High antibody response to two-dose SARS-CoV-2 messenger RNA vaccination in patients with rheumatic and musculoskeletal diseases

SARS-CoV-2 mRNA vaccination elicited high immunogenicity in immunocompetent people in the original vaccine trials,[1 2] though recent studies have shown blunted immunogenicity in patients with rheumatic and musculoskeletal diseases (RMDs) after a single dose and case reports of non-response after two doses.[3 4] We previously detailed antibody response in patients with RMD following the first dose of SARS-CoV-2 mRNA vaccination and herein report response and factors associated with response to two-dose vaccination in a larger cohort.

As previously reported,[3] patients aged ≥18 years old with RMD were recruited to participate in this prospective, observational cohort via social media outreach to national RMD organisations between 12 July 2020 and 16 March 2021. Demographics, diagnoses and therapeutic regimens were collected via participant report through the Research Electronic Data Capture tool. One month after dose 2 (D2), participants underwent SARS-CoV-2 antibody testing on the semiquantitative Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay, which measures total antibody (IgM and IgG) to the SARS-CoV-2 S receptor-binding domain (RBD) protein,[5] the target of the mRNA vaccines. Results range from <0.4 to >250 U/mL with a positive response defined as >0.79 U/mL. Associations were evaluated using Fisher's exact and Wilcoxon rank-sum tests. Participants provided informed consent.

We studied 404 participants who received two doses of the SARS-CoV-2 mRNA vaccine (online supplemental table 1). The median (IQR) age was 44 (36–57), 96% were female, 9% were non-white, 49% received the Pfizer/BioNTech vaccine and 51% received Moderna, 4% had a prevaccination history of COVID-19 diagnosis and no participant reported postvaccination COVID-19 diagnosis. Most common diagnoses included inflammatory arthritis (45%) and systemic lupus erythematosus (22%). The most frequently prescribed medications were hydroxychloroquine (42%) and glucocorticoids (29%), while 51% were on combination therapy. Participants completed anti-RBD testing at a median of 29 days after D2.

Anti-SARS-CoV-2 RBD antibodies were positive in 378/404 (94%) participants (95% CI 91% to 96%) (online supplemental table 1). Median anti-RBD titre was above the upper limit of the assay (>250 U/mL), while lower median titres were observed in participants on regimens including mycophenolate (8 U/mL) and rituximab (<0.4 U/mL) (figure 1, online supplemental table 2). Tumour necrosis factor inhibitor use was associated with a positive antibody response (100% positive, p<0.001), while regimens including mycophenolate (73% positive, p<0.001), rituximab (26% positive, p<0.001) or glucocorticoids (82% positive, p<0.001) and a diagnosis of myositis (79% positive, p=0.01) were associated with a negative response. Of note, 4/5 (80%) negative responders with myositis and 18/21 (86%) negative responders on glucocorticoids were on regimens including mycophenolate or rituximab; all eight on glucocorticoid monotherapy had an anti-RBD titre >250 U/mL.

In this study of humoral response to two-dose SARS-CoV-2 mRNA vaccination in patients with RMD, the vast majority of participants developed anti-RBD antibodies. Among negative responders, most were on regimens containing mycophenolate or rituximab. Glucocorticoid use was also associated with a negative response, though all of these individuals were on concomitant lymphocyte-depleting therapy. Compared with patients with RMD following D1 (74% seroconversion),[3] this study showed increased seroconversion following two-dose vaccination (94% seroconversion). Similarly, seroconversion for those on mycophenolate-based regimens was 73% after two doses compared with 27% after D1, while the response for those on rituximab remained poor (33% seroconversion after D1, 26% seroconversion after D2). Despite a blunted humoral response in participants on these regimens, the rate of seroconversion was comparable with those seen in the original vaccine trials and existing studies on patients with RMD.[1 2 6]

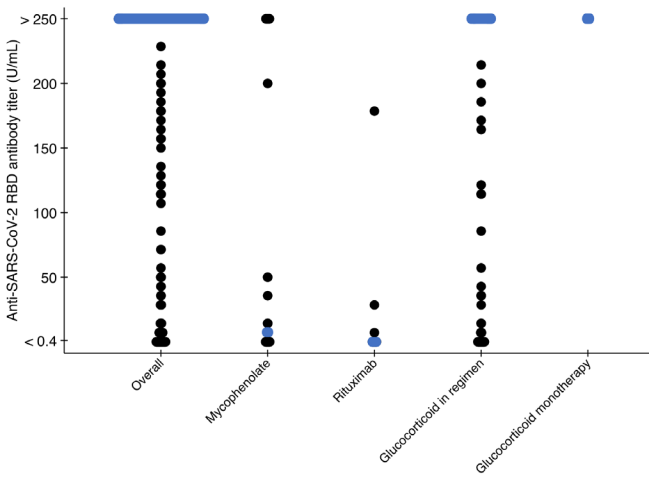

Figure 1 Anti-SARS-CoV-2 RBD antibody titre overall (n=403*) and by medications associated with a negative antibody response: mycophenolate included in regimen (n=41), rituximab included in regimen (n=19), glucocorticoid included in regimen (n=116) and glucocorticoid monotherapy (n=8) in patients with RMD after two-dose SARS-CoV-2 mRNA vaccination. Results range from <0.4 to >250 U/mL with positive antibody defined as an anti-SARS-CoV-2 RBD antibody titre >0.79 U/mL by the manufacturer; blue data points indicate median titre. *One titre value was missing from the total N (404). RBD, receptor binding domain; RMD, rheumatic and musculoskeletal disease.

Limitations of this study include a younger, generally female, racially homogenous population and limited information on immunomodulatory timing and dosage. Additionally, we did not evaluate for asymptomatic COVID-19 infection, and disease activity was not assessed.

While certain lymphocyte-depleting therapies were associated with failure to develop a humoral response, reassuringly, the majority of patients with RMD on a variety of immunosuppressive regimens had a robust antibody response to SARS-CoV-2 mRNA vaccination.

Jake A Ruddy,[1,2] Caoilfhionn Marie Connolly ,[2] Brian J Boyarsky ,[1] William A Werbel,[3] Lisa Christopher-Stine,[2] Jacqueline Garonzik-Wang,[1] Dorry L Segev,[1,4] Julie J Paik [2]

[1]Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[2]Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[3]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[4]Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA

Correspondence to Dr Dorry L Segev, Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; dorry@jhmi.edu

Handling editor Josef S Smolen

Twitter Caoilfhionn Marie Connolly @CaoilfhionnMD

Acknowledgements We also acknowledge the following individuals for their assistance with this study: Allan B Massie, PhD, Robin K Avery MD, Michael T Ou, BS, Ross S Greenberg, BS, and Iulia Barber, BS.

Contributors All authors contributed to study design. JAR and BJB contributed to data collection. All authors contributed to data analysis and interpretation. All authors contributed to drafting of the manuscript.

Funding This research was made possible with generous support of the Ben-Dov family. This work was supported by grant number F32DK124941 (Boyarsky), 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).

Disclaimer 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 organisations imply endorsement by the US Government.

Competing interests DLS has the following financial disclosures: consulting and speaking honoraria from Sanofi, Novartis, CSL Behring, Jazz Pharmaceuticals, Veloxis, Mallincrodt and Thermo Fisher Scientific. LC-S has the following financial disclosures: consultant fees from Janssen, Boehringer-Ingelheim, Mallinckrodt, EMD-Serono, Allogene and ArgenX.

Patient consent for publication Not required.

Ethics approval This study was approved by the Johns Hopkins School of Medicine Institutional Review Board (IRB00248540).

Provenance and peer review Not commissioned; externally peer reviewed.

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220656).

JAR and CMC contributed equally.

DLS and JJP are joint senior authors.

To cite Ruddy JA, Connolly CM, Boyarsky BJ, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2021-220656

Received 27 April 2021
Accepted 9 May 2021

Ann Rheum Dis 2021;**0**:1–2. doi:10.1136/annrheumdis-2021-220656

ORCID iDs
Caoilfhionn Marie Connolly http://orcid.org/0000-0002-1898-3530
Brian J Boyarsky http://orcid.org/0000-0001-6902-9854
Julie J Paik http://orcid.org/0000-0001-8436-1601

REFERENCES

1 Walsh EE, Frenck RW, Falsey AR, *et al*. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. *N Engl J Med* 2020;383:2439–50.
2 Widge AT, Rouphael NG, Jackson LA, *et al*. Durability of responses after SARS-CoV-2 mRNA-1273 vaccination. *N Engl J Med* 2021;384:80–2.
3 Boyarsky BJ, Ruddy JA, Connolly CM, *et al*. Antibody response to a single dose of SARS-CoV-2 mRNA vaccine in patients with rheumatic and musculoskeletal diseases. *Ann Rheum Dis* 2021:annrheumdis-2021-220289.
4 Connolly CM, Boyarsky BJ, Ruddy JA. Absence of humoral response after two-dose SARS-CoV-2 messenger RNA vaccination in patients with rheumatic and musculoskeletal diseases: a case series. *Ann Intern Med* 2021:M21–1451.
5 Higgins V, Fabros A, Kulasingam V. Quantitative measurement of Anti-SARS-CoV-2 antibodies: analytical and clinical evaluation. *J Clin Microbiol* 2021;59:e03149-20.
6 Geisen UM, Berner DK, Tran F, *et al*. Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort. *Ann Rheum Dis* 2021:annrheumdis-2021-220272.

Supplemental Table 1. Demographic and clinical characteristics of patients with RMD after two-dose SARS-CoV-2 mRNA vaccination, stratified by anti-SARS-CoV-2 RBD antibody response

	Overall (n=404)	**Negative antibody** (n=26)*	**Positive antibody** (n=378)*	p-value†
Age, median (IQR)	44 (36, 57)	46 (39, 57)	44 (36, 57)	0.8
Female sex, no. (%)‡	385 (96)	25 (6)	360 (94)	0.9
Non-white, no. (%)‡	37 (9)	4 (11)	33 (89)	0.3
Diagnosis, no. (%)				
Inflammatory arthritis§	180 (45)	1 (1)	179 (99)	<0.001
Systemic lupus erythematosus	87 (22)	9 (10)	78 (90)	0.1
Sjögren's syndrome	19 (5)	2 (11)	17 (89)	0.3
Myositis	24 (6)	5 (21)	19 (79)	0.01
Systemic sclerosis	2 (1)	0 (0)	2 (100)	-
Vasculitis‖	8 (2)	4 (50)	4 (50)	-
Overlap connective tissue disease¶	84 (21)	5 (6)	79 (94)	0.9
Vaccine, no. (%)‡				
Pfizer/BioNTech	198 (49)	14 (7)	184 (93)	0.7
Moderna	204 (51)	12 (6)	192 (94)	
Days from D2 to testing, median (IQR)	29 (28, 32)	29 (27, 32)	29 (28, 32)	0.9
Days from D1 to D2, median (IQR)	27 (21, 28)	23 (21, 28)	27 (21, 28)	0.6
Prior COVID-19 diagnosis, no. (%)‡	17 (4)	0 (0)	17 (100)	0.6
Therapy included in regimen, no. (%)				
Conventional DMARD				
Azathioprine	35 (9)	5 (14)	30 (86)	0.1
Cyclosporine	1 (0.2)	0 (0)	1 (100)	-
Hydroxychloroquine	170 (42)	10 (6)	160 (94)	0.8
Leflunomide	19 (5)	0 (0)	19 (100)	0.6
Methotrexate	94 (23)	2 (2)	92 (98)	0.1
Mycophenolate**	41 (10)	11 (27)	30 (73)	<0.001
Sirolimus	1 (0.2)	0 (0)	1 (100)	-
Sulfasalazine	15 (4)	1 (7)	14 (93)	0.9
Tacrolimus	8 (2)	3 (38)	5 (63)	-
Biologic				
Abatacept	24 (6)	0 (0)	24 (100)	0.4
Belimumab	56 (14)	3 (5)	53 (95)	0.9

Interleukin inhibitors	31 (8)	1 (3)	30 (97)	0.7
Anakinra	1 (0.2)	0 (0)	1 (100)	-
Guselkumab	1 (0.2)	0 (0)	1 (100)	-
IL-6 inhibitors**	7 (2)	1 (14)	6 (86)	-
IL-17 inhibitors**	14 (3)	0 (0)	14 (100)	0.9
Ustekinumab	9 (100)	0 (0)	9 (100)	-
JAK inhibitor**	15 (4)	0 (0)	15 (100)	0.6
Rituximab	19 (5)	14 (74)	5 (26)	<0.001
TNF inhibitor**	98 (24)	0 (0)	98 (100)	<0.001
Immunomodulatory**	22 (5)	3 (14)	19 (86)	0.2
Glucocorticoid overall**	117 (29)	21 (18)	96 (82)	<0.001
Glucocorticoid monotherapy**	8 (2)	0 (0)	8 (100)	-
Combination therapy††	208 (51)	24 (12)	184 (88)	<0.001

* The percentages in these columns are shown as percent of each category in the overall column. Positive antibody was defined as an anti-SARS-CoV-2 RBD antibody titer >0.79 U/mL.

† Comparisons were between the negative and positive antibody groups. Categories with an overall n<10 were not analyzed and all tests were two-sided with an α=0.05.

‡ The denominators for these categories differ from the total N as 1 participant selected “prefer not to answer” for sex, 8 selected “prefer not to answer” for race, 2 did not respond to the vaccine manufacturer question, and 1 did not respond to the prior COVID-19 diagnosis question.

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

|| Polyarteritis nodosa, Behcet's syndrome, polymyalgia rheumatica, temporal arteritis, eosinophilic granulomatosis polyangiitis, granulomatous polyangiitis, Henoch-Schonlein purpura, microscopic polyangiitis, or Takayasu arteritis

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

** Mycophenolate includes mycophenolic acid and mycophenolate mofetil. Interleukin (IL)-6 inhibitors include sarilumab and tocilizumab. IL-17 inhibitors include ixekizumab and secukinumab. Janus kinase (JAK) inhibitors include tofacitinib and upadacitinib. TNF inhibitors include adalimumab, certolizumab, etanercept, golimumab, and infliximab. Glucocorticoid includes prednisone and prednisone equivalents. Immunomodulatory includes intravenous immunoglobulin (IVIg) and subcutaneous Immunoglobulin (SCIg).

†† Denotes a combination of conventional DMARD, biologic, glucocorticoid, or immunomodulatory therapy

Supplemental Table 2. Anti-SARS-CoV-2 RBD antibody titer of patients with RMD one month after two-dose SARS-CoV-2 mRNA vaccination by demographics and clinical characteristics

	N*	**Titer**, median U/mL (IQR)†
Overall	403	>250 (>250, >250)
Age > 55‡	110	>250 (171, >250)
Female sex	384	>250 (>250, >250)
Non-white	37	>250 (>250, >250)
Diagnosis		
Inflammatory arthritis§	180	>250 (>250, >250)
Systemic lupus erythematosus	87	>250 (210, >250)
Sjögren's syndrome	19	>250 (>250, >250)
Myositis	24	91 (2, >250)
Systemic sclerosis	2	>250 (>250, >250)
Vasculitis‖	7	<0.4 (<0.4, >250)
Overlap connective tissue disease¶	84	>250 (201, >250)
Vaccine		
Pfizer/BioNTech	198	>250 (155, >250)
Moderna	203	>250 (>250, >250)
Prior COVID-19 diagnosis	17	>250 (>250, >250)
Therapy included in regimen		
Conventional DMARD		
Azathioprine	35	>250 (31, >250)
Cyclosporine	1	>250
Hydroxychloroquine	170	>250 (232, >250)
Leflunomide	19	>250 (193, >250)
Methotrexate	94	>250 (>250, >250)
Mycophenolate**	41	8 (0.8, >250)
Sirolimus	1	>250
Sulfasalazine	15	>250 (118, >250)
Tacrolimus	8	6 (<0.4, >250)
Biologic		
Abatacept	24	>250 (15, >250)
Belimumab	56	>250 (230, >250)
Interleukin inhibitor	30	>250 (>250, >250)

Anakinra	1	>250
Guselkumab	1	>250
IL-6 inhibitors**	6	>250 (84, >250)
IL-17 inhibitors**	13	>250 (>250, >250)
Ustekinumab	9	>250 (>250, >250)
JAK inhibitor**	15	>250 (232, >250)
Rituximab	19	<0.4 (<0.4, 1)
TNF inhibitor**	98	>250 (>250, >250)
Glucocorticoid overall**	116	>250 (11, >250)
Glucocorticoid monotherapy**	8	>250 (>250, >250)
Immunomodulatory**	22	184 (2, >250)
Combination therapy††	207	>250 (48, >250)

* 1 titer value was missing from the total N (404).

† Titers could range from <0.4 to >250.

‡ Age was dichotomized into ≤55 and >55 based on early vaccine trials.[1]

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

|| Polyarteritis nodosa, Behcet's syndrome, polymyalgia rheumatica, temporal arteritis, eosinophilic granulomatosis polyangiitis, granulomatous polyangiitis, Henoch-Schonlein purpura, microscopic polyangiitis, or Takayasu arteritis

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

** Mycophenolate includes mycophenolic acid and mycophenolate mofetil. Interleukin (IL)-6 inhibitors include sarilumab and tocilizumab. IL-17 inhibitors include ixekizumab and secukinumab. Janus kinase (JAK) inhibitors include tofacitinib and upadacitinib. TNF inhibitors include adalimumab, certolizumab, etanercept, golimumab, and infliximab. Glucocorticoid includes prednisone and prednisone equivalents. Immunomodulatory includes intravenous immunoglobulin (IVIg) and subcutaneous Immunoglobulin (SCIg).

†† Denotes a combination of conventional DMARD, biologic, glucocorticoid, or immunomodulatory therapy