Letters

RESEARCH LETTER

Immunogenicity of a Single Dose of SARS-CoV-2 Messenger RNA Vaccine in Solid Organ Transplant Recipients

Immunocompromised individuals have been excluded from studies of SARS-CoV-2 messenger RNA (mRNA) vaccines. In such patients, the immune response to vaccination may be blunted. To better understand the immunogenicity of mRNA vaccines in immunocompromised individuals, we quantified the humoral response to the first dose in solid organ transplant recipients.

Methods | Transplant recipients across the US were recruited though social media to participate in this prospective cohort, and those who underwent SARS-CoV-2 vaccination between December 16, 2020, and February 5, 2021, were included. The study was approved by the Johns Hopkins University institutional review board and participants provided informed consent electronically. Participants underwent either at-home blood sampling with the TAPII blood collection device (Seventh Sense Biosystems) or standard venipuncture.

The TAPII samples were tested using an enzyme immunoassay (EUROIMMUN) that tests for antibodies to the S1 domain of the SARS-CoV-2 spike protein.[1] The venipuncture samples were tested using the anti-SARS-CoV-2 S enzyme immunoassay (Roche Elecsys) that tests for antibodies against the receptor-binding domain of the SARS-CoV-2 spike protein. Both tests are semiquantitative, correspond to mRNA vaccine antigens, and are consistently correlated with neutralizing immunity.[2-4] The sensitivity and specificity of the enzyme immunoassays are excellent for detection of the antispike humoral response to SARS-CoV-2 infection (sensitivity of 87.1% and specificity of 98.9% for EUROIMMUN[3] and sensitivity of 84.0% and specificity of 100% for Roche Elecsys[4]) and are analogous to the antispike antibody assays used during immunogenicity assessments in mRNA vaccine clinical trials.

We assessed the proportion of patients who developed a positive antibody response with exact binomial 95% CIs. We evaluated the associations among demographic and clinical characteristics, vaccine type, and positive antibody response using modified Poisson regression with a robust variance estimator. A sensitivity analysis of vaccine type limited to those tested 14 to 21 days after vaccination was performed. All tests were 2-sided with $\alpha = .05$. Analyses were performed using Stata version 16.1 (StataCorp).

Results | There were 436 transplant recipients included in the study (**Table**). None had a prior polymerase chain reaction–confirmed diagnosis of COVID-19. The median age was 55.9 years (interquartile range [IQR], 41.3-67.4 years), 61% were women, and 89% were White transplant recipients; 52% received the BNT162b2 vaccine (Pfizer-BioNTech) and 48% received the mRNA-1273 vaccine (Moderna). The median time since transplant was 6.2 years (IQR, 2.7-12.7 years). The maintenance immunosuppression regimen included tacrolimus (83%), corticosteroids (54%), mycophenolate (66%), azathioprine (9%), sirolimus (4%), and everolimus (2%). At a median of 20 days (IQR, 17-24 days) after the first dose of vaccine, antibody (anti-S1 or anti–receptor-binding domain) was detectable in 76 of 436 participants (17%; 95% CI, 14%-21%).

Transplant recipients receiving anti–metabolite maintenance immunosuppression therapy were less likely to develop an antibody response than those not receiving such immunosuppression therapy (37% vs 63%, respectively; adjusted incidence rate ratio [IRR], 0.22 [95% CI, 0.15-0.34]; $P < .001$) (Table). Older transplant recipients were less likely to develop an antibody response (adjusted IRR, 0.83 [95% CI, 0.73-0.93] per 10 years; $P = .002$). Those who received mRNA-1273 were more likely to develop an antibody response than those receiving BNT162b2 (69% vs 31%, respectively; adjusted IRR, 2.15 [95% CI, 1.29-3.57]; $P = .003$). This association was similar in a sensitivity analysis limited to those tested 14 to 21 days after vaccination (n = 245; adjusted IRR, 2.29 [95% CI, 1.32-3.94]; $P = .003$).

Discussion | In this study of immunogenicity of the first dose of the mRNA SARS-CoV-2 vaccine among solid organ transplant recipients, the majority of participants did not mount appreciable antispike antibody responses. However, younger participants, those not receiving anti–metabolite maintenance immunosuppression, and those who received the mRNA-1273 vaccine were more likely to develop antibody responses. These results contrast with the robust early immunogenicity observed in mRNA vaccine trials, including 100% antispike seroconversion by day 15 following vaccination with mRNA-1273[5] and by day 21 following vaccination with BNT162b2.[6]

Limitations include a convenience sample that may lack generalizability, lack of serial measurements after vaccination, and lack of a concurrent control group without immunosuppression. In addition, these data represent the humoral response to the first dose of a 2-dose series.

These findings of poor antispike antibody responses in organ transplant recipients after the first dose of mRNA vaccines suggest that such patients may remain at higher early risk for COVID-19 despite vaccination. Deeper immunophenotyping of transplant recipients after vaccination, including characterization of memory B-cell and T-cell responses, will be important in determining vaccination strategies as well as immunologic responses after the second dose.

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Table. Demographic and Clinical Characteristics of Study Participants, Stratified by Immune Response to the First Dose of SARS-CoV-2 Messenger RNA Vaccine, and Associations With Developing an Antibody Response (N = 436)

	Antibody, No. (%)					
	Detectable (n = 76)	Undetectable (n = 360)	Bivariable IRR (95% CI)	*P* value	Adjusted multivariable IRR (95% CI)[a]	*P* value
Age group, y						
18-39	30 (39)	69 (19)	0.81 (0.71-0.93)[b]	.003	0.83 (0.73-0.93)	.002
40-59	18 (24)	132 (37)				
≥60	28 (37)	159 (44)				
Sex[c]						
Female	48 (64)	212 (59)	1.12 (0.73-1.73)[d]	.60		
Male	27 (36)	138 (41)				
Race[c,e]						
Non-White[f]	8 (11)	38 (11)	0.99 (0.51-1.94)[g]	.99		
White	67 (89)	312 (89)				
Type of organ transplant[h]						
Kidney	31 (41)	188 (53)	0.68 (0.45-1.04)[i]	.07		
Liver	28 (37)	50 (14)				
Heart	9 (12)	57 (16)				
Lung	4 (5)	45 (13)				
Pancreas	1 (1)	4 (1)				
Other (multiorgan)	2 (3)	12 (3)				
Time since transplant, y[j]						
<3	13 (17)	106 (30)	1.88 (1.21-2.93)[k]	.005	1.45 (0.96-2.20)	.08
3-6	12 (16)	77 (22)				
7-11	19 (25)	82 (23)				
≥12	31 (41)	89 (25)				
Type of regimen						
Includes anti-metabolite maintenance immunosuppression[l]	28 (37)	292 (81)	0.21 (0.14-0.32)[m]	<.001	0.22 (0.15-0.34)	<.001
Does not include anti-metabolite maintenance immunosuppression	48 (63)	68 (19)				
Vaccine[n]						
mRNA-1273 (Moderna)	52 (69)	152 (43)	2.14 (1.24-3.69)[o]	.006	2.15 (1.29-3.57)	.003
BNT162b2 (Pfizer-BioNTech)	23 (31)	200 (57)				
Enzyme immunoassay manufacturer[p]						
Roche Elecsys	64 (84)	266 (74)	1.71 (0.96-3.05)[q]	.07		
EUROIMMUN	12 (16)	94 (26)				

Abbreviation: IRR, incidence rate ratio.

[a] Model adjusted for age, years since transplant, antimetabolite maintenance immunosuppression, days since vaccination, and vaccine type.

[b] Per 10-year increase in age.

[c] Missing data for 11 participants (1 in detectable category and 10 in undetectable category).

[d] Comparison of female vs male.

[e] The options were defined by the investigators and classified by the participants. Race/ethnicity was assessed to evaluate potential race/ethnicity differences in immune response.

[f] Includes Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Arab or Middle Eastern, and multiracial.

[g] Comparison of non-White vs White.

[h] Missing data for 5 participants (1 in detectable category and 4 in undetectable category).

[i] Comparison of kidney transplant recipient vs non-kidney transplant recipient.

[j] Missing data for 7 participants (1 in detectable category and 6 in undetectable category).

[k] Comparison of 6 or more years since transplant vs less than 6 years since transplant. This was used as a cutoff since it was the median time since transplant.

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

[m] Comparison of other maintenance immunosuppression vs anti-metabolite maintenance immunosuppression.

[n] Missing data for 9 participants (1 in detectable category and 8 in undetectable category).

[o] Comparison of mRNA-1273 vs BNT162b2. Also adjusted for number of days between vaccination and antibody testing (median of 21 days for mRNA-1273 and 20 days for BNT162b2).

[p] The antibody-positive cutoffs (determined by the manufacturer) were 0.80 U/mL or greater for Roche Elecsys and 1.1 or greater arbitrary units for EUROIMMUN.

[q] Comparison of Roche Elecsys vs EUROIMMUN.

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Excess Deaths From COVID-19 and Other Causes in the US, March 1, 2020, to January 2, 2021

A study analyzing US mortality in March-July 2020 reported a 20% increase in excess deaths, only partly explained by COVID-19. Surges in excess deaths varied in timing and duration across states and were accompanied by increased mortality from non–COVID-19 causes.[1] This study updates the analysis for the remainder of 2020.

Methods | The Supplement details the methods. A Poisson regression model used mortality data from 2014-2019 to predict US expected deaths in 2020. Observed deaths in weeks ending March 1, 2020, through January 2, 2021, were taken from provisional, unweighted death counts for the District of Columbia and 49 states, excluding North Carolina for insufficient data. Data sources included the National Center for Health Statistics[2-4] and US Census Bureau.[5] Data for 8 geographic regions were grouped into distinctive surge patterns. COVID-19 deaths included all deaths for which COVID-19 was cited as an underlying or contributing cause.

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Supplemental content

Temporal changes in mortality rates from non–COVID-19 causes (eg, Alzheimer disease/dementia, heart disease, diabetes, and 9 other grouped causes; see Supplement) were examined. Data included all deaths in which non–COVID-19 conditions were listed as the underlying cause of death (potentially including deaths for which COVID-19 was a contributing cause). The Joinpoint regression program version 4.8.0.1 (Statistical Research and Applications Branch, National Cancer Institute) was used to specify the weeks (joinpoints) when slopes changed (measured by the annual percentage change [APC]) and their statistical significance (2-sided test, $\alpha = .05$ threshold).

Results | Between March 1, 2020, and January 2, 2021, the US experienced 2 801 439 deaths, 22.9% more than expected, representing 522 368 excess deaths (**Table**). The excess death rate was higher among non-Hispanic Black (208.4 deaths per 100 000) than non-Hispanic White or Hispanic populations (157.0 and 139.8 deaths per 100 000, respectively); these groups accounted for 16.9%, 61.1%, and 16.7% of excess deaths, respectively. The US experienced 4 surge patterns: in New England and the Northeast, excess deaths surged in the spring; in the Southeast and Southwest, in the summer and early winter; in the Plains, Rocky Mountains, and far West,