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is ever-changing with new variants. These future studies might provide rationale for additional vaccine doses for patients who are immunosuppressed or use of novel vaccines against contemporary viral variants.

In summary, these important results confirm that the COVID-19 vaccines were highly effective against infection and severity among patients with immune-mediated inflammatory diseases. These findings should encourage continued uptake of COVID-19 vaccination and future research related to waning effects, the effectiveness of additional vaccine doses, and influence of specific immunosuppressive medications.

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Factors associated with poor antibody response to third-dose SARS-CoV-2 vaccination in patients with rheumatic and musculoskeletal diseases

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Many immunosuppressed patients with rheumatic and musculoskeletal disease have a poor antibody response to two-dose SARS-COV-2 mRNA vaccination,[1,2] prompting widescale authorisation of a third vaccine dose for these patients. High antibody concentrations are required to overcome immune evasion by variants of concern in immunocompetent patients,[3] and although a third dose augments the immune response against SARS-CoV-2 in some immunosuppressed patients,[4,5] it is uncertain whether this response is sufficient for protection. Thus, identifying patients with rheumatic and musculoskeletal disease with poor response following a third dose is important in the selection of appropriate candidates for further medical interventions such as additional vaccine doses or prophylactic therapies. Herein, we describe the antibody response and factors associated with poor antibody response following a third vaccine dose in immunosuppressed patients with rheumatic and musculoskeletal disease.

Patients with rheumatic and musculoskeletal disease (aged ≥18 years) in the USA on immunosuppression without previous known COVID-19 who completed three-dose SARS-CoV-2 vaccination (two-dose mRNA series followed by single mRNA or adenoviral vector dose) were recruited via a social media campaign and provided informed consent electronically. This study was approved by the Johns Hopkins Institutional Review Board (IRB00248540). Clinical characteristics were collected via participant report. Serial antibody responses were assessed using the semi-quantitative Roche Elecsys

(Rotreuz, Switzerland) anti-SARS-CoV-2 S enzyme immunoassay, which measures total antibody to the SARS-CoV-2 S-receptor binding domain (RBD; range 0·4 with upper limit >2500 U/mL), and is recognised as a consistent correlate of neutralising antibody.[6] Poor antibody response was defined as anti-RBD titre less than 500 U/mL on the basis of predicted correlates of protective plasma neutralising capacity in COVID-19 vaccine trials.[7,8] Participant demographics and clinical characteristics were stratified by antibody response (appendix pp 1–2). Poisson regression with robust standard error was done to evaluate factors identified a priori to be associated with poor antibody response (age, third dose vaccine type, immunosuppression, and number of immunosuppressive therapies).

We evaluated serial anti-RBD titres in 511 participants (appendix p 1). 471 (92%) were women, 38 (7%) were men, and the median age was 50 years (IQR 41–60). The most common diagnosis was inflammatory arthritis (210 [41%] of 511). Participants completed standard vaccination with BNT162b2 (271 [53%] of 511) or mRNA-1273 (240 [47%]). At a median of 159 days (IQR 92–185) after participants' second dose, anti-RBD titres were negative (anti-RBD <0·8 U/mL) in 57 (11%) of 511 participants, and the median anti-RBD titre was 238 U/mL (IQR 47·9–839·6).

For their third vaccine dose, participants either received BNT162b2 (266 [52%] of 511), mRNA-1273 (240 [47%]), or Ad.26.COV2.S (5 [1%]), with most (485 [95%]) receiving a homologous third-dose vaccination. Repeat anti-RBD testing was done at a median of 30 days (IQR 28–34) after dose three. 233 (46%) of 511 participants reported holding immunosuppression peri-D3. Methotrexate was the most commonly held medication; 82 (62%) of 133 prescribed methotrexate withheld immunosuppression for a median of 1 (IQR1–2) doses in the peri-D3 period (appendix p 3). An increased antibody titre was seen in most participants (470 [92%] of 511) following the third dose.

Of those participants who were negative before the third dose, 23 (40%) of 57 showed de novo humoral response, of whom 16 (70%) of 23 were on regimens containing rituximab or mycophenolate mofetil, and 34 (60%) remained negative following the third dose (figure). The proportion of participants with titres of at least 2500 U/mL following a third dose was similar irrespective of homologous or heterologous third-dose vaccination (379 [78%] of 485 vs 17 [65%] of 26, p=0·1). Participants on immunosuppressant regimens containing rituximab were 10 times more likely to have a poor response following a third dose (adjusted incident rate ratio [aIRR] 10·00 [95% CI 6·61–15·13]; p<0·0010), and those on mycophenolate were twice as likely to have a poor response (aIRR 2·01 [95% CI 1·25–3·23]; p=0·0040; appendix p 3). 28 (7%) of 386 participants reported disease flare requiring treatment from a physician within 1 month of vaccination; appendix pp 1–2); no patient reported the need for intravenous therapy or hospital admission for treatment of flare.

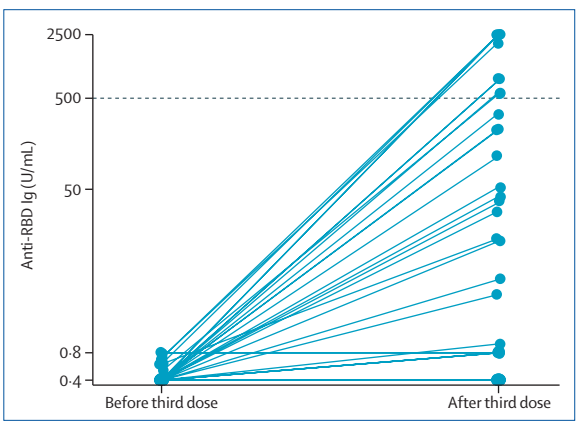

Figure: **Anti-SARS-CoV-2 RBD antibody titres before and after a third dose in patients negative for anti-RBD antibodies after the second vaccine dose**
Ig=immunoglobin. RBD=receptor binding domain.

Limitations of this study include that neutralisation capacity was not measured directly and there was not a healthy control group as a comparator. Antibody response is durable over 6 months, but titres might wane over time,[8] which might have affected titres before the third dose. We did not assess B-cell or T-cell responses. A larger sample size is required to determine differential immunogenicity of homologous versus heterologous vaccine schedules, as well as determination of optimal perivaccination modulation of immunosuppression. Disease flares were based on patient report. Although administration of a third dose of SARS-CoV-2 vaccine has been associated with a significantly lower rate of COVID-19 infection in immunocompetent persons compared to two-dose vaccination,[9,10] associations between vaccine doses and antibody titres and clinical outcomes in immunosuppressed patients is required.

In summary, we observed an augmented humoral response in the majority (92%) of patients with rheumatic and musculoskeletal disease following a third

See Online for appendix

dose of SARS-CoV-2 vaccination, highlighting the benefit of a three-dose vaccination schedule for these patients. We also identified a subset of patients, namely those on regimens containing either mycophenolate or CD20-depleting therapy, in which antibody responses remained suboptimal after a third dose. These patients are ideal candidates for prophylactic therapies or might require additional vaccine doses to confer increased protection against COVID-19 infection. The rapidly evolving SARS-CoV-2 requires continued development and refinement of medical countermeasures such as antibody testing, vaccine schedule, and prophylactic therapies to enhance the protection of these vulnerable patients.

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Methotrexate and TNF inhibitors affect long-term immunogenicity to COVID-19 vaccination in patients with immune-mediated inflammatory disease

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Studies have revealed that patients with immune-mediated inflammatory diseases, especially those on immunomodulatory medication, have attenuated immunogenicity to COVID-19 vaccination.[1,2] These findings have informed American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) recommendations regarding use of immunomodulatory therapies peri-vaccination. Recent longitudinal studies in immunocompetent adults have found waning humoral immunity by 6-months post-vaccination.[3,4] However, despite an already diminished initial response to immunisation in patients with immune-mediated inflammatory diseases, there are scarce data regarding their longer-term humoral response.

We hypothesised that patients with immune-mediated inflammatory diseases who are treated chronically with certain disease-modifying rheumatic drugs (ie, methotrexate) or anti-cytokine therapies (ie, TNF inhibitors), would have lower rates of