Antibody response to a single dose of SARS-CoV-2 mRNA vaccine in patients with rheumatic and musculoskeletal diseases

The immune response to SARS-CoV-2 messenger RNA (mRNA) vaccines in patients with rheumatic and musculoskeletal diseases (RMD) is undefined because these individuals were largely excluded from phase I–III studies. To better understand the immune response to vaccination in this patient population, we studied the antibody response in patients with RMD who completed the first dose of SARS-CoV-2 mRNA vaccination.

Participants with RMD across the USA were recruited to participate in this prospective cohort via social media. Those with prior SARS-CoV-2 were excluded. We collected demographics, RMD diagnoses and immunomodulatory regimens and tested for SARS-CoV-2 antibodies at baseline and prior to the second vaccine dose. Antibody testing was conducted on the semiquantitative Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay (EIA) which tests for antibodies against the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein.[1] We evaluated the association between demographic/clinical characteristics and positive antibody response using Fisher's exact test and Wilcoxon rank-sum test.

We studied 123 participants who received their first SARS-CoV-2 vaccination dose between 8 January 2021 and 12 February 2021; 52% underwent BNT162b2, and 48% underwent mRNA-1273 (table 1). The most common reported RMD diagnoses were inflammatory arthritis (28%), systemic lupus erythematosus (SLE) (20%), Sjogren's syndrome (13%) and overlap connective tissue diseases(29%). Whereas 28% reported not taking immunomodulatory agents, the remainder reported regimens including non-biologic disease-modifying antirheumatic drugs (DMARDs) (19%), biologic DMARDs (14%) and combination therapy (37%).

Table 1 Demographic and clinical characteristics of study participants, stratified by immune response to the first dose of SARS-CoV-2 mRNA vaccine

	Overall (n=123)	Detectable antibody (n=91)	Undetectable antibody (n=32)	P value*
Age, median (IQR)	50 (41, 61)	46 (37, 61)	57 (43, 68)	0.06
Female sex, n (%)	117 (95)	87 (96)	30 (94)	0.7
Non-white, n (%)	12 (10)	11 (12)	1 (3)	0.2
Diagnosis, n (%)				
Inflammatory arthritis†	34 (28)	29 (32)	5 (16)	0.5
Systemic lupus erythematous	24 (20)	16 (18)	8 (25)	
Sjogren's syndrome	16 (13)	12 (13)	4 (12)	
Myositis	7 (6)	4 (4)	3 (9)	
Vasculitis	2 (2)	1 (1)	1 (3)	
Overlap connective tissue disease‡	35 (29)	25 (27)	10 (31)	
Other	5 (4)	4 (4)	1 (3)	
Therapy, n (%)				
None	34 (28)	28 (31)	6 (19)	0.5
Non-biologic DMARD§	23 (19)	16 (18)	7 (22)	
Biologic DMARD¶	17 (14)	11 (12)	6 (19)	
Corticosteroid monotherapy**	4 (3)	4 (4)	0 (0)	
Combination therapy	45 (37)	32 (35)	13 (41)	

*Comparing the detectable antibody group with the undetectable antibody group.
†Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, reactive arthritis and inflammatory bowel disease-associated arthritis.
‡Overlap connective tissue disease denotes a combination of two or more of the above conditions, also includes systemic sclerosis.
§Azathioprine, hydroxychloroquine, leflunomide, methotrexate, mycophenolate, sulfasalazine and tacrolimus.
¶Adalimumab, certolizumab, etanercept, infliximab, tocilizumab, ustekinumab, ixekizumab, belimumab, rituximab, tofacitinib and abatacept.
**Prednisone and prednisone equivalents.
DMARD, disease-modifying antirheumatic drug; mRNA, messenger RNA.

Table 2 Participant immunomodulatory therapy,* stratified by humoral immune response to the first dose of SARS-CoV-2 mRNA vaccine

	Detectable antibody (n=91)	Undetectable antibody (n=32)	P value
Medication, n (%)			
Non-biologic			
Azathioprine	9 (10)	4 (12)	0.7
Hydroxychloroquine	27 (30)	10 (31)	0.9
Mycophenolate†	3 (3)	8 (25)	0.001
Sulfasalazine	4 (4)	1 (3)	0.9
Tacrolimus	0 (0)	2 (6)	0.07
Leflunomide	2 (2)	2 (6)	0.3
Methotrexate	10 (11)	3 (9)	0.9
Biologic			
Abatacept	3 (3)	3 (9)	0.5
Belimumab	5 (5)	5 (16)	0.1
Interleukin inhibitor‡	6 (7)	0 (0)	0.3
Rituximab	2 (2)	4 (12)	0.04
TNF inhibitor§	16 (18)	1 (3)	0.07
Tofacitinib	2 (2)	1 (3)	0.9

*Since participants could report more than one medication, the total N in this table is greater than the stated cohort size.
†Mycophenolic acid or mycophenolate mofetil.
‡Interleukin inhibitors: tocilizumab, ustekinumab and ixekizumab.
§TNF inhibitors: adalimumab certolizumab, etanercept and infliximab.
mRNA, messenger RNA; TNF, tumour necrosis factor.

At a median (IQR) of 22 (18-26) days after the first vaccine dose, 74% (binomial exact 95% CI, 65% to 81%) had a detectable anti-RBD antibody response (online supplemental table 1). Younger participants appeared more likely to develop an antibody response (p=0.06). No differences were detected between disease groups or overall immunomodulatory therapy categories. However, those on regimens including mycophenolate or rituximab were less likely to develop an antibody response (p=0.001 and p=0.04, respectively) (table 2). Nearly all patients (94%) on anti-tumour necrosis factor (TNF) inhibitor therapy had detectable antibodies.

In this study of the immune response to the first dose of the SARS-CoV-2 mRNA vaccine in patients with RMD, the majority of participants developed detectable anti-SARS-CoV-2 RBD antibodies; however, patients on regimens including mycophenolate or rituximab were less likely to develop an antibody response. Overall, there were no major differences by diagnosis or being on immunomodulatory therapy (versus not being on therapy), though consistent with prior studies younger patients were more likely to develop antibody responses. Nearly all patients on anti-TNF therapy developed detectable antibody. These associations warrant further investigation.

Rituximab and methotrexate have been shown to reduce humoral responses to influenza and pneumococcal vaccines.[2 3] We found that patients on rituximab were less likely to develop

Ann Rheum Dis: first published as 10.1136/annrheumdis-2021-220289 on 23 March 2021. Downloaded from http://ard.bmj.com/ on April 6, 2021 at Universite de Bordeaux. Protected by copyright.

antibody response, yet methotrexate did not negatively impact antibody development. In addition, we found that patients on mycophenolate were less likely to develop antibody response to mRNA vaccination, consistent with observed experience of SARS-CoV-2 mRNA vaccination in the solid organ transplant population[4] and reduced response to human papillomavirus vaccination in patients with SLE.[5]

Limitations of this study include a small, non-randomised sample; limited information on immunomodulatory dosage and timing; lack of serial measurements; and use of an EIA designed to detect antibody response after natural infection. Furthermore, these are data on the first-dose response to a two-dose series.

Nearly half of the patients with RMD have expressed hesitancy or unwillingness to receive a SARS-CoV-2 mRNA vaccine due to a paucity of data[6]; however, this report can provide reassurance to patients and their providers. We did, however, observe that certain lymphocyte-modulating therapies were associated with poorer humoral vaccine response; potential exploratory strategies to increase immunogenicity in this subgroup may involve adjustment in immunomodulatory therapy, dosage or timing around vaccination.

Brian J Boyarsky ,[1] **Jake A Ruddy** ,[1] **Caoilfhionn M Connolly** ,[2] **Michael T Ou** ,[1] **William A Werbel** ,[3] **Jacqueline M Garonzik-Wang** ,[1] **Dorry L Segev** ,[1,4] **Julie J Paik** [2]

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

Correspondence to Dr Dorry L Segev, Epidemiology Research Group in Organ Transplantation, Johns Hopkins, Baltimore MD 21205, Maryland, USA; dorry@jhmi.edu

Handling editor Josef S Smolen

Twitter Brian J Boyarsky @BrianBoyarsky, Caoilfhionn M Connolly @CaoilfhionnMD, Jacqueline M Garonzik-Wang @jgaronzikwang and Dorry L Segev @Dorry_Segev

Contributors All authors contributed equally to the manuscript.

Funding This research was made possible with generous support of the Ben-Dov family. This work was supported by grant numbers F32DK124941 (Boyarsky) and K23DK115908 (Garonzik-Wang) from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), by K24AI144954 (Segev) from National Institute of Allergy and Infectious Diseases (NIAID), by K23AR073927 (Paik) from NIAMS and by grant gSAN-201C0WW from the Transplantation and Immunology Research Network of the American Society of Transplantation (Werbel). 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.

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.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

This article is made freely available for use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

© Author(s) (or their employer(s)) 2021. No commercial re-use. See rights and permissions. Published by BMJ.

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220289).

BJB and JAR are joint first authors.

DLS and JJP are joint senior authors.

Check for updates

To cite Boyarsky BJ, Ruddy JA, Connolly CM, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2021-220289

Received 5 March 2021
Revised 9 March 2021
Accepted 11 March 2021

Ann Rheum Dis 2021;**0**:1–2. doi:10.1136/annrheumdis-2021-220289

ORCID iDs
Brian J Boyarsky http://orcid.org/0000-0001-6902-9854
Jake A Ruddy http://orcid.org/0000-0002-1323-8857
Caoilfhionn M Connolly http://orcid.org/0000-0002-1898-3530
Michael T Ou http://orcid.org/0000-0002-9768-5004
William A Werbel http://orcid.org/0000-0003-2943-5895
Jacqueline M Garonzik-Wang http://orcid.org/0000-0002-2789-7503
Dorry L Segev http://orcid.org/0000-0002-1924-4801
Julie J Paik http://orcid.org/0000-0001-8436-1601

REFERENCES

1 Higgins V, Fabros A, Kulasingam V. Quantitative measurement of anti-SARS-CoV-2 antibodies: analytical and clinical evaluation. *J Clin Microbiol* 2021. doi:10.1128/JCM.03149-20. [Epub ahead of print: 22 Jan 2021].
2 Bingham CO, Looney RJ, Deodhar A, *et al*. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. *Arthritis Rheum* 2010;62:64–74.
3 Park JK, Lee YJ, Shin K, *et al*. Impact of temporary methotrexate discontinuation for 2 weeks on immunogenicity of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. *Ann Rheum Dis* 2018;77:898–904.
4 Boyarsky BJ, Werbel WA, Avery RK, *et al*. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. *JAMA* 2021. doi:10.1001/jama.2021.4385. [Epub ahead of print: 15 Mar 2021].
5 McMahan ZH, Bingham CO. Effects of biological and non-biological immunomodulatory therapies on the immunogenicity of vaccines in patients with rheumatic diseases. *Arthritis Res Ther* 2014;16:506.
6 Felten R, Dubois M, Ugarte-Gil MF, *et al*. Vaccination against COVID-19: expectations and concerns of patients with autoimmune and rheumatic diseases. *Lancet Rheumatol* 2021;16. doi:10.1016/S2665-9913(21)00039-4. [Epub ahead of print: 22 Feb 2021].

Ann Rheum Dis: first published as 10.1136/annrheumdis-2021-220289 on 23 March 2021. Downloaded from http://ard.bmj.com/ on April 6, 2021 at Universite de Bordeaux. Protected by copyright.