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BRIEF COMMUNICATION

WILEY

Responsiveness to second and third dose of mRNA COVID-19 vaccination in adolescent and young adult heart transplant recipients

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Abstract

Background: Third-dose mRNA COVID-19 vaccine is currently recommended in the United States for SOT recipients based in part on data showing diminished immune response, including Ab production, after a two-dose regimen. Data on vaccine response in adolescent and young adult SOT recipients are limited, including no data reported on third-dose responsiveness.

Methods: Results of serologic testing in a convenience sample of 28 vaccinated adolescent and young adult HT recipients at a single institution were collected from the medical record and summarized.

Results: At a median of 98.5 days (IQR 59–150) after second dose, 17 (61%) had an Ab response. Among 12 who had serology before and after third-dose vaccination, four of seven who were negative prior to third dose became positive at a median of 34 days (IQR 31–39.5) following third dose. No myocarditis, acute rejection, graft dysfunction, graft loss, or deaths were observed.

Conclusions: These findings support recommendations for the routine administration of three doses of mRNA vaccines in adolescent and young adult HT recipients and show a potential subpopulation in whom the fourth dose should be contemplated.

KEYWORDS
COVID-19 mRNA vaccine, heart transplant, pediatric, SARS-CoV-2

1 | INTRODUCTION

A third dose of the COVID-19 mRNA vaccine is recommended in the United States for SOT recipients based in part on data showing poor immune response, including Ab production, after a two-dose regimen.[1-6] Presently, data on responsiveness to COVID-19 mRNA vaccination in adolescent SOT recipients consist of a handful of reports showing diminished Ab production after a two-dose regimen among predominantly liver and renal transplant recipients (73%) relative to healthy adolescents.[7-10] We sought to characterize Ab production in response to COVID-19 mRNA vaccination, including response to third-dose vaccination, in a convenience sample of adolescent and young adult HT recipients.

Abbreviations: Ab, antibody; BC, Beckmann Coulter; equiv, equivocal; F, female; HT, heart transplant; ISx, immunosuppression; IQR, immunosuppression; M, male; mmf, mycophenolate mofetil; Mo, Moderna; PB, pfizer/BioNTech; pred, prednisone/prednisolone; Pt, patient; quant, quantitative; R, Roche; sirol, sirolimus; SOT, solid organ transplant; tac, tacrolimus.

2 | METHODS

This study was approved by the University of Pittsburgh Human Research Protections Office (PRO19050115) and no informed consent was required. All clinical data were abstracted from clinical care records. Ab data were abstracted from the electronic medical record after provider prescribed testing or given to the care team by Pt/parents for consideration in care decisions when obtained by a nontransplant team provider. We recommended serologic assessment around third-dose vaccination for age-eligible recipients to guide decision-making about timing of vaccination based on the lack of data on COVID-19 vaccine responsiveness in this population, the higher incidence of COVID-19 mRNA vaccine-associated myocarditis in adolescents and young adults, and the age-related lower risk of severe COVID-19. Only some recipients obtained this recommended testing. Ab determinations were made using commercially available, semiquantitative SARS-CoV-2 IgG spike protein assays (R Elecsys Anti-SARS-CoV-2 S, Siemens SARS-CoV-2 IgG, and BC Access SARS-CoV-2 IgG Ab test).[11-13]

Symptoms after vaccine doses were provided by free response from the Pt/parent to a specific inquiry from the transplant nurse coordinator or physician provider during clinical interactions. Symptoms were not routinely assessed after each vaccine dose nor, when assessed, were they assessed at a specific time after vaccination.

Data were collected through October 31, 2021. Data are presented as median (IQR) or count (%). Comparisons were tested using Mann–Whitney *U* or Fisher's exact test, as appropriate. Univariable logistic regression was used to assess for relationship between the presence of Ab after second vaccine dose and age at HT, time from HT to vaccination, and time from second dose to Ab assessment. All statistical comparisons were performed using StataSE 14.0 (StataCorp) and significance assessed by two-sided alpha <0.05.

3 | RESULTS

We identified 59 pediatric and young adult HT recipients (31% F) who received at least two doses of an mRNA COVID-19 vaccine. Median age at HT was 5.9 years (IQR 0.6–14.0), median age at first-dose vaccination was 17.9 years (IQR 15.2–22.1), and time from HT to first dose was 10.8 years (IQR 5.7–15.9). Of these, 28 individuals (48%) had serologic testing following second-dose vaccination (Table 1). There was no difference in demographics between those with or without serology except that fewer who received the Mo vaccine had serology obtained (Mo: 3/15 (20%) vs. PB: 25/44 (57%); $p = .027$). At a median of 98.5 days (IQR 59–150) after second dose, 17 (61%) had an Ab response. None had a confirmed or suspected SARS-CoV-2 infection throughout the observation period. There were no associations of age at HT (OR 1.1, $p = .26$), time from HT to vaccination (OR 0.93, $p = .24$), or time from second vaccine dose (OR 1.01, $p = .25$) to Ab presence/absence.

Maintenance immunosuppressive medications at the time of first-dose vaccination among the 28 recipients with serologic assessment following second-dose vaccination were tac and mycophenolic acid ($n = 15$, 54%); sirol monotherapy ($n = 3$, 11%); tac monotherapy ($n = 2$, 7%); sirol and mycophenolic acid ($n = 2$, 7%); sirol, mycophenolic acid, and prednisone ($n = 2$, 7%); tac, mycophenolic acid, and

TABLE 1 Characteristics of and Ab response in adolescent and young adult HT recipients who received two doses of mRNA COVID-19 vaccine

	All with post-second dose serology ($n = 28$)	Seropositive ($n = 17$)	Seronegative ($n = 11$)	*p*-value*
Age at HT (years)	5.75 (1.15–11)	5.8 (4–12.1)	1.4 (0.3–9.9)	.23
F sex	10 (36%)	7 (41%)	3 (27%)	.69
Age at first dose (years)	16.5 (14.4–19.1)	16.1 (14–17.6)	17.2 (14.7–20.2)	.72
Time from HT to first dose (years)	10.25 (5.3–16.4)	7.5 (4.8–12.2)	15.0 (5.9–19.1)	.29
mRNA vaccination				.99
Mo	3 (11%)	2 (12%)	1 (9%)	
PB	25 (89%)	15 (88%)	10 (91%)	
Time from first to second dose (days)	21 (21–23.5)	21 (21–22)	21 (21–24)	.6
Seropositive after second dose	17 (61%)			
Time from second dose to serology (days)	98.5 (59–150)	105 (81–148)	85 (28–152)	.3
Assay				.47
R	19 (68%)	13 (77%)	6 (55%)	
BC	8 (29%)	4 (24%)	4 (36%)	
Siemens	1 (4%)	0	1 (9%)	
R semiquantitative result (U/ml)	26 (0.5–628.1)	476.3 (26–1116)	0.4 (0.3–0.5)	<.001
BC semiquantitative result (index)	0.89 (0.6–4.0)	4.0 (1–9.7)	0.6 (0.2–0.8)	

*Seropositive versus seronegative.

prednisone (n = 1, 4%); tac and azathioprine (n = 1, 4%); tac and sirol (n = 1, 4%); and sirol and prednisone (n = 1, 4%). Median 12-h tac and 24-h sirol trough levels around the first-dose vaccination were 5.5 mg/dl (IQR 4.3–6.4) and 6.5 mg/dl (IQR 6.0–7.4), respectively. For those on mycophenolic acid (n = 20, 71%) and/or pred (n = 4, 14%), median daily doses were 20.8 mg/kg (IQR 14.3–31.1) and 0.04 mg/kg (IQR 0.03–0.07), respectively. There was a trend toward lower Ab responsiveness for those on an antimetabolite versus not (52% vs. 86%, p = .19).

Twelve individuals who had serologic assessment after second-dose vaccination received a third-dose vaccination of the same manufacturer and had serologic assessment after the third dose (Table 2). Time from second- to third-dose vaccination was a median of 97.5 days (IQR 79–137). Seven (58%) individuals in this group had no Ab response after second-dose vaccination. At a median of 34 days (IQR 31–39.5) after third-dose vaccination, four of these seven (57%) had an Ab response and one had an equiv response (Table 3). Of the two who were negative after third dose, one was just over 3 months from HT at the time of his first dose and received his third dose just after 8 months from HT. The other was transplanted before 6 weeks of age and has a history of post-transplant lymphoproliferative disorder (treated successfully with chemotherapy 4 years prior) and has since been maintained on sirol monotherapy with no history of acute rejection at >15 years from HT.

In a convenience sampling of symptoms occurring after each vaccine dose among all vaccine recipients, most recipients did not report any symptoms after their first vaccine dose (n = 33, 56%). The most common symptoms after the first dose were sore arm (n = 15, 25%), fatigue (n = 7, 12%), headache (n = 33, 5%), and fever/feverish, dyspnea, anorexia/gastrointestinal upset, site pain, and nausea (each n = 1, 2%). After second and third doses, the proportion with no symptoms decreased to 44% (n = 26) and 13% (n = 4), respectively, while sore arm (n = 16, 27%; n = 7, 22%) and fatigue (n = 10, 17%; n = 6, 19%) were most prevalent. In one F HT recipient, chest pain/tightness was reported within 6 h of her second dose of the PB vaccine. She had a reassuring examination, stable right ventricular conduction delay pattern without ST segment abnormalities on ECG, normal chest radiograph, and normal serum troponin and B-type natriuretic peptide level. No other safety concerns were identified, including no acute rejection, graft dysfunction, graft loss, or death over a median of 207 days (IQR 169–244) from first vaccine dose.

4 | DISCUSSION

In this single-center analysis, 61% of adolescent and young adult HT recipients had detectable SARS-CoV-2 spike protein Ab at a median of just over 3 months from second-dose vaccination. This is far below

TABLE 2 Characteristics of and Ab response among adolescent and young adult HT recipients who received three doses of mRNA COVID-19 vaccine

	All (n = 12)	Positive after third dose (n = 9)	Negative/equiv after third dose (n = 3)
Age at HT (years)	7.9 (4.5–11.0)	6.3 (5.9–9.9)	0.1, 0.9, 16.9
F sex	5 (42%)	4 (44%)	1 (33%)
Age at first dose (years)	15.9 (14.6–17.4)	15.8 (14–16.9)	15.1, 20.2, 17.2
Time from HT to first dose (years)	8.5 (5.4–13.9)	7.1 (5.9–10.9)	15, 19.3, 0.3
Time from first to second dose (days)	21 (21–23)	21 (21–22)	21, 21, 27
Time from second dose to serology (days)	83 (39.5–125.5)	81 (50–92)	29, 129, 134
Seronegative after second dose	7 (58%)	4 (44%)	3 (100%)
Time from second to third dose (days)	97.5 (79–137)	87 (31–114)	63, 136, 138
Time from serology after second dose to third dose (days)	14.5 (3–32)	22 (2–32)	4, 7, 34
Time from third dose to serology (days)	34 (31–39.5)	34 (30–37)	32, 39, 40
mRNA COVID-19 vaccine			
Mo	1 (8%)	1 (11%)	0
PB	11 (92%)	8 (89%)	3 (100%)
Assay			
R Elecsys	10 (83%)	8 (89%)	2 (66%)
BC	2 (17%)	1 (11%)	1 (33%)
R semiquantitative result (U/ml)[a]	1921 (51.2–>2500)	2252.5 (1410.2–>2500)	<0.4, <0.4
BC semiquantitative result (index)	0.89, 2.07	2.07	0.89

Note: Data reported as count (%), median (IQR) when $n \geq 4$, or raw data separated by commas when $n < 4$.

[a]Because results may be >2500 U/ml, medians reported may be greater than reported.

TABLE 3 Characteristics and response to the third dose of COVID-19 mRNA vaccine among adolescent and young adult HT recipients without Ab production following second dose

Pt	Vaccine	Sex	Age at HT (years)	Age at dose 1 (years)	HT to dose 1 (years)	ISx at dose 1	Dose 2 to dose 3 (days)	Serotesting after dose 2				Serotesting after dose 3			
								Days after dose 2	Days before dose 3	Serostatus	Quant Ab[a]	Assay	Days after dose 3	Serostatus	QuantAb[a]	Assay
1	PB	M	16.9	17.2	0.3	tac-mmf	138	134	4	neg	0.78	BC	39	neg	<0.4	R
2	PB	F	0.1	15.1	15	sirol	63	29	34	neg	<0.4	R	40	neg	<0.4	R
3	PB	M	0.9	20.2	19.3	sirol-mmf-pred	136	129	7	neg	0.08	BC	32	equiv	0.89	BC
4	Mo	M	5.9	21.7	15.9	tac-mmf	175	175	0	neg	0.35	BC	28	**pos**	2.07	BC
5	PB	M	0.3	13.1	12.8	sirol-mmf-pred	87	85	2	neg	0.5	R	28	**pos**	51.2	R
6	PB	M	9.9	15.8	5.9	tac-mmf	30	24	6	neg	0.5	R	37	**pos**	982.4	R
7	PB	M	6.3	12.4	6.1	tac-mmf-pred	81	28	53	neg	0.6	R	34	**pos**	>2500	R

[a]Units are U/ml for R and index for BC.

the >98% responsiveness seen in healthy children and adolescents in response to the mRNA vaccines,[14,15] but similar to data reported among adult[1] and adolescent SOT recipients[7-10] with Ab response after two doses of mRNA COVID-19 vaccine. Encouragingly, we observed Ab production after third mRNA COVID-19 vaccine dose among four of seven (57%) adolescent and young adult HT recipients who were negative after their second dose. This compares favorably to the recently reported 44% of 59 adult SOT recipients who converted from negative to positive after a third PB COVID-19 vaccine dose.[16] Although we found no significant difference in response to second-dose vaccination between those taking and not taking an antimetabolite, this may reflect limited statistical power given our small sample size rather than a true lack of association as has been observed in prior studies.[1,7,8] Our findings are noteworthy because they provide additional data on Ab production after second dose, data on ISx regimen, dosing, and trough levels, and novel third-dose response data in adolescent and young adult transplant recipients.

Current United States Centers for Disease Control and Prevention guidance is for SOT recipients ages 12 and older to receive a fourth (booster) vaccine dose at ≥5 months after completion of a three-dose primary vaccination series.[17] Our data show that at least some adolescent HT recipients will remain negative after a three-dose series. Future recommendations for this age group will need to consider this finding, clinical outcomes of this group, and future developments in the pandemic.

Limitations of our study include the small sample size, free response data collection regarding side effects, and heterogeneity of ISx regimens, timing of Ab assessments relative to vaccine doses, and Ab assessment assays. Specifically regarding vaccine side effect reporting, our methodology prohibits direct comparison to data reported from other studies that was collected in a prospective, standardized manner. Also, there were individuals in our care who were vaccinated but did not have Ab assessments. However, we did not find any relationships between Ab presence/absence after second dose and age at HT, time from HT to vaccination, or time from second vaccine dose to assessment. Also, while we do not believe any of the Pts in this report had infection with SARS-CoV-2 (all data were collected well before the intensive wave of infections in the United States from the Omicron variant, and families were queried on known exposures), we cannot rule out asymptomatic or mildly symptomatic SARS-CoV-2 infection before or during the observation period as anti-nucleocapsid Ab was not assessed. Accordingly, such infections would overestimate the vaccine responsiveness we observed. It is also important to acknowledge that Ab presence is only one marker of vaccine responsiveness and cannot be used to determine immunity or susceptibility to SARS-CoV-2 infection. Results of serologic assessment after vaccination in nonimmunocompromised individuals using the same assays may have provided additional perspective on our findings, though in healthy children and adolescents, Ab responsiveness to the PB vaccine has been generally excellent.[14,15]

In summary, we observed SARS-CoV-2 spike protein Ab production after the second dose of mRNA vaccination in adolescents and young adult HT recipients is inferior to age-matched peers, but akin

to what has been reported in similar-sized cohorts of adolescent SOT, mostly liver and renal, SOT recipients as well as a larger cohort of older adult SOT recipients. Third-dose vaccination prompted Ab production among seronegative recipients, though some still remain negative after third-dose vaccination, indicative of a subpopulation in whom the fourth dose should be contemplated. We observed no serious adverse events associated with mRNA vaccination. These findings support recommendations for routine administration of three doses of mRNA vaccines in adolescent and young adult HT recipients.

CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Brian Feingold conceptualized the study, analyzed the data, drafted the manuscript, and critically revised the manuscript. Pamela Berman, Allison Huston, Brenda Stinner, and Allison Moninger collected data and critically revised the manuscript. Shawn C. West, Kirsten Rose-Felker, Matthew D. Zinn, Susan A. Miller, and Marian G. Michaels contributed to the study design, data collection, and critical revision of the manuscript.

DATA AVAILABILITY STATEMENT

Data available on request, contingent on the authors' institutional policies governing such conveyance due to privacy/ethical restrictions.

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