Received: 10 June 2022 | Revised: 30 June 2022 | Accepted: 7 July 2022

DOI: 10.1111/ctr.14772

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

LETTER TO THE EDITOR

Immunogenicity of Ad26.COV2.S prime and two subsequent doses of mRNA SARS-CoV-2 vaccines in solid organ transplant recipients: A case series

Heterologous vaccination has been explored in small populations of solid organ transplant recipients (SOTRs),[1-4] yet 38% of participants had persistently suboptimal response indicating potential role for further vaccine doses.[1] The US CDC currently recommends immunocompromised adults who received an Ad26.COV2.S prime to receive one additional dose of SARS-CoV-2 mRNA vaccine, either BNT162b2 or mRNA-1273, followed by two mRNA vaccine boosters, although the efficacy of this strategy in immunocompromised persons is not known. We evaluated serial antispike antibody responses and reactogenicity among SOTRs who received two doses of mRNA vaccine following Ad26.COV2.S prime.

Within our previously described observational cohort,[2,3] 11 SOTRs reported an Ad26.COV2.S-prime (D1) followed by two doses of BNT162b2 ($n = 5$) or mRNA-1273 ($n = 6$). SOTRs who reported pre-D1 SARS-CoV-2 infection were excluded. The highest antibody results collected after doses 2 (D2) and 3 (D3) on the Roche Elecsys Anti-SARS-CoV-2 enzyme immunoassay (EIA) (antireceptor binding domain [RBD], negative < 0.8 U/ml) or EUROIMMUN EIA (anti-S1, negative < 1.1 AU) were compared. High-positive (anti-RBD ≥250 U/ml or anti-S1 ≥4 AU) levels were defined according to reported association with neutralization of wild-type virus.[4] Post-D3 questionnaires on adverse events and side effects were collected. The study was approved by the Johns Hopkins IRB #00248540. Participants provided electronic informed consent.

The median (interquartile range [IQR]) age was 58 (40, 67) years, five were female, seven were white, and nine were kidney-only transplant recipients. The median (IQR) time since transplant was 13 (5, 18) years. Peri-vaccination immunosuppressive regimens included calcineurin inhibitors ($n = 7$), antimetabolites ($n = 11$), steroids ($n = 5$), and mTOR inhibitors ($n = 2$); three reported triple immunosuppressant medications, defined as calcineurin inhibitor, antimetabolite, and steroid use.

The median (IQR) time between D1 and D2 was 164 (75, 224) days, and between D2 and D3 was 28 (24, 80) days. Antispike seropositivity rates increased from 40%, 73%, to 91% after D1, D2, and D3, respectively. Of the three SOTRs that were seronegative post-D2, two converted to seropositive post-D3 (Table 1). High-positive titers were present in all 10 post-D3 sero-responders. More mRNA-1273-vaccinated than BNT162b2-vaccinated recipients had high-positive levels post-D2 (4/6 [67%] vs. 2/5 [40%]) and post-D3 (6/6 [100%] vs. 4/5 [80%]). The one persistently seronegative participant received BNT162b2 for D2 and D3. This participant was a 30-year-old female kidney-only transplant recipient who was 5 years post-transplant surgery and reported mycophenolate and tacrolimus as their only immunosuppression medications. The participant did not report any breakthrough infection.

Eight SOTRs completed reactogenicity surveys, primarily characterized by mild or moderate local pain ($n = 6$), fatigue ($n = 4$), and/or headache ($n = 4$). No serious vaccine-associated reactions, including myocarditis, anaphylaxis, or vaccine-associated thrombosis, nor diagnosis of rejection, autoimmune or neurologic conditions, or need for hospitalization post-D3 were reported.

One participant reported a home test-confirmed breakthrough SARS-CoV-2 infection 47 days after D3 (mRNA-1273). This patient was a 40-year-old female liver-only transplant recipient who was 0.4 years post-transplant surgery when she reported receiving Ad26.COV2.S. This participant reported triple immunosuppression therapy during the peri-vaccination period. The anti-RBD was 6.5 U/ml 20 days post-D2. No pre-infection sample was collected after D3, but their anti-RBD was >2500 U/ml 29 days post-breakthrough.

The breakthrough case occurred in the second week of the US Omicron BA.1 wave, during which the Delta variant was co-circulating and represented the predominant variant per CDC monitoring.[6] Symptoms included 7 days of mild cough and pharyngitis, during which the monoclonal antibody bamlanivimab/etesevimab was administered (on day 2). No oral antiviral medications were used.

Despite suboptimal antibody response to the Ad26.COV2.S prime, two subsequent mRNA vaccines increased antibody titers to high levels for the majority of participants, with acceptable side effects. This series suggests that a heterologous vaccine regimen may be a reasonable option for SOTRs, though lack of sero-response, despite two mRNA boosters, suggests that some recipients may remain at risk for SARS-CoV-2 infection. Comparison of the humoral and cellular responses to three-dose heterologous versus homologous vaccination is needed.

TABLE 1 SOTRs who received Ad.26.COV2.S and subsequent dose 2 (D2) and 3 (D3) mRNA SARS-CoV-2 vaccinations

Age[a] sex allograft	Years since transplant	IS regimen	D2 and D3	Days between D1–D2	Days between D2–D3	Highest post-D1 titers	Highest post-D2 titers	Highest post-D3 titers	Days between D3 and post-D3 titers
60 M kidney and liver	3	MMF sirolimus	BNT162b2	133	21	**Neg**[b]	1324 R	>2500 R	122
30F kidney	5	MMF tacrolimus	BNT162b2	69	21	**0.4 R**	**0.1 E**	<**0.8 R**	27
40 F kidney	13	Azathioprine tacrolimus	BNT162b2	169	80	283 R	>2500 R	>2500 R	41
40 F kidney	8	MPA tacrolimus steroid	BNT162b2	95	24	<**0.8 R**	47 R	531 R	29
70 M kidney	18	MPA belatacept steroid	BNT162b2	243	48	–	<**0.8 R**	7.82 E	111
40 F liver	0.4	MMF tacrolimus steroid	mRNA-1273	75	166	<**0.8 R**	6.5 R	>2500 R[c]	76
60 M kidney	15	MMF tacrolimus	mRNA-1273	73	28	<**0.8 R**	**0.97 E**	287 R	31
70 M kidney	45	MMF steroid	mRNA-1273	259	27	<**0.8 R**	1273 R	2021 R	19
70 M kidney	19	MMF tacrolimus	mRNA-1273	172	30	4.9 R	>2500 R	>2500 R	13
40 F kidney	9	Azathioprine sirolimus	mRNA-1273	164	28	115 R	>2500 R	>2500 R	181
60 M kidney	16	MMF steroid	mRNA-1273	224	121	56 R	>2500 R	19324	34

Highest antibody titer after each vaccine dose is reported with respective assay. Negative antibody levels are according to manufacturer cutoff and in bold. Negative sero-response cutoff: anti-RBD < 0.8 U/ml or anti-S1 < 1.1 AU.

Abbreviations: E, EUROIMMUN anti-S1 EIA (units: AU); F, female; IS, peri-vaccination immunosuppression; M, male; MMF, mycophenolate mofetil; MPA, mycophenolic acid; R, Roche anti-RBD EIA (units: U/ml).

[a]Age rounded to the nearest decade to protect health information.

[b]Self-reported assay result (titer not available).

[c]Post SARS-CoV-2 breakthrough infection level 29 days after SARS-CoV-2 test confirmation.

ACKNOWLEDGMENTS

The authors thank the participants of the Johns Hopkins COVID-19 Transplant Vaccine Study, without whom this research could not be possible. They also thank the members of the study team, including Brian J. Boyarsky MD, PhD; Nicole F Hernandez, BS; Alexa Jefferis, BS; Ananda Thomas, BA; Faith Obilo; Letitia Thomas; Rivka Abedon; Chunyi Xia; Kim Hall; Mary Sears; Alex; Jonathan Susilo. They also thank Andrew H. Karaba, MD, PhD; and Ms. Yolanda Eby for project support and guidance. This research was made possible with the generous support of the Ben-Dov family and the Trokhan Patterson family. This work was supported by Grants T32DK007732 (Dr. Chang), 5T32DK007713 (Dr. Alejo), K01DK101677 (Dr. Massie), K01DK114388 (Dr. Levan), and K23DK115908 (Dr. Garonzik-Wang) from the National Institute of Diabetes and Digestive and Kidney Diseases; The ASTS Fryer Resident Scientist Award (Dr. Mitchell); K24AI144954 (Dr. Segev), K23AI157893 and 3U01AI138897-04S1 (Dr. Werbel) from the National Institute of Allergy and Infectious Disease.

CONFLICT OF INTEREST

DLS has the following financial disclosures: consulting and/or speaking honoraria from Sanofi, Novartis, CSL Behring, Jazz Pharmaceuticals, Veloxis, Mallinckrodt, Thermo Fisher Scientific, Regeneron, Astra Zeneca, Caredx, Transmedics, Kamada, MediGo, Takeda/Shire, and Bridge to Life. RKA has study/grant support from Aicuris, Astellas, Chimerix, Merck, Oxford Immunotec, Qiagen, Regeneron, Takeda/Shire, and Vir/GSK and is an Associate Reviewer for Transplantation. MLL is the Social Media Editor for Transplantation and is a consultant for Takeda/Shire and Patients Like Me. The remaining authors of this manuscript have no conflicts of interest to disclose.

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DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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