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Antibody durability 6 months after two doses of SARS-CoV-2 mRNA vaccines in patients with rheumatic and musculoskeletal disease

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Antibody response following SARS-CoV-2 vaccination has been shown for up to 6 months in immunocompetent populations.[1] Although we previously described overall stability of SARS-CoV-2 antibody titres at 3 months in patients with rheumatic and musculoskeletal disease,[2,3] few longitudinal data exist beyond 3 months in immunosuppressed patients with rheumatic and musculoskeletal disease. Additionally, with the US Food and Drug Administration authorisation of third vaccine doses for immunosuppressed individuals,[4,5] the optimal timing for such doses in this patient group remains unknown. In this Comment, we describe antibody responses in a cohort of patients with rheumatic and musculoskeletal diseases on immunosuppression 6 months after completing the two-dose SARS-CoV-2 mRNA vaccine series.

We studied adults with rheumatic and musculoskeletal disease on immunosuppression who had received two doses of mRNA vaccine (BNT162b2 or mRNA-1273) between Jan 5 and April 28, 2021. Participants gave informed consent to participate before taking part in this study. This study was approved by the Johns Hopkins Institutional Review Board (IRB00248540). As previously described, demographics and clinical characteristics were collected via electronic questionnaire.[5] Serial antibody testing was undertaken at months 1, 3, and 6 after the second vaccine dose with an anti-SARS-CoV-2 S enzyme immunoassay (Roche Elecsys, Rotkreuz, Switzerland), which tests for antibodies against the receptor binding domain (RBD) of the spike protein and represents a consistent correlate of immunity.[6] Low positive antibody response was defined as anti-RBD pan immunoglobulin (Ig) 0·8–50·0 units per mL and high positive antibody response was defined as anti-RBD pan Ig of at least 50·0 units per mL on the basis of plasma-neutralising capacity in patients with convalescent COVID-19 and a modelling study across SARS-CoV-2 vaccine trials.[7,8] Participants with previous SARS-CoV-2 infection and recipients of additional vaccine doses before antibody testing at 6 months were excluded. We adapted survival methods to address right truncation of titres, in which the exact titre value was known for some participants and was only known to have exceeded a particular value (>250·0 units per mL or >2500·0 units per mL [ie, censorship]) for others. This methodology was used to calculate the medians (IQR).

Of 326 participants, 302 (93%) were female and median age was 49 years (IQR 39–59; appendix p 1). Inflammatory arthritis was the most common disorder, diagnosed in 139 (43%) patients. Hydroxychloroquine was the most frequently reported conventional synthetic disease modifying antirheumatic drug (135 patients [41%]), whereas TNF inhibitors were the most common biological therapy (84 patients [26%]). The majority of participants (207 [63%]) were on combination therapy, which was defined as two or more concomitant immunosuppressive medications.

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At a median of 29 days (IQR 28–32) after the second dose, 312 (96%) of 326 patients had positive anti-spike titres with a median titre of 1175 units per mL (447·0 to >2500·0; table). Among participants with a positive titre at 1 month, only two (<1%) had a titre below the threshold of positivity at 6 months. At a median of 91 days (87–93) after the second dose, 311 patients (95%) had positive anti-spike titres with a median titre of 647·5 units per mL (165·2–1373·0). At a median of 181 days (176–187) after the second dose, 313 participants (96%) had positive anti-spike titres with a median titre of 419 units per mL (91·9–861·0).

Overall, 313 (96%) of 326 patients had positive antibody titres 6 months after two doses of the mRNA vaccines. Of 287 participants with high positive titre values at 1 month, 250 (87%) had a high positive titre value at 6 months, compared with 37 (13%) with a low positive value. A greater proportion of participants who had received the mRNA-1273 vaccine had high positive antibody titres than did those who had received the BNT162b2 vaccine (89%

	Negative response	Low positive response	High positive response	Total at 1 month
Negative response at 1 month	11/14 (79%)	2/14 (14%)	1/14 (7%)	14/326 (4%)
Low positive response at 1 month	2/25 (8%)	14/25 (56%)	9/25 (36%)	25/326 (8%)
High positive response at 1 month	0/287 (0%)	37/287 (13%)	250/287 (87%)	287/326 (88%)
Total at 6 months	13/326 (4%)	53/326 (16%)	260/326 (80%)	..

Data are n/N (%). Anti-spike antibody response was defined per manufacturer data for the anti-SARS-CoV-2 S enzyme immunoassay (Roche Elecsys, Rotkreuz, Switzerland): negative was an anti-RBD pan Ig of <0·8 units per mL, low positive was an anti-RBD pan Ig of 0·8–50·0 units per mL, and high positive was an anti-RBD pan Ig of ≥50 units per mL. The initial ceiling of 250·0 units per mL increased to 2500·0 units per mL (positive ≥0·8 units per mL) in April, 2021. RBD=receptor binding domain. Ig=immunoglobulin.

Table: **Anti-spike antibody response 6 months after two doses of SARS-CoV-2 mRNA vaccine in patients with rheumatic and musculoskeletal disease stratified by antibody response at 1 month**

vs 72%; p<0·001; appendix p 1), with median titre of 612·4 units per mL (158·6–1042·0) in mRNA-1273 recipients and of 194·8 units/mL (40·9–618·0) in BNT162b2 recipients at 6 months. Additionally, a greater proportion of participants on monotherapy had high positive antibody titres than did those on combination therapy (94% *vs* 71%; p<0·001). Among the 12 participants with an augmented antibody response over 6 months, all individuals reported use of antimetabolites (ten with mycophenolate and two with methotrexate), whereas four participants were noted to have a decay in titre from 3 months to 6 months. All 13 patients (4%) with negative response at 6 months were on lymphodepleting therapy consisting of rituximab (ten patients), abatacept (two), or belimumab (one) in combination with another immunosuppressive therapy; nine (69%) were on concomitant glucocorticoid therapy.

Limitations of this study included an absence of an immunocompetent control group and an absence of data on both memory B cells and cellular response. We included patients without known COVID-19; however, given that we did not complete anti-nucleocapsid testing, asymptomatic infection could not be excluded.

Antibody response against SARS-CoV-2 decreased by 2·8 times from 1 month to 6 months, but remained above the threshold of predicted neutralising capacity[8] in the majority of patients 6 months after two doses of mRNA vaccine. Participants who had received the mRNA-1273 vaccine or reported use of immunosuppressive monotherapy were more likely to have a high positive antibody response at 6 months than were participants who had received the BNT162b2 vaccine or those who reported use of combination immunosuppression. Consistent with previous findings, patients on lymphodepleting or combination immunosuppression more commonly had an undetectable antibody response than did patients on other immunosuppressive therapies.[5,9] Notably, we observed increased titres in a small proportion of our cohort. All of these participants reported antimetabolite use, which might suggest a delayed antibody response in patients on some lymphodepleting therapies and is consistent with previous findings.[3,10]

Longitudinal studies evaluating the effects of differential immunosuppression and vaccine platform, as well as clinical correlates of protection, are required to inform the optimal vaccination schedule to ensure durable protective immunity in this susceptible patient population.

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Systemic sclerosis and COVID-19 vaccines: a SPIN Cohort study

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There is little information on the safety of COVID-19 vaccines in patients with autoimmune rheumatic diseases, and patient concerns about possible adverse outcomes in these diseases contribute to vaccine hesitancy.[1–3] One study reported that people with systemic sclerosis (n=104) might be more hesitant to receive a COVID-19 vaccine than those with other rheumatic diseases (n=111).[4] The only large study on vaccine experiences in patients with autoimmune rheumatic diseases (n=2860) found that patient-reported adverse reactions were similar in nature and prevalence to those in the general population;[5] however, results were not reported separately for patients with systemic sclerosis.

We surveyed participants in the international Scleroderma Patient-centered Intervention Network (SPIN) Cohort to evaluate the proportion of participants who were vaccinated against COVID-19, whether changes were made to medications before vaccination, adverse reactions and associated factors, degree of vaccine hesitancy, and perceptions about factors that are potentially important to vaccination decisions.

Detailed methods are provided in the appendix (pp 2–5). The SPIN COVID-19 Patient Advisory Team was involved in survey development. The SPIN COVID-19 Vaccine Survey (appendix pp 7–20) was done between April 9, 2021, and May 15, 2021, in English and French, with the software Qualtrics. Participants from the SPIN Cohort were invited to complete the survey by email and popup invitations for patients who completed routine cohort assessments during the study period. Responses were linked to sociodemographic and clinical data that had been previously collected through the cohort. The study received ethics approval as an amendment to the SPIN Cohort study, and written informed consent was obtained from the participants.

Participants indicated whether they had received zero, one, or two doses of a COVID-19 vaccine, and individuals who had received a vaccine were asked about the brand, vaccination date, any adjustments made to their medication, and any adverse reactions they had after each vaccine dose. Participants who had not been vaccinated were asked how likely they were to be vaccinated on a seven-point Likert scale. Participants who reported that they were unsure, more unlikely than likely, unlikely, or would certainly not get vaccinated were categorised as hesitant. All participants rated factors that were potentially important to vaccine decisions on a five-point Likert scale. Multivariable logistic regression was done to assess associations of local (sore arm) reactions and systemic reactions, separately, with age, sex, race or ethnicity, country, systemic sclerosis disease subtype, immunosuppressant use, vaccine brand, and history of COVID-19 infection.

Of 1410 active participants in the SPIN Cohort, 1000 consented to the survey, and 932 (66%) completed

For more on **SPIN** see https://www.spinsclero.com/"

See **Online** for appendix