Temporary hold of mycophenolate augments humoral response to SARS-CoV-2 vaccination in patients with rheumatic and musculoskeletal diseases: a case series

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 1 week after vaccination to enhance immunogenicity in this vulnerable population.[3] Thus, we sought to analyse the impact of withholding perivaccination mycophenolate in 24 patients with RMD.

We leveraged our observational prospective cohort of patients with RMD without prior COVID-19 who underwent SARS-CoV-2 vaccination between 17 December 2020 and 13 May 2021.[2] Information on demographics, diagnoses, immunosuppressive regimens and management of perivaccination immunosuppression was collected via electronic questionnaire. One month following vaccination, venipuncture samples were obtained and tested on the semiquantitative 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 neutralising antibody.[4] We compared the percentage of participants with detectable anti-RBD antibody in the group that withheld mycophenolate (n=24) to the group that continued mycophenolate (n=171) using Fisher's exact test (online 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 vs 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. Overall, 13% received the Janssen/Johnson and Johnson 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 two times per day dosing of mycophenolate, with a median (IQR) total daily dose of 2000 mg (1625–3000 mg). The median (IQR) number of doses held was 20 (8–34). Thirteen participants (54%) withheld before vaccination, nine (38%) withheld both before and after vaccination, while two (8%) withheld after vaccination. Among those who withheld both before and after vaccination, the majority (seven out of nine) held for the same duration before and after, while the remaining two 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

Table 1 Clinical characteristics of participants with rheumatic and musculoskeletal diseases who withheld perivaccination mycophenolate

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

*The assay ranges from<0.4 to >250 units/mL. Positive antibody was defined as an anti-SARS-CoV-2 receptor binding domain antibody titre>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.
††Systemic lupus erythematosus.

antibody response compared with 112/171 who continued therapy (92% vs 65%, p=0.01). Those who withheld therapy were more likely to have a positive antibody response (OR 5.8, 95% CI 1.3 to 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 to 44.31 p=0.01) (online supplemental table 2). Since the rare disease assumption was not met, this OR 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 vs 7 U/L, p=0.004) (online supplemental figure 1). Two participants reported flare of their underlying disease requiring treatment in the perivaccination period; these were treated with topical and oral glucocorticoids, respectively.

In this case series, we describe 24 patients with RMD who withheld mycophenolate in the perivaccination 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-randomised 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 generalisability of these preliminary findings warrants further investigation. Evidence-based, personalised approaches to perivaccination immunosuppression modulation will be key in safely optimising responses to SARS-CoV-2 vaccination for vulnerable populations.

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 organisations for dissemination to their patient communities once published.

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