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Absence of Humoral Response After Two-Dose SARS-CoV-2 Messenger RNA Vaccination in Patients With Rheumatic and Musculoskeletal Diseases: A Case Series

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Author, Article and Disclosure Information

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Background: Patients with rheumatic and musculoskeletal diseases (RMDs) are at increased risk for SARS-CoV-2 infection because of both the immunomodulatory effects of their underlying diseases and treatment with immunosuppressive agents. Early data have suggested limited immunogenicity of SARS-CoV-2 messenger RNA (mRNA) vaccines in immunocompromised patients (1), and although most patients with RMDs developed a robust response to the first dose of the mRNA vaccine (2), an important subset of patients did not mount an appreciable humoral response. Thus, we sought to analyze a subset of 20 patients with RMDs who did not develop a detectable antibody response 1 month after completion of 2-dose mRNA vaccination against SARS-CoV-2.

Objective: To evaluate the clinical characteristics of patients with RMDs and absence of a humoral vaccine response.

Case Report: Patients aged 18 years or older with RMDs were recruited to participate in this prospective cohort assessing SARS-CoV-2 vaccine response through a digital

campaign between 7 December 2020 and 11 March 2021. Demographic characteristics, diagnoses, and immunosuppressive regimens were collected. One month after the second dose, venipuncture samples were obtained and tested on the semiquantitative Elecsys anti–SARS-CoV-2 S enzyme immunoassay (Roche), which tests for antibodies against the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein—a consistent correlate of neutralizing antibody (3). Twenty participants with undetectable anti-RBD antibodies were included in this case series. This study was approved by the Johns Hopkins Institutional Review Board.

Twenty participants did not have detectable anti-RBD antibodies (<0.4 U/mL) at a median of 30 days (interquartile range, 28 to 36 days) after the second dose of the SARS-CoV-2 mRNA vaccine (Table). Most were female (95%) and White (90%), and the median age was 46 years (interquartile range, 37 to 51 years). Sixty percent received the Pfizer-BioNTech and 40% received the Moderna mRNA vaccine series. The most common diagnosis was systemic lupus erythematosus (50%), followed by myositis (25%) and vasculitis (15%). The final 2 participants reported Sjögren syndrome and sarcoidosis. Most participants were receiving multiple immunosuppressive agents (90%); maintenance corticosteroids were a part of 16 participant regimens (80%), with a median dose of 5 mg (range, 2.5 to 55 mg). Rituximab (55%) was the most commonly prescribed biologic agent, whereas mycophenolate (50%) was the most frequently reported disease-modifying antirheumatic drug. The median timing of rituximab infusion before dose 1 was 14 weeks (interquartile range, 7 to 19 weeks). Only 2 participants (10%) were not receiving rituximab or mycophenolate; rather, they were treated with belimumab and a combination of azathioprine and tacrolimus, respectively. Three participants (15%) reported use of intravenous immunoglobulin. There were no reported diagnoses of COVID-19 during follow-up.

Table. Clinical Characteristics of Participants With RMD and Absence of Humoral Response 1 Month After 2-Dose SARS-CoV-2 Messenger RNA Vaccination

Table. Clinical Characteristics of Participants With RMD and Absence of Humoral Response 1 Month After 2-Dose SARS-CoV-2 Messenger RNA Vaccination

Participant	Age, y	Sex	Race	Diagnosis	Vaccine Manufacturer	Time From Dose 2 to Antibody Testing, d	Disease-Modifying Antirheumatic Drug and/or Biologic	Total Daily Dose of Prednisone, mg
1	57	Female	White	Myositis	Moderna	28	Methotrexate and rituximab	5
2	37	Female	White	Myositis	Moderna	27	Azathioprine and tacrolimus	14
3	70	Female	White	Myositis	Moderna	26	Hydroxychloroquine, IVIg, and mycophenolate	NA
4	51	Female	White	Myositis	Pfizer-BioNTech	30	Rituximab	5
5	52	Female	White	Myositis	Pfizer-BioNTech	33	Rituximab	3
6	55	Male	White	Sarcoidosis	Pfizer-BioNTech	51	Infliximab and mycophenolate	3
7	22	Female	White	Sjögren syndrome	Moderna	41	Rituximab	NA
8	48	Female	White	Systemic lupus erythematosus	Moderna	32	Hydroxychloroquine, mycophenolate, and tacrolimus	5
9	50	Female	White	Systemic lupus erythematosus	Moderna	28	Hydroxychloroquine, IVIg, mycophenolate, and rituximab	5
10	57	Female	White	Systemic lupus erythematosus	Moderna	27	Hydroxychloroquine, mycophenolate, and rituximab	5
11	37	Female	White	Systemic lupus erythematosus	Pfizer-BioNTech	41	Mycophenolate	5
12	42	Female	White	Systemic lupus erythematosus	Pfizer-BioNTech	22	Belimumab and mycophenolate	5
13	42	Female	American Indian or Alaska Native	Systemic lupus erythematosus	Pfizer-BioNTech	29	Hydroxychloroquine and mycophenolate	5
14	47	Female	Asian	Systemic lupus erythematosus	Pfizer-BioNTech	39	Belimumab	5
15	51	Female	White	Systemic lupus erythematosus	Pfizer-BioNTech	28	Rituximab	5
16	35	Female	White	Systemic lupus erythematosus	Pfizer-BioNTech	29	Methotrexate, sulfasalazine, and rituximab	2.5
17	44	Female	White	Systemic lupus erythematosus	Pfizer-BioNTech	34	Hydroxychloroquine and mycophenolate	5
18	31	Female	White	Vasculitis	Moderna	26	Azathioprine, IVIg, and rituximab	NA
19	33	Female	White	Vasculitis	Pfizer-BioNTech	38	Mycophenolate and rituximab	55
20	39	Female	White	Vasculitis	Pfizer-BioNTech	31	Rituximab	NA

IVIg = intravenous immunoglobulin; NA = not applicable; RMD = rheumatic and musculoskeletal diseases.

Discussion: In this case series, we describe the clinical characteristics of 20 patients with RMDs who did not develop detectable anti-RBD antibodies 1 month after SARS-CoV-2 mRNA vaccination. Systemic lupus erythematosus was the most common diagnosis. Rituximab and mycophenolate were the most commonly prescribed disease-modifying therapies. Although rituximab and methotrexate have been shown to reduce humoral response to both influenza and pneumococcal vaccines (4), impairment of vaccine response by other conventional disease-modifying antirheumatic drugs has not been shown. However, mycophenolate has recently been associated with a diminished humoral response to the first dose of SARS-CoV-2 mRNA vaccination in transplant recipients and patients with RMDs (1, 2).

A unifying factor among patients in this case series was the use of either a B-lymphocyte–depleting agent or medication that affects lymphocytes. This supports the critical role of B-cell immunocompetence in generating appropriate response to

vaccine antigen and contrasts with the robust anti-RBD responses seen in other patients with RMDs (2). Of note, participants reported rituximab infusion at a median of 14 weeks before the first vaccine dose. Rituximab has been associated with worse outcomes in patients with RMDs and SARS-CoV-2 infection (5), and thus it is of further concern that these patients may not derive protection from vaccination.

Limitations of this study include its lack of external validity given homogeneity in age and sex of the case series as well as its nonrandomized design.

Additional research is required to further characterize the humoral and cellular responses to SARS-CoV-2 vaccination in patients with RMDs. Optimization of vaccine response in patients receiving B-cell–modulating agents may require perivaccination adjustment in dosing and timing of these agents. Patients receiving these medications should be aware of the potential for suboptimal vaccine response and the need for ongoing vigilance in observing nonpharmacologic preventive measures.

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