Effect of Mycophenolate Mofetil Dosing on Antibody Response to SARS-CoV-2 Vaccination in Heart and Lung Transplant Recipients

Jonathan Mitchell, MBBS,[1] Teresa P-Y. Chiang, MD, MPH,[1] Jennifer L. Alejo, MD,[1] Amy Chang, MD,[1] Aura T. Abedon, BS,[1] Robin K. Avery, MD,[2] Aaron A. R. Tobian, MD, PhD,[3] Allan B. Massie, PhD,[1,4] Macey L. Levan, JD, PhD,[1,5] Daniel S. Warren, PhD,[1] Jacqueline M. Garonzik-Wang, MD, PhD,[6] Dorry L. Segev, MD, PhD,[1,4] and William A. Werbel, MD[2]

Solid organ transplant recipients (SOTRs) demonstrate variable antibody responses after 2 doses of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccine.[1] Mycophenolate mofetil (MMF) use is associated with poor immunogenicity in SOTRs, but limited data exist on heart and lung transplant recipients (HLTRs). An increased risk of breakthrough infection in SOTRs[2] has prompted interest in other methods to augment immune protection in this population, such as targeted immunosuppression reduction. This study assesses the effect of cumulative daily dose of MMF on antispike antibody titers after 2 doses of a SARS-CoV-2 mRNA vaccine in HLTRs.

HLTRs without a previously confirmed coronavirus disease 2019 infection (N = 212) were recruited as previously described.[1] Immunosuppression regimens were self-reported, and participants were stratified into 4 groups based on reported total daily dose of MMF: zero MMF, low dose (<1000 mg/d), moderate dose (1000–2000 mg/d), and high dose (≥2000 mg/d). Patients receiving mycophenolic acid were excluded. Antispike antibody testing was performed at 1, 3, and 6 mo after dose 2 using commercially available assays, as previously described.[1,3] The study was approved by the Johns Hopkins Institutional Review Board.

Clinical characteristics were compared using Wilcoxon rank-sum test for continuous and Fisher exact test for categorical variables. Multivariable Poisson regression with robust SE was used to estimate the risk of a negative antibody response associated with the MMF dose categories, adjusting for age, sex, vaccine type (mRNA-1273 versus BNT162b2), time since transplant, and steroid use. Analyses were performed using Stata 15.1/SE for Windows (College Station, TX).

At vaccination, 94 (44.3%) HLTRs reported receiving no MMF, 33 (15.6%) reported low-dose, 54 (25.7%) reported moderate-dose, and 31 (14.8%) reported high-dose regimens (Table 1). After adjustment, the risk of negative response in the low dose was comparable with that in the zero MMF group (risk ratio = $_{0.65}1.15_{2.05}$; $P = 0.63$). However, the moderate- and high-dose groups had >2-fold higher risk of negative antibody response (risk ratio = $_{1.34}2.04_{3.10}$ and $_{1.83}2.77_{4.21}$, respectively; $P < 0.01$).

In this study of the effect of MMF dosing on antibody response to mRNA vaccination against SARS-CoV-2 in

Received 23 November 2021. Revision received 28 December 2021.

Accepted 11 January 2022.

[1] Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD.

[2] Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD.

[3] Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD.

[4] Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD.

[5] Department of Acute and Chronic Care, Johns Hopkins University School of Nursing, Baltimore, MD.

[6] Department of Surgery, University of Wisconsin School of Medicine & Public Health, Madison, WI.

J.M. and T.P.-Y.C. contributed equally.

J.M., T.P.-Y.C., J.L.A., A.C., A.T.A., R.K.A., A.A.R.T., A.B.M., M.L.L., D.S.W., J.M.G.-W., D.L.S., and W.A.W. participated in conception or design of the work; the acquisition, analysis, or interpretation of data for the work; drafting of the work; revising the work critically for important intellectual content; and final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

This research was made possible with the generous support of the Ben-Dov family and the Trokhan Patterson family. This work was supported by the American Society of Transplant Surgeons Jon Fryer Resident Scientist Award (J.M.); grants T32DK007713 (J.L.A.), T32DK007732 (A.C.), K01DK114388-03 (M.L.L.), K01DK101677 (A.B.M.), and K23DK115908 (J.M.G.-W.) from the National Institute of Diabetes and Digestive and Kidney Diseases; and grants K23AI157893 and U01AI138897 (W.A.W.) and K24AI144954 (D.L.S.) from the National Institute of Allergy and Infectious Diseases.

The analyses described here are the sole responsibility of the authors and do not necessarily reflect the views or policies of the Department of Health and Human Services or the National Institutes of Health, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government.

D.L.S. received consulting and speaking honoraria from Sanofi, Novartis, CLS Behring, Jazz Pharmaceuticals, Veloxis, Mallinckrodt, and Thermo Fisher Scientific. R.K.A. has study/grant support from Aicuris, Astellas, Chimerix, Merck, Oxford Immunotec, Qiagen, Regeneron, Takeda/Shire, and Vir/GSK, and he is an associate editor for Transplantation. M.L.L. is the Social Media Editor for Transplantation. The other authors declare no conflicts of interest.

Correspondence: Dorry L. Segev, MD, PhD, Department of Surgery, Johns Hopkins University School of Medicine, 2000 E Monument St, Baltimore, MD 21205. (dorry@jhmi.edu).

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0041-1337/20/1065-e269

DOI: 10.1097/TP.0000000000004090

TABLE 1.

Demographics of heart and lung transplant recipients based on daily MMF dose category

Factor	Zero MMF	Low <1000 mg/d	Moderate 1000–1999 mg	High ≥2000 mg	*P*
N	94	33	54	31	
Vaccine series					0.66
BNT162b2	49 (52.1%)	18 (54.5%)	30 (55.6%)	20 (64.5%)	
mRNA-1273	45 (47.9%)	15 (45.5%)	24 (44.4%)	11 (35.5%)	
Age, median (IQR)	58.5 (41.9–68.9)	66.2 (50.8–70.2)	65.4 (48.5–70.3)	59.1 (41.2–66.4)	0.26
Sex					0.88
Male	45 (47.9%)	16 (48.5%)	25 (46.3%)	17 (54.8%)	
Female	48 (51.1%)	17 (51.5%)	29 (53.7%)	14 (45.2%)	
Other	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Years since transplant at dose 1, median (IQR)	6.6 (2.7–11.2)	5.5 (3.0–10.7)	5.2 (2.6–9.8)	4.3 (2.8–11.0)	0.64
History of rejection[a]	5 (5.61%)	0 (0%)	1 (1.81%)	1 (3.33%)	0.51
Organ transplanted					0.049
Lung	36 (38.3%)	23 (69.7%)	22 (40.7%)	13 (41.9%)	
Heart	55 (58.5%)	10 (30.3%)	32 (59.3%)	18 (58.1%)	
Heart and lung	3 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Azathioprine	15 (16.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.001
Calcineurin inhibitor	92 (97.9%)	30 (90.9%)	53 (98.1%)	28 (90.3%)	0.081
Tacrolimus	84 (89.4%)	28 (84.8%)	52 (96.3%)	27 (87.1%)	0.23
Steroids	58 (61.7%)	24 (72.7%)	25 (46.3%)	17 (54.8%)	0.094
mTOR inhibitor	42 (44.7%)	4 (12.1%)	3 (5.6%)	4 (12.9%)	<0.001
Triple immunosuppression[b]	0 (0.0%)	21 (63.6%)	25 (46.3%)	16 (51.6%)	<0.001

[a]History of rejection in the 6 mo preceding vaccination.
[b]Triple immunosuppression consisted of any combination of MMF, calcineurin inhibitor, steroid, azathioprine, or mTOR inhibitor.
IQR, interquartile range; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin.

HLTRs, an MMF dose of >1000 mg/d was associated with increased risk of negative antibody response after a 2-dose SARS-CoV-2 mRNA vaccine series. Though the association of MMF use with poor antibody responses to SARS-CoV-2 vaccination in HLTRs has been previously reported,[4] this is the first study to delineate the effect of MMF dosing on the antibody response in this population. There was a possibility for recall bias, as MMF doses were self-reported. Data regarding changes to MMF dose leading up to vaccination were unavailable. Additionally, although antibodies to the S1/receptor-binding domain are correlated with plasma neutralizing activity,[5] neutralizing titers were not formally assessed.

In conclusion, higher MMF doses increase the risk of a negative antibody response to the 2-dose mRNA vaccine series in HLTRs. These findings may help guide approaches to third and booster doses, variant-specific next-generation vaccines, and the potential role for transient immunosuppression reduction strategies in ongoing trials where appropriate.

ACKNOWLEDGMENTS

The authors thank the participants of the Johns Hopkins transplant vaccine study, without whom this work would be impossible. They also thank the Johns Hopkins transplant vaccine study team, including Brian Boyarsky, MD, PhD; Mayan Teles, BS; Carolyn Sidoti, BS; Michael T. Ou, BS; Ross S. Greenberg, BA; Jake A. Ruddy, BS; Muhammad Asad Munir, MBBS; Michelle R. Krach, MS; and Iulia Barbur, BSE. They also thank Andrew H. Karaba, MD, PhD, and Ms Yolanda Eby for project support and guidance.

REFERENCES

1. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA*. 2021;325:2204–2206.
2. Qin CX, Moore LW, Anjan S, et al. Risk of breakthrough SARS-CoV-2 infections in adult transplant recipients. *Transplantation*. 2021;105:e265–e266.
3. Werbel WA, Boyarsky BJ, Ou MT, et al. Safety and immunogenicity of a third dose of SARS-CoV-2 vaccine in solid organ transplant recipients: a case series. *Ann Intern Med*. 2021;174:1330–1332.
4. Hallett AM, Greenberg RS, Boyarsky BJ, et al. SARS-CoV-2 messenger RNA vaccine antibody response and reactogenicity in heart and lung transplant recipients. *J Heart Lung Transplant*. 2021;40:1579–1588.
5. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27:1205–1211.