

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.

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 erythematosus	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.

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%).

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 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 population⁴ 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 data⁶; 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.

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