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Authors

Crane, Clarkson
Phebus, Erin
Ingulli, Elizabeth

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BRIEF REPORT

Antibody response to 2- and 3-dose SARS-CoV-2 mRNA vaccination in pediatric and adolescent kidney transplant recipients

Clarkson Crane[1] · Erin Phebus[2] · Elizabeth Ingulli[1]

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Abstract

Background Additional "booster" doses of mRNA SARS-CoV-2 vaccines have become standard of care for immunosuppressed patients, including kidney transplant recipients (KTR). While these additional doses have been shown to be efficacious in the adult KTR population, there is paucity of data for pediatric and adolescent KTR.

Methods We conducted a retrospective single-center observational study to determine the proportion of pediatric and adolescent KTR who seroconverted following two- and three-dose regimens of an mRNA SARS-CoV-2 vaccine series.

Results Forty-three pediatric and adolescent KTR at our center received at least two doses of an mRNA SARS-CoV-2 vaccine. Seroconversion was noted in 56% of those who received a 2-dose series and increased to 85% in those who received a third dose. In the 16 patients who did not seroconvert after a two-dose series, 12 (75%) seroconverted following the third dose. No serious adverse effects of immunization were noted.

Conclusions Our results demonstrate that additional SARS-CoV-2 vaccine doses are not only safe and efficacious in pediatric and adolescent KTR, but may be necessary to optimize antibody response.

Keywords SARS-CoV-2 · mRNA vaccination · Pediatrics · Kidney transplant

Introduction

We previously reported on the immunogenicity and safety of a 2-dose mRNA SARS-CoV-2 vaccination series in adolescent kidney transplant recipients (KTR) at our center [1]. Since that time, there have been additional reports describing the humoral immune response to the vaccine in pediatric solid organ transplant (SOT) patients with similar findings [2–4]. However, there remains a paucity of pediatric data, and the humoral response to a third "booster" has not been reported in this population. We report an update on the safety and immunogenicity of vaccination for younger pediatric and adolescent KTR and those who have received a booster dose at our center.

✉ Clarkson Crane
crcrane@health.ucsd.edu

[1] Department of Pediatrics, Division of Pediatric Nephrology, Rady Children's Hospital, University of California at San Diego, 3020 Children's Way MC 5173, San Diego, CA 92123, USA

[2] Kidney Transplant Program, Rady Children's Hospital, San Diego, CA, USA

Methods

The prospective and retrospective kidney transplant database at Rady Children's Hospital, San Diego, was utilized to identify eligible KTR who had received at least two doses of a SARS-CoV-2 vaccine from the time the vaccine became available in January, 2021 until February 1, 2022. The delta variant of SARS-CoV-2 was the most predominant local strain during most of the duration of data collection. KTR were excluded if they were vaccinated prior to transplant, were within 6 months post-transplant, or received blood products or B-cell depleting therapy within the prior 6 months.

Data were extracted from the electronic health record. Variables obtained included age, sex, time from transplant, COVID-19 disease, rejection, and type and dose of antimetabolite at time of vaccination. SARS-CoV-2 anti-spike protein (anti-S) assays were obtained as part of routine follow-up appointments. We utilized the Abbott chemiluminescent microparticle immunoassay and seroconversion was considered an antibody titer greater than 50 AU/mL.

Continuous variables are reported as mean and standard deviations (SD) or as median and interquartile range (IQR).

Categorical variables are described as frequency and percentages. Categorical characteristics between those who seroconverted and those who did not were compared with Fisher's exact test. Antibody titers and antimetabolite dosing in both groups were compared with the Mann–Whitney *U* test. Pearson correlation was utilized to determine the relationship between mycophenolate dosing and difference in antibody titers between vaccine doses. Two-sided $P < 0.05$ was considered statistically significant. Statistical analysis was performed with IBM SSPS v27 (Armonk, NY, USA).

The institutional review boards at the University of California, San Diego and Rady Children's Hospital, San Diego approved this study as part of the center's Retrospective and Prospective Kidney Transplant Database.

Results

Of the 58 eligible KTR, 43 (74%) received at least two doses of mRNA SARS-CoV-2 vaccine. Among those aged five to 11 years old, six were vaccine-hesitant and three (50%) later had COVID-19 disease. In the 12- to 15-year-old age group, five declined vaccination and three (60%) had COVID-19. Of the four patients over 16 years old who were not vaccinated, all later had COVID-19. Among those who received the vaccine, there were two patients excluded due to receiving B-cell deleting therapies. One seroconverted after a two-dose vaccine series but received rituximab therapy prior to the third dose. In this case, the anti-S antibody titer remained positive but decreased after both rituximab and a third vaccine dose. In the other case, the patient had received rituximab prior to all vaccine doses and did not seroconvert after two or three doses.

Forty-three pediatric and adolescent KTR received 2-doses of an mRNA SARS-CoV-2 vaccine and 30 (70%) received a third booster dose. Forty (93%) received BNT162b2 (Pfizer-BioNTech), two (5%) received mRNA-1273 (Moderna) vaccine, and one received a mixed vaccine series. The median age was 18 years (IQR 15–20) and 26 (61%) were male. Duration from transplant was a median of 5 years (IQR 2–9). Anti-S titers were obtained a median of 56 days (IQR 30–85) after dose 2 and 39 days (IQR 28–59) after dose 3.

Among those included, 24 patients (56%) seroconverted and had S-antibody titer > 50 AU/mL following a two-dose vaccine series. Of the 26 subjects having received a third dose in whom antibody titers were obtained, 22 (85%) seroconverted. Among the entire cohort, there was a seroconversion rate of 84% (36 of 43 patients). Of the 16 subjects who did not seroconvert after a two-dose series, 12 (75%) seroconverted following the third dose. Anti-S titers were significantly higher in those who received a third dose (Fig. 1). Seroconversion following a 2-dose series was significantly associated with a younger age group ($p = 0.04$). Use of MMF was associated with lack of seroconversion ($p = 0.01$). Characteristics of patients who seroconverted after 2 and 3 vaccine doses are described in Table 1. In those responding only after a third dose, there was a significant increase in anti-S titer from 9.4 (IQR 4–25) AU/mL to 682 (IQR 362–2454) AU/mL ($p < 0.01$) versus an increase from 4.9 (IQR 4–6) AU/mL to 7.4 (IQR 6–10) AU/mL ($p = 0.3$) in those who did not. Although non-significant, there was a weak correlation between a lower MMF dose (mg/kg/day) and a higher increase in anti-S titer (AU/mL) between the second and third dose ($r = 0.25$, $p = 0.13$).

Three patients in the cohort were also receiving treatment for chronic active antibody-mediated rejection with

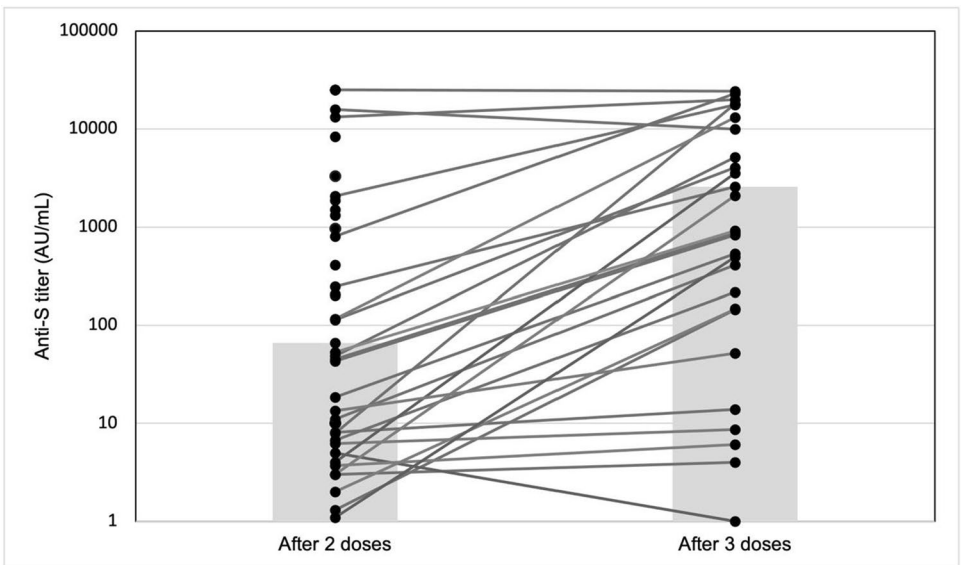

Fig. 1 Anti-S antibody titer after 2 and 3 doses of a SARS-CoV-2 vaccine. Data points are titers of individual patients, background bars demonstrating median antibody titer for each group in AU/mL.

Table 1 Characteristics of patients who seroconverted after 2 and 3 doses of an mRNA SARS-CoV-2 vaccine.

n (%)	Seroconversion after 2-dose series (total *n* = 43)			Seroconversion after 3-dose series (total *n* = 26)		
	Yes	No	***p***-value	Yes	No	***p***-value
Overall	24 (56)	19 (44)		22 (85)	4 (15)	
Age group			0.04			0.6
< 12 years old	4	0		N/A		
12–16 years old	2	6		4	1	
> 16 years old	18	13		18	3	
Time since transplant			0.24			0.82
6 months to 1 year	2	0		1	0	
1–5 years	12	8		10	1	
5–10 years	7	4		6	1	
> 10 years	3	7		5	2	
Antimetabolite therapy						
MMF	17	19	0.01	20	4	0.71
Aza	6	0	0.02	2	0	0.71
MMF dose ($mg/m^2/day \pm SD$)	714 (± 106)	726 (± 119)	0.66	711 (± 106)	765 (± 144)	0.21
COVID-19 infection						
Prior to vaccination	7	0		2	0	
After vaccination	4	4		4	0	

Abbreviations: *MMF*, mycophenolate mofetil, *Aza*, azathioprine, *SD*, standard deviation

the anti-IL-6 monoclonal antibody, tocilizumab. Two of three did not seroconvert after a second dose but did have a positive antibody response after a third. Among all patients, there were no serious adverse events reported after vaccination. Two patients had for-cause kidney biopsies done within the 6-month period after the vaccine to follow-up previously diagnosed rejection that showed acute on chronic rejection. There were no other episodes of acute rejections or diagnosis of de novo glomerular disease in the period following vaccination.

Discussion

In this retrospective observational cohort, 84% of pediatric and adolescent KTR mounted a humoral response to the SARS-CoV-2 mRNA vaccine. Most notably, the addition of a third dose improved the rate of seroconversion from 56 to 85%. Response after the two-dose series is consistent with prior reports of pediatric SOT patients [4] and better when compared to the adult population [5]. The addition of a third dose improves rates of seroconversion and may be necessary to overcome the effects of immunosuppression in this population. While data are limited, this is also consistent with findings from reports in adult SOT recipients [6–9].

Acknowledging the small sample size, it is worthy to note seroconversion after a 2-dose series was significantly better in younger age groups, lending support to the argument that pediatric SOT recipients are able to mount a more robust immune response to vaccination compared to adult patients, as is consistent with prior reports [1, 4]. This effect did not hold for the overall group or those who received a 3-dose series, likely due to fewer younger patients having received a third dose at the time of data collection. Also consistent with prior reports [1, 2, 5], those taking an MMF-containing regimen were also significantly less likely to seroconvert following the 2-dose series. While there was a trend toward lower antibody titers with higher MMF dose, this correlation was not significant.

Immunosuppression management in SOT recipients is characterized by balancing risk of rejection with risk of infection. The suboptimal response to SARS-CoV-2 in KTR compared to non-immunosuppressed individuals is a result of an immunosuppression regimen's intended effect of blunting T-cell proliferation and subsequent B-cell activation to an antigenic stimulus. Humoral and T-cell responses in adult KTR have been shown to be influenced by intensity of the immunosuppression regimen [10]. However, even in immunosuppressed patients, the underlying immunologic machinery has the potential to "break through" after repeated exposure and stimuli. Once this threshold is overcome, seroconversion, and presumably neutralizing antibody formation and T-cell response, will be robust. This is supported by our data where antibody titers increased to a significantly higher degree in those who seroconverted and

overcame this "threshold" after a third immunization compared to those who did not.

With regard to safety, all patients tolerated immunization without significant adverse effects. There were two episodes of acute on chronic rejection diagnosed after the immunization series was completed. While this raises potential concern about immunization priming the immune system for allograft rejection, there is no evidence to suggest causality nor has an association been reported in large adult cohorts [5]. Additionally, both biopsies were done as a follow-up for previously diagnosed rejection and re-demonstrations of a chronic active process.

While our sample size is small and reflects retrospective single-center data, our results provide further evidence that vaccination is safe and efficacious in pediatric and adolescent KTR and is novel in its description of response to a third vaccine dose. As many adult centers are now recommending a fourth mRNA vaccine dose to SOT recipients, our results support continued efforts to vaccinate unimmunized pediatric KTR and provide additional "booster" doses to those who have not yet received one. As new SARS-CoV-2 variants emerge, larger cohorts and ongoing studies are needed to ensure optimal care for this vulnerable population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00467-022-05661-8.

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Author contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by CC and EP. The first draft of the manuscript was written by CC and EI commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The datasets generated during and/or analyzed during the current study are published in a publicly available repository and available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate The Retrospective and Prospective Kidney Transplant Database involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of the University of California San Diego and Rady Children's Hospital approved this study. Need for consent was waived by IRB due to minimal risk to participants.

Consent for publication Need for consent was waived by IRB due to minimal risk to participants.

Conflict of interest The authors declare no competing interests.

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