

## High antibody response to two-dose SARS-CoV-2 messenger RNA vaccination in patients with rheumatic and musculoskeletal diseases

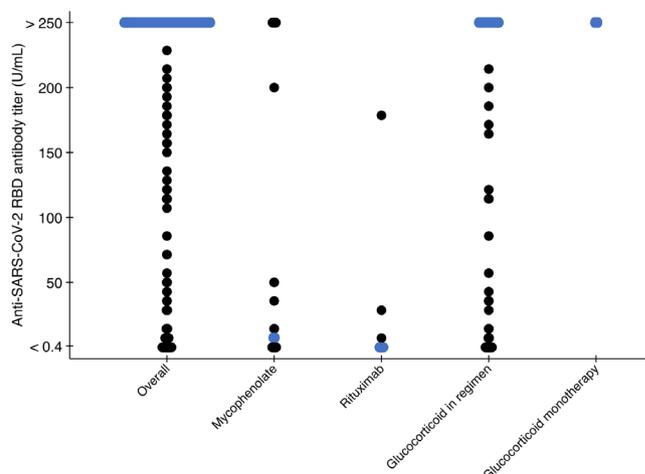
SARS-CoV-2 mRNA vaccination elicited high immunogenicity in immunocompetent people in the original vaccine trials,<sup>1 2</sup> though recent studies have shown blunted immunogenicity in patients with rheumatic and musculoskeletal diseases (RMDs) after a single dose and case reports of non-response after two doses.<sup>3 4</sup> We previously detailed antibody response in patients with RMD following the first dose of SARS-CoV-2 mRNA vaccination and herein report response and factors associated with response to two-dose vaccination in a larger cohort.

As previously reported,<sup>3</sup> patients aged  $\geq 18$  years old with RMD were recruited to participate in this prospective, observational cohort via social media outreach to national RMD organisations between 12 July 2020 and 16 March 2021. Demographics, diagnoses and therapeutic regimens were collected via participant report through the Research Electronic Data Capture tool. One month after dose 2 (D2), participants underwent SARS-CoV-2 antibody testing on the semiquantitative Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay, which measures total antibody (IgM and IgG) to the SARS-CoV-2 S receptor-binding domain (RBD) protein,<sup>5</sup> the target of the mRNA vaccines. Results range from  $<0.4$  to  $>250$  U/mL with a positive response defined as  $>0.79$  U/mL. Associations were evaluated using Fisher's exact and Wilcoxon rank-sum tests. Participants provided informed consent.

We studied 404 participants who received two doses of the SARS-CoV-2 mRNA vaccine (online supplemental table 1). The median (IQR) age was 44 (36–57), 96% were female, 9% were non-white, 49% received the Pfizer/BioNTech vaccine and 51% received Moderna, 4% had a prevaccination history of COVID-19 diagnosis and no participant reported postvaccination COVID-19 diagnosis. Most common diagnoses included inflammatory arthritis (45%) and systemic lupus erythematosus (22%). The most frequently prescribed medications were hydroxychloroquine (42%) and glucocorticoids (29%), while 51% were on combination therapy. Participants completed anti-RBD testing at a median of 29 days after D2.

Anti-SARS-CoV-2 RBD antibodies were positive in 378/404 (94%) participants (95% CI 91% to 96%) (online supplemental table 1). Median anti-RBD titre was above the upper limit of the assay ( $>250$  U/mL), while lower median titres were observed in participants on regimens including mycophenolate (8 U/mL) and rituximab ( $<0.4$  U/mL) (figure 1, online supplemental table 2). Tumour necrosis factor inhibitor use was associated with a positive antibody response (100% positive,  $p<0.001$ ), while regimens including mycophenolate (73% positive,  $p<0.001$ ), rituximab (26% positive,  $p<0.001$ ) or glucocorticoids (82% positive,  $p<0.001$ ) and a diagnosis of myositis (79% positive,  $p=0.01$ ) were associated with a negative response. Of note, 4/5 (80%) negative responders with myositis and 18/21 (86%) negative responders on glucocorticoids were on regimens including mycophenolate or rituximab; all eight on glucocorticoid monotherapy had an anti-RBD titre  $>250$  U/mL.

In this study of humoral response to two-dose SARS-CoV-2 mRNA vaccination in patients with RMD, the vast majority of participants developed anti-RBD antibodies. Among negative responders, most were on regimens containing mycophenolate or rituximab. Glucocorticoid use was also associated with



**Figure 1** Anti-SARS-CoV-2 RBD antibody titre overall (n=403\*) and by medications associated with a negative antibody response: mycophenolate included in regimen (n=41), rituximab included in regimen (n=19), glucocorticoid included in regimen (n=116) and glucocorticoid monotherapy (n=8) in patients with RMD after two-dose SARS-CoV-2 mRNA vaccination. Results range from  $<0.4$  to  $>250$  U/mL with positive antibody defined as an anti-SARS-CoV-2 RBD antibody titre  $>0.79$  U/mL by the manufacturer; blue data points indicate median titre. \*One titre value was missing from the total N (404). RBD, receptor binding domain; RMD, rheumatic and musculoskeletal disease.

a negative response, though all of these individuals were on concomitant lymphocyte-depleting therapy. Compared with patients with RMD following D1 (74% seroconversion),<sup>3</sup> this study showed increased seroconversion following two-dose vaccination (94% seroconversion). Similarly, seroconversion for those on mycophenolate-based regimens was 73% after two doses compared with 27% after D1, while the response for those on rituximab remained poor (33% seroconversion after D1, 26% seroconversion after D2). Despite a blunted humoral response in participants on these regimens, the rate of seroconversion was comparable with those seen in the original vaccine trials and existing studies on patients with RMD.<sup>1 2 6</sup>

Limitations of this study include a younger, generally female, racially homogenous population and limited information on immunomodulatory timing and dosage. Additionally, we did not evaluate for asymptomatic COVID-19 infection, and disease activity was not assessed.

While certain lymphocyte-depleting therapies were associated with failure to develop a humoral response, reassuringly, the majority of patients with RMD on a variety of immunosuppressive regimens had a robust antibody response to SARS-CoV-2 mRNA vaccination.

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