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LETTER TO THE EDITOR

Improved humoral immunogenicity with mRNA-1273 versus BNT162b2 as third vaccine dose among solid organ transplant recipients seronegative after two BNT162b2 doses

1 | INTRODUCTION

Fewer than 45% of solid organ transplant recipients (SOTRs) mount a detectable antispike antibody level after two doses of mRNA SARS-CoV-2 vaccination (D2).[1] Various vaccination strategies, including mixing platforms, have been proposed, but there is no consensus on the optimal vaccination sequence to improve immunogenicity.[2,3] Although using similar technology, the mRNA-1273 vaccine has been associated with higher peak antibody responses than the use of BNT162b2 in immunosuppressed populations, potentially related to a higher vaccine antigen dose.[3,4] We therefore studied whether the use of mRNA-1273 versus BNT162b2 as a third primary vaccine dose (D3) might generate a more robust antibody response in SOTR who remained seronegative after two doses of BNT162b2.

2 | METHODS

From our national observational study, approved by the Johns Hopkins Institutional Review Board (IRB00248540),[4] we included adult SOTRs who tested seronegative after two doses of BNT162b2 and received either a D3-BNT162b2 or D3-mRNA-1273. Seronegativity was defined as an anti-receptor-binding domain (anti-RBD) level of < .8 U/ml per Roche Elecsys Anti-SARS-CoV-2 S enzyme immunoassay. SOTRs using belatacept or with any self-reported SARS-CoV-2 infection were excluded. The proportion of those who seroconverted at 1 month post-D3 (negative to positive) was compared between D3 groups using Fisher's exact testing. The proportion of those with neutralizing responses at 1 month post-D3 was analyzed using multivariable Poisson regression with robust standard error, adjusting for mycophenolate use, age, and time since transplantation. Neutralizing response was defined as an antibody level of ≥250 U/ml, which has previously been reported to be associated with plasma neutralizing capacity against the ancestral SARS-CoV-2 variant in SOTRs.[5] Participants provided electronic informed consent.

3 | RESULTS

Among 97 SOTRs who tested seronegative after two doses of BNT162b2, 14 received mRNA-1273 and 83 received BNT162b2 for their third SARS-CoV-2 vaccine; 13/14 received D3-mRNA-1273 before FDA authorization of the half-dose booster around late October 2021. Demographic and immunosuppressive characteristics were similar between D3-mRNA-1273 and D3-BNT162b2 groups, as was the interval between D2 and D3, and the time to antibody sampling post-D3 (Table 1). There were fewer lungs ($n = 1$ vs. $n = 11$, $P = < .99$) or liver ($n = 0$ vs. $n = 13$, $P = .21$) recipients in the D3-mRNA-1273 group than the D3-BNT162b2 group, though not statistically significantly different.

The proportion of SOTRs with persistent seronegativity post-D3 was similar between D3-mRNA-1273 and D3-BNT162b2 (43% vs. 48%, $P = .78$). The median post-D3 antibody was higher, though not statistically significantly different, in the D3-mRNA-1273 versus D3-BNT162b2 group (234 [< .8–1144] vs. 2 [< .8–126] U/ml, $P = .14$) (Figure 1). However, the proportion of those with neutralizing responses post-D3 was statistically significantly higher in the D3-mRNA-1273 versus D3-BNT162b2 group (50% vs. 19%, $P = .02$). After adjusting for demographic and transplant characteristics, the D3-mRNA-1273 group had a 2.71-fold higher rate of developing neutralizing responses post-D3 (incidence rate ratio [95% CI] 2.71 [1.34–5.48], $P = .006$).

4 | DISCUSSION

In SOTRs who failed to generate an antibody response to two doses of BNT162b2, seroconversion was similar, yet higher, following a third dose of mRNA-1273 versus BNT162b2 vaccine, and neutralizing titers were more common following mRNA-1273. As has been hypothesized, this may be due to higher mRNA dose in mRNA-1273 or other aspects of vaccine formulation.[2,4] Although not a randomized trial,

TABLE 1 Clinical and transplant characteristics of solid organ transplant recipients who tested seronegative after receiving a two-dose BNT162b2 series, categorized by type of third mRNA SARS-CoV-2 vaccine received

	D3-mRNA1273 $n = 14$	D3-BNT162b2 $n = 83$	*P* value
Age at time of vaccination, median (IQR)	63 (58–68)	65 (50–70)	.98
Female, *n* (%)	9 (75)	47 (59)	.36
White, *n* (%)	11 (79)	72 (87)	>.99
Allograft, *n* (%)			.15
Kidney	12 (86)	48 (58)	
Liver	0	12 (14)	
Lung	0	11 (13)	
Heart	1 (7)	9 (11)	
kidney and liver	0	1 (1)	
kidney and pancreas	0	1 (1)	
liver and heart	0	1 (1)	
heart and lung	1 (7)	0 (0)	
Years since transplant, median (IQR)	9 (3–15)	4 (2–10)	.08
Peri-vaccination Immunosuppression Regimen[a], *n* (%)			
Calcineurin inhibitor (CNI)	10 (71)	72 (87)	.14
Antimetabolite	13 (93)	71 (86)	.68
Mycophenolate	12 (86)	70 (84)	.90
Steroids	11 (79)	47 (57)	.12
mTOR inhibitor	3 (21)	13 (16)	.59
Triple IS: steroids, CNI, antimetabolite	7 (50)	37 (45)	.71
Days between D2 and D3 vaccine, median (IQR)	146 (107, 177)	172 (145, 188)	.08
Days between D3 and post-D3 titer collection, median (IQR)	31 (28, 31)	29 (22, 32)	.41
Anti-RBD serostatus 1 month post-D3, *n* (%)			.78
Seronegative	6 (43)	40 (48)	
Seropositive	8 (57)	43 (52)	
Neutralizing[b] response 1 month post-D3, *n* (%)			.02
No	7 (50)	67 (81)	
Yes	7 (50)	16 (19)	

Categorical and continuous outcomes were analyzed using Fisher's exact and Wilcoxon rank-sum test, respectively.

[a]Listed maintenance immunosuppressions are not mutually exclusive.

[b]Neutralizing response, defined as anti-RBD ≥250 U/ml, has been reported to be associated with neutralizing activity against ancestral strain of SARS-CoV-2.[5]

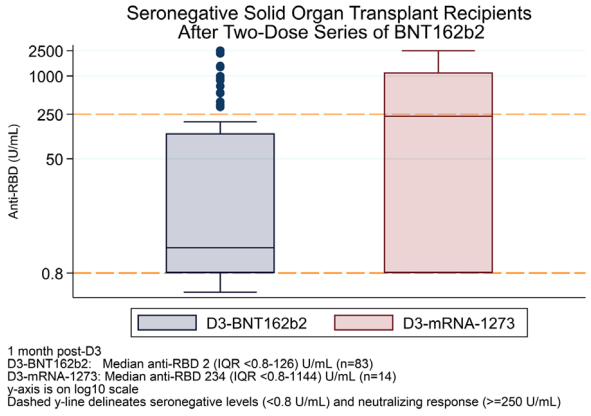

FIGURE 1 Box and whisker plot of anti-RBD antibody response to a D3-BNT162b2 or D3-mRNA-1273 among solid organ transplant recipients who tested seronegative after completing a two-dose series of BNT162b2 SARS-CoV-2 vaccination

characteristics of the two vaccine groups were similar and the impact of mRNA-1273 persisted after adjustment of key clinical factors. This finding, coupled with emerging data indicating that mixing mRNA vaccine platforms could improve immunogenicity due to differences in antibody effector functions,[2] suggests potential benefit of utilizing mRNA-1273 following a two-dose BNT162b2 prime in low responders.

Limitations include the retrospective study design, small sample size, lack of nucleocapsid tests for subclinical infections, and formal neutralization testing against variants of concern. Future directions include dedicated randomized trials comparing humoral and cellular responses after mixed vaccine sequences, as well as studies on vaccine efficacy to assess for differential risk of SARS-CoV-2 breakthrough.

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DISCLOSURES

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CONFLICTS OF INTEREST

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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