HHS Public Access

Author manuscript

Ann Rheum Dis. Author manuscript; available in PMC 2024 April 22.

Published in final edited form as:

Ann Rheum Dis. 2022 February ; 81(2): 293–295. doi:10.1136/annrheumdis-2021-221252.

Temporary Hold of Mycophenolate Augments Humoral Response to SARS-CoV-2 Vaccination in Patients with Rheumatic and Musculoskeletal Diseases: A Case Series

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• Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
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• Drafting the work or revising it critically for important intellectual content
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• Agreement 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.
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PATIENT AND PUBLIC INVOLVEMENT

Patients were not involved in the design, conduct, or dissemination of the study, though this study was motivated by questions frequently posed by patients. The study has a public website (https://vaccineresponse.org/) and email account where we welcomed participants and the public to contact the research team. Results of the study will be shared with national RMD organizations for dissemination to their patient communities once published.

COMPETING INTERESTS

Dorry L. Segev, MD PhD has the following financial disclosures: consulting and speaking honoraria from Sanofi, Novartis, CSL Behring, Jazz Pharmaceuticals, Veloxis, Mallincrodt, Thermo Fisher Scientific.

Lisa Christopher-Stine has the following financial disclosures: consultant fees from Janssen, Boehringer-Ingelheim, Mallinckrodt, EMD-Serono, Allogene, and ArgenX.

The other authors of this manuscript have no financial disclosures or completing interest to disclose as described by *Annals of the Rheumatic Diseases.*

ETHICAL APPROVAL

This study was approved by the Johns Hopkins Institutional Review Board (IRB00248540). Participants gave informed consent to participate before taking part in this study.

DATA SHARING STATEMENT

Data are available upon reasonable request.

Keywords

COVID-19; SARS-CoV-2; mRNA vaccination; rheumatic disease; mycophenolic acid; antimetabolite

Mycophenolate is the mainstay of treatment for many organ and life-threatening manifestations of rheumatic and musculoskeletal diseases (RMD). In contrast to most patients with RMD, those taking mycophenolate have an attenuated humoral response to SARS-CoV-2 mRNA vaccination (1,2). The American College of Rheumatology recently recommended withholding mycophenolate for one week after vaccination to enhance immunogenicity in this vulnerable population (3). Thus, we sought to analyze the impact of withholding peri-vaccination mycophenolate in 24 RMD patients.

We leveraged our observational prospective cohort of RMD patients without prior COVID-19 who underwent SARS-CoV-2 vaccination between 12/17/2020 to 05/13/2021 (2). Information on demographics, diagnoses, immunosuppressive regimens, and management of peri-vaccination immunosuppression were collected via electronic questionnaire. One month following vaccination, venipuncture samples were obtained and tested on the semi-quantitative Roche Elecsys® anti-SARS-CoV-2 S enzyme immunoassay which tests for antibodies against the receptor binding domain (RBD) of the SARS-CoV-2 spike protein; a consistent correlate of neutralizing antibody (4). We compared the percentage of participants with detectable anti-RBD antibody in the group that that withheld mycophenolate (n=24) to the group that continued mycophenolate (n=171) using Fisher's exact test (Supplemental Table 1). Crude and adjusted logistic regression analyses were performed to assess associations between antibody response and the primary variable of withholding mycophenolate, as well as after adjusting for clinical characteristics (age, sex, race, vaccine type [mRNA v. adenovirus vector], use of rituximab, and glucocorticoids). Wilcoxon rank-sum test was used to compare anti-RBD titers of the patients who withheld therapy to those who continued therapy. This study was approved by the Johns Hopkins Institutional Review Board (IRB00248540).

We studied 24 patients who withheld mycophenolate (Table 1). Most were female (96%) with a median (IQR) age 51 (40–58) years. 13% received the Janssen/Johnson and Johnson (J&J) vaccine while the remainder completed two-dose Pfizer/BioNTech or Moderna mRNA series. The most common diagnoses were systemic lupus erythematosus (25%) and myositis (20%). Most participants reported twice daily dosing of mycophenolate, with a median (IQR) total daily dose of 2000mg (1625–3000mg). The median (IQR) number of doses held was 20 (8–34). Thirteen participants (54%) withheld before vaccination, 9 (38%) withheld both before and after vaccination, while 2 (8%) withheld after vaccination. Among those who withheld both before and after vaccination, the majority (7/9) held for same duration before and after, while the remaining 2 participants held more doses after vaccination.

At a median (IQR) of 32 (28–35) days after vaccination, 22/24 participants who withheld mycophenolate had detectable antibody response compared to 112/171 who continued therapy (92% versus 65%, p=0.01). Those who withheld therapy were more likely to have a positive antibody response (OR 5.8, 95% CI 1.3–25.5 p=0.02). In the adjusted logistic

regression model, the association between withholding mycophenolate and positive response remained statistically significant (aOR 7.24, 95% CI 1.72–44.31 p=0.01) (Supplemental Table 2). Since the rare disease assumption was not met, this odds ratio cannot be interpreted as a relative chance of a positive response. Median anti-RBD Ig titers in the withholding group were significantly higher than the group that continued therapy (125 v. 7U/L, p=0.004) (Supplemental Figure 1). Two participants reported flare of their underlying disease requiring treatment in the peri-vaccination period; these were treated with topical and oral glucocorticoids respectively.

In this case series, we describe 24 RMD patients who withheld mycophenolate in the peri-vaccination period of whom (92%) had a detectable humoral response, which was more frequent and robust than among participants who continued therapy.

The small sample size did not allow for evaluation of optimal duration of withholding therapy. Further limitations of this study include non-randomized design,lack of data on cellular response and limited information on dosing of other immunosuppressive agents.

These early results suggest that a temporary hold in mycophenolate therapy is safe and augments the humoral response to SARS-CoV-2 vaccination in diverse patients with RMD. Given the limited immunogenicity to SARS-CoV-2 vaccination in other immunosuppressed patients (5), the generalizability of these preliminary findings warrants further investigation. Evidence-based, personalized approaches to peri-vaccination immunosuppression modulation will be key in safely optimizing responses to SARS-CoV-2 vaccination for vulnerable populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

No additional acknowledgments.

FUNDING

This work was made possible by the generous support of the Ben Dov family. This work was supported by grant number F32DK124941 (Boyarsky), 5T32DK007713 (Alejo),K01DK101677 (Massie) and K23DK115908 (Garonzik-Wang) from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), K24AI144954 (Segev) from National Institute of Allergy and Infectious Diseases (NIAID), K23AR073927 (Paik) from National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAIM). The analyses described here are the responsibility of the authors alone and do not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products or organizations imply endorsement by the US Government.

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Table 1.

Clinical characteristics of RMD participants who withheld peri-vaccination mycophenolate

Participant	Age	Sex	Race	Diagnosis	Vaccine type	Mycophenolate Dose	Number of doses held	Concurrent Therapy	Antibody Titer *	Flare
1	36	M	White	CT-ILD†	Moderna	2000mg	3	No	>250	No
2	62	F	White	CT-ILD†	Pfizer	500mg	88	Prednisone	>250	No
3	19	F	White	IA≠	Pfizer	1000mg	5	Abatacept	16	Yes
4	58	F	White	IA≠	Pfizer	2000mg	28	Tofacitinib	>250	No
5	46	F	White	Myositis	J+J	2000mg	NA	Prednisone	82	No
6	53	F	White	Myositis	J+J	2500mg	56	Prednisone	206	No
7	46	F	White	Myositis	Pfizer	3000mg	20	IVIG§, HCQ//	40	No
8	54	F	White	Myositis	Pfizer	3000mg	NA	No	<0.40	No
9	35	F	White	Myositis	Moderna	3000mg	24	No	>250	No
10	71	F	White	Overlap CTD¶	Moderna	2000mg	4	Rituximab	9.0	No
11	58	F	White	Overlap CTD¶	Moderna	2000mg	9	HCQ//, Prednisone	8	No
12	55	F	White	Overlap CTD¶	Moderna	2000mg	30	HCQ//, Prednisone	8	No
13	64	F	White	Overlap CTD¶	Pfizer	500mg	38	No	>250	No
14	70	M	White	Scleroderma	Moderna	3000mg	42	Rituximab	<0.40	Yes
15	36	F	White	Scleroderma	Pfizer	3000mg	14	No	35	No
16	40	F	White	Scleroderma	Pfizer	2500mg	28	No	244	No
17	42	F	White	Scleroderma	Pfizer	3000mg	8	Abatacept	22	No
18	63	F	White	Sjogren's	Pfizer	2500mg	NA	No	12	No
19	49	F	White	SLE	J+J	3000mg	13	No	>250	No
20	54	F	White	SLE	Moderna	1000mg	10	HCQ≠	>250	No
21	50	F	Black	SLE	Pfizer	3000mg	98	Belimumab, Prednisone	>250	No
22	31	F	White	SLE	Pfizer	2000mg	10	HCQ≠, Prednisone	80	No
23	38	F	White	SLE	Pfizer	1500mg	20	Prednisone	168	No
24	51	F	White	SLE	Moderna	1000mg	5	Abatacept	>250	No

*The assay ranges from <0.4 to >250 units/mL. Positive antibody was defined as an anti-SARS-CoV-2 RBD antibody titer >0.79 units/mL

† Denotes connective tissue disease related ILD

‡ Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, or inflammatory bowel disease associated arthritis

§ Intravenous Immunoglobulin

// Hydroxychloroquine

¶ Denotes a combination of two or more of the rheumatic conditions