocompetent vaccinees.[6]

Limitations of this study include a sample that may lack external validity, lack of an immunocompetent control group, lack of assessment of postvaccination SARS-CoV-2, and lack of exploration of memory B-cell or T-cell responses.

Although this study demonstrates an improvement in antispike antibody responses in transplant recipients after dose 2 compared with dose 1, these data suggest that a substantial proportion of transplant recipients likely remain at risk for COVID-19 after 2 doses of mRNA vaccine. Future studies should address interventions to improve vaccine responses in this population, including additional booster doses or immunosuppression modulation.

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1. Walsh EE, Frenck RW Jr, Falsey AR, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. *N Engl J Med*. 2020;383(25):2439-2450. doi:10.1056/NEJMoa2027906

2. Jackson LA, Anderson EJ, Rouphael NG, et al; mRNA-1273 Study Group. An mRNA vaccine against SARS-CoV-2. *N Engl J Med*. 2020;383(20):1920-1931. doi:10.1056/NEJMoa2022483

3. Boyarsky BJ, Werbel WA, Avery RK, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. *JAMA*. Published online March 15, 2021. doi:10.1001/jama.2021.4385

4. Klein SL, Pekosz A, Park HS, et al. Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population. *J Clin Invest*. 2020;130(11):6141-6150. doi:10.1172/JCI142004

5. Patel EU, Bloch EM, Clarke W, et al. Comparative performance of five commercially available serologic assays to detect antibodies to SARS-CoV-2 and identify individuals with high neutralizing titers. *J Clin Microbiol*. Published online January 21, 2021. doi:10.1128/JCM.02257-20

6. Mueller T. Antibodies against severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) in individuals with and without COVID-19 vaccination: a method comparison of two different commercially available serological assays from the same manufacturer. *Clin Chim Acta*. 2021;518:9-16. doi:10.1016/j.cca.2021.03.007

Concentration of Patient Care Among Buprenorphine-Prescribing Clinicians in the US

In the US, buprenorphine to treat opioid use disorder can be prescribed only by qualified clinicians. Policy initiatives and advocacy, such as efforts to remove the training requirements required for buprenorphine prescribing, have commonly focused on enlarging the pool of clinicians allowed to prescribe buprenorphine[1]; current legislation under consideration in the US Congress would eliminate these requirements.[2] However, many trained buprenorphine prescribers are not actively prescribing[3] or are treating few patients,[4,5] and the overall concentration of patient care among prescribers is not well characterized. We quantified the total amount of buprenorphine care delivered by active prescribers and to what extent that varies across specialties.

Methods | Using IQVIA prescription data,[6] which captures approximately 90% of all prescriptions filled at retail pharmacies in the US, we identified clinicians who prescribed buprenorphine formulations indicated for opioid use disorder at least once between January 2017 and December 2018. We defined an active buprenorphine patient as a patient possessing buprenorphine from a prescription; a patient filling a 30-day prescription on September 15 was defined as an active patient in both September and October. For each prescriber, we calculated 3 outcomes: (1) months actively prescribing, defined as having at least 1 active patient; (2) monthly patient caseload (total number of active patients); and (3) total patient-months of care (sum of all active patient-months across 2017-2018). Prescriber specialty