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Effect of mycophenolate mofetil dose on antibody response following initial SARS-CoV-2 vaccination in patients with systemic sclerosis

Published Online
April 27, 2022
https://doi.org/10.1016/
S2665-9913(22)00100-X

An attenuated response to SARS-CoV-2 vaccination has been observed in several immunosuppressed populations.[1,2] Among patients with rheumatic diseases, the use of lymphocyte depleting therapies, such as mycophenolate mofetil and rituximab, have been associated with reduced rates of seroconversion.[2] Mycophenolate mofetil is the mainstay of immunosuppressant therapy for patients with systemic sclerosis,[3] and is often used to treat skin and lung involvement. Lung disease, specifically, has been associated with increased morbidity and mortality from COVID-19.[4] Given the risk of both poor vaccine response and severe COVID-19 outcomes in this patient population, we sought to identify factors associated with negative antibody response after initial SARS-CoV-2 vaccination in a well characterised cohort of patients with systemic sclerosis.

	Patients with positive antibody response (n=70)	Patients with negative antibody response (n=30)	Total (n=100)	p value
2013 American College of Rheumatology criteria	68/70 (97%)	26/30 (87%)	94/100 (94%)	0·064
Age, years*	59·4 (49·1–66·1)	60·5 (50·0–64·0)	60·4 (49·6–64·9)	0·88
Sex				
Female	64/70 (91%)	25/30 (83%)	89/100 (89%)	0·24
Male	6/70 (9%)	5/30 (17%)	11/100 (11%)	0.24
Race and ethnicity				
White	55/70 (79%)	18/30 (60%)	73/100 (73%)	0·080
Black	9/70 (13%)	3/30 (10%)	12/100 (12%)	1·00
South Asian	3/70 (4%)	2/30 (7%)	5/100 (5%)	0·64
East Asian	1/70 (1%)	4/30 (13%)	5/100 (5%)	0·030
Middle Eastern	1/70 (1%)	1/30 (3%)	2/100 (2%)	0·51
Hispanic or Latino	4/63 (6%)	3/28 (11%)	7/91 (8%)	0·67
Other	1/70 (1%)	2/30 (7%)	3/100 (3%)	0·21
Ever smoker	21/59 (36%)	10/27 (37%)	31/86 (36%)	0·90
BMI >30 kg/m²	19/70 (27%)	4/27 (15%)	23/100 (23%)	0·13
Age of systemic sclerosis onset, years†	39·4 (28·9–52·5)	47·0 (28·9–53·2)	42·2 (28·9–52·9)	0·54
Disease duration, years*	15·5 (8·2–20·8)	9·8 (4·9–19·8)	14·0 (7·6–20·3)	0·14
Diffuse cutaneous subtype	33/70 (47%)	18/30 (60%)	51/100 (51%)	0·24
Maximum modified Rodnan skin score	7 (4–20)	14 (4–25)	10 (4–21)	0·43
Lowest FVC <70%	29/52 (56%)	13/24 (54%)	42/76 (55%)	0·90
Maximum right ventricular systolic pressure >40 mm Hg	16/42 (38%)	6/18 (33%)	22/60 (37%)	0·73
Renal crisis	0/70 (0%)	1/30 (3%)	1/100 (1%)	0·30
Maximum Medsger Raynaud's severity score ≥2‡	32/57 (56%)	16/26 (62%)	48/83 (58%)	0·64
Maximum Medsger lung severity score ≥2‡	40/55 (73%)	18/26 (69%)	58/81 (72%)	0·75
Maximum Medsger heart score ≥2‡	13/58 (22%)	5/24 (21%)	18/82 (22%)	0·88
Maximum Medsger gastrointestinal score ≥2‡	38/58 (66%)	13/26 (50%)	51/84 (61%)	0·18
Maximum Medsger kidney score ≥2‡	1/57 (2%)	2/25 (8%)	3/82 (4%)	0·22

(Table continues on next page)

We used the research registry from the Johns Hopkins Scleroderma Center (Baltimore, MD, USA) to identify patients with systemic sclerosis who had undergone initial SARS-CoV-2 vaccination (with either a two-dose mRNA vaccine or single-dose adenoviral vector) between Jan 6 and Aug 22, 2021, and had a clinically obtained SARS-CoV-2 antibody test following vaccination. The registry is a prospective longitudinal cohort that includes patients who meet the 2013 criteria from the American College of Rheumatology–European League Against Rheumatism for systemic sclerosis, the 1980 criteria from the American College of Rheumatology for systemic sclerosis, or who have at least three of five features of CREST syndrome (ie, calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasias). Patients with previous COVID-19 or transplant recipients were excluded. Patients underwent testing of total anti-spike SARS-CoV-2 IgG using commercially available assays, which included the anti-SARS-CoV-2 S1 IgG (Johns Hopkins, Baltimore, MD, USA; positive >1·24 arbitrary units [AU]/mL), semiquantitative anti-SARS-CoV-2 S1/S2 IgG (Quest, Secaucus, NJ, USA; positive ≥1 AU/mL), and anti-S1/receptor binding domain (RBD) IgG (Labcorp, Burlington, NC, USA; positive >0·8 U/mL). The Johns Hopkins Institutional Review Board approved this study (IRB00290754), and participants gave written informed consent before entry into the Johns Hopkins Scleroderma registry.

To characterise clinical phenotypes, variables included systemic sclerosis subtype, age of onset, disease duration, and autoantibodies specific to systemic sclerosis. Disease severity was characterised by use of maximum values of the modified Rodnan skin score; Medsger heart, kidney, lung, and muscle severity scores; and right ventricular systolic pressure on echocardiogram. Minimum forced vital capacity and diffusing capacity of the lungs for carbon monoxide on pulmonary function tests were used. Vaccine type and dates were obtained from chart review. Differences in clinical characteristics were compared between antibody response (ie, positive or negative) using a χ^2 test, Fisher's exact test, log-binomial, or Wilcoxon rank-sum tests, as appropriate.

We evaluated anti-SARS-CoV-2 IgG in 100 patients (table); 89 (89%) were female with a median age of 60·4 years (IQR 49·6–64·9). Among 99 patients whose vaccine type was known, 54 (55%) received two doses of BNT162b2 (Pfizer–BioNTech), 41 (41%) had two doses of mRNA-1273 (Moderna), and four (4%) had a single dose of Ad26.COV2.S vaccine (Johnson & Johnson). 51 (51%) of 100 patients had diffuse cutaneous systemic sclerosis. Of those with pulmonary function test data, 42 (55%) of 76 patients had a forced vital capacity of less than 70% predicted, and 22 (37%) of 60 patients had right ventricular systolic pressure above 40 mm Hg. Of the total cohort, most (86 [86%]) were prescribed immunosuppressant therapy; 14 (14%) were on two or more immunosuppressant therapies. The most prescribed therapy was mycophenolate mofetil (65 [65%]), with a median daily dose of 2 g (IQR 1·5–3·0). Among the 65 patients receiving mycophenolate mofetil, four (6%) held peri-vaccination immunosuppression.

70 (70%) patients had positive antibody response at a median of 83·5 days (IQR 48·0–124·5) following primary vaccination. There was no significant difference in clinical phenotypes, disease severity, vaccine type, or time to antibody testing; however, there was a greater proportion of patients with RNA polymerase III antibody in the group testing negative for anti-SARS-CoV-2 IgG. Among patients with a negative antibody response, a greater proportion had been prescribed mycophenolate mofetil (24 [80%] of 30 *vs* 41 [59%] of 70; p=0·04) and had received rituximab within 15 months before vaccination (nine [30%] *vs* four [6%]; p=0·0010), compared with those with a positive antibody response. Among patients receiving mycophenolate mofetil, those

	Patients with positive antibody response (n=70)	Patients with negative antibody response (n=30)	Total (n=100)	p value
(Continued from previous page)				
Maximum Medsger muscle score ≥2‡	6/58 (10%)	4/26 (15%)	10/84 (12%)	0·49
Anti-centromere antibodies	5/52 (10%)	0/24 (0%)	5/76 (7%)	0·17
Anti-topoisomerase I antibodies	18/51 (35%)	10/25 (40%)	28/76 (37%)	0·69
RNA polymerase III antibodies§	10/41 (24%)	9/17 (53%)	19/58 (33%)	0·035
Vaccine type				
BNT162b2	40/70 (57%)	14/29 (48%)	54/99 (55%)	0·42
mRNA-1273	28/70 (40%)	13/29 (45%)	41/99 (41%)	0·66
Ad26.COV2.S	2/70 (3%)	2/29 (7%)	4/99 (4%)	0·58
Time from vaccination to testing, days	77 (36–124)	86·5 (57–126)	83·5 (48–124·5)	0·24
Immunosuppressant therapy¶	56/70 (80%)	30/30 (100%)	86/100 (86%)	0·0090
Mycophenolate therapy‖	41/70 (59%)	24/30 (80%)	65/100 (65%)	0·04
Daily mycophenolate dose, mg‖	2000 (1000–2000)	2500 (2000–3000)	2000 (1500–3000)	0·0080
Mycophenolate dose, g/day‖	..	..	..	0·010
<2·0	15/41 (37%)	3/24 (13%)	18/65 (28%)	..
2·0 to <3·0	17/41 (41%)	10/24 (42%)	27/65 (42%)	..
3·0	9/41 (22%)	11/24 (46%)	20/65 (31%)	..
Methotrexate therapy	13/70 (19%)	4/30 (13%)	17/100 (17%)	0·52
Weekly methotrexate dose, mg	20 (15–20)	17·5 (12·5–22·5)	20 (15–20)	1·00
Rituximab therapy (within 15 months of vaccine)**	4/70 (6%)	9/30 (30%)	13/100 (13%)	0·0010
Hydroxychloroquine	16/70 (23%)	2/30 (7%)	18/100 (18%)	0·053
Prednisone	18/70 (26%)	5/30 (17%)	23/100 (23%)	0·33
Prednisone dose, mg	8 (6–8)	6 (5–8)	8 (5–8)	0·58
>1 immunosuppressant medication¶	9/70 (13%)	5/30 (17%)	14/100 (14%)	0·62
Withheld immunosuppression	9/56 (16%)	2/23 (9%)	11/79 (14%)	0·49
Withheld mycophenolate	4/40 (10%)	0/23 (0%)	4/63 (6%)	0·29
Withheld methotrexate	4/14 (29%)	2/3 (67%)	6/17 (35%)	0·52

Data are n (%) or median (IQR). FVC=forced vital capacity. *Age and disease duration were calculated at vaccination. †Onset of systemic sclerosis defined by the date of the first non-Raynaud's disease symptom. ‡Moderate-to-severe Raynaud's disease score: digital pits, ulceration, or gangrene. Moderate-to-severe lung score: FVC, diffusing capacity for carbon monoxide, or both <70% predicted, and mild-to-severe pH or oxygen dependence. Moderate-to-severe heart score: left ventricular ejection fraction <45%, clinical signs of left or right heart failure, or sustained clinically important arrhythmia. Moderate-to-severe gastrointestinal score: high-dose acid reflux medications, antibiotics for bacterial overgrowth, malabsorption syndrome, episodes of pseudo-obstruction or total parental nutrition requirement. Moderate-to-severe kidney score: serum creatinine ≥1·7 mg/dL or at least two urine proteins. Moderate-to-severe muscle score: strength of ≤3/5 in the upper or lower extremities or the requirement of ambulatory aids. §All patients with RNA polymerase III antibodies were on mycophenolate mofetil, except for one who was on rituximab. Among patients with RNA polymerase III antibodies who had a negative humoral response, median mycophenolate mofetil dose was 2750 mg per day. Among patients with RNA polymerase III antibodies who had a positive humoral response, median mycophenolate mofetil dose was 1250 mg per day. ¶Defined as more than one disease-modifying anti-rheumatic drug, biological therapy, or glucocorticoid dose (>5 mg prednisone or equivalent). ‖Includes mycophenolic acid and mycophenolate mofetil; mycophenolate 500 mg is equivalent to 360 mg mycophenolic acid. **All patients who had ever received rituximab infusion therapy received it within 15 months of vaccine.

Table: **Demographics, clinical features, and immunosuppressive therapy in patients with systemic sclerosis, stratified by anti-SARS-CoV-2 antibody response**

with negative antibody response had been prescribed a higher dose (2·5 g *vs* 2·0 g; p=0·010) than had patients with a positive antibody response, and those receiving high-dose mycophenolate mofetil (3·0 g) were less likely to have antibody response than were those receiving a low dose (<3·0 g; p=0·010).

Limitations of this study include the retrospective design, convenience sampling, and heterogeneity in SARS-CoV-2- antibody assay. Given differential sensitivity and specificity of antibody assays, we used serological response as the outcome of interest, as opposed to absolute antibody titre. Testing was performed at a median 3 months following vaccination and, although antibody titres can decay over time, serological response has been shown to be durable at this timepoint.[5] Small sample size might have limited our ability to detect other associations. Strengths of this study include novel information in a well phenotyped cohort of patients with systemic sclerosis.

In conclusion, 30 (30%) of 100 patients with systemic sclerosis who were tested for anti-SARS-CoV-2 IgG did not show evidence of an antibody response following initial SARS-CoV-2 vaccination. Consistent with previous findings,[2,6,7] use of mycophenolate mofetil or rituximab was associated with negative antibody response. To our knowledge, this is the first report to investigate the effects of mycophenolate mofetil dose on anti-SARS-CoV-2 IgG antibody response in patients with systemic sclerosis, with patients on high-dose mycophenolate mofetil the least likely to have detectable antibodies. Although a temporary peri-vaccination hold of mycophenolate mofetil augments humoral response in transplant recipients and in patients with rheumatic diseases,[8,9] this might not be appropriate for all patients; temporary use of low-dose mycophenolate mofetil might represent an alternative strategy to enhance SARS-CoV-2 vaccine response. Our findings highlight the need for ongoing studies to evaluate additional strategies, such as peri-vaccination modulation of immunosuppression, additional vaccine doses, and consideration of pre-exposure prophylaxis to protect this susceptible patient population.

RW and CMC contributed equally. CAM reports consulting fees from Boehringer Ingelheim and payment for expert testimony from the National Vaccine Injury Compensation Program–US Department of Health and Human Services. All other authors declare no competing interests. This work was supported in part by grant numbers K23AR073927 (JJP), T32 AR048522–18 (RW), R01 AR073208 (AAS), and P30 AR070254 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases–National Institutes of Health; the Scleroderma Research Foundation; the Martha McCrory Professorship (FW); and the Johns Hopkins in Health initiative. We thank Adrianne Woods for data management.

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