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### Safety and immunogenicity of fifth dose SARS-CoV-2 vaccination in patients with autoimmune disease: a case series

#### Rheumatology key message

- Dose 5 SARS-CoV-2 vaccine is well tolerated and induces a robust antibody response in most immunosuppressed patients with autoimmune diseases.

DEAR EDITOR, The rapid evolution of the SARS-CoV-2 virus and resultant immune escape requires significantly higher circulating antibody levels to overcome immune evasion and prevent infection [1]. Immunosuppressed patients with autoimmune diseases can have attenuated responses to SARS-CoV-2 vaccination, with some having low anti-spike binding antibody levels after four vaccine doses [2]; these patients have increased rates of breakthrough COVID-19 and associated morbidity and mortality [3]. To mitigate the risk of SARS-CoV-2 infection among this vulnerable population, the Food and Drug Administration (FDA) authorized a second booster dose following a three-dose primary series of SARS-CoV-2 vaccination (i.e. a fifth dose [D5]) [4]. While primary vaccination is well tolerated in this population [5], given the potent immune response elicited by booster doses [2] and common recommendation for peri-vaccine immunosuppressive holds [6], there is concern that sequential antigenic priming events could have detrimental impact on underlying autoimmune disease. Thus, we sought to evaluate post-vaccination reactogenicity and antibody responses of immunosuppressed patients with autoimmune diseases following D5.

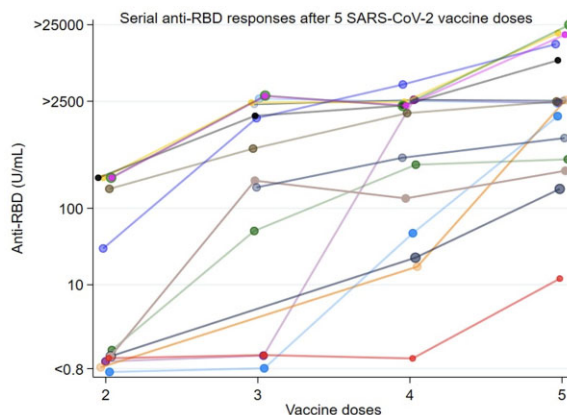
Patients with autoimmune diseases were recruited via digital outreach to a national, prospective, observational cohort study from 12/2020–4/2021. Participants provided informed consent electronically. Sixteen adult participants reported initial three-dose primary SARS-CoV-2 vaccination followed by two additional booster doses between 5 August 2021 and 20 May 2022; response to four vaccine doses was previously reported for seven participants [2]. Serial semi-quantitative SARS-CoV-2 antibody testing was completed on the Roche Elecsys® (Roche Elecsys, Rotkreuz, Switzerland) anti-SARS-CoV-2 S enzyme immunoassay (range 0.4–2500 U/ml, later expanded to 25 000 U/ml on 28 May 2022; positive >0.8 U/ml). Participants completed questionnaires detailing local and systemic reactions that were captured using an ordinal scale; graded as ‘mild’ (no interference

with daily activity) ‘moderate’ (some interference) or ‘severe’ (prevention of daily activity) on day 7 post-D5 followed by a questionnaire regarding flare of underlying autoimmune disease on day 30 post-D5 as previously described [5].

Of the 16 participants, 11 were female, with median (IQR) age of 55 (46,71) years (Supplementary Table S1, available at *Rheumatology* online); 13 were white, two were multi-racial, and one was Asian. There was a diverse spectrum of autoimmune diagnoses. Mycophenolate mofetil (MMF) was the most common immunosuppressive therapy (6/16), with median (IQR) daily dose of 2250 mg (1500, 3250 mg). Participants received either BNT162b2 (6/16) or mRNA-1273 (10/16) for D5, at median (IQR) 126 (45, 160) days post-D4. Half (8/16) reported holding at least one immunosuppressive medication peri-D5.

Although 6/16 were seronegative post-D2, a minority remained seronegative post-D3 (2/16) and only one participant remained seronegative post-D4 (Fig. 1). Pre-D5 sampling occurred at a median (IQR) 29 (27, 34) days post-D4, with a median (IQR) anti-RBD titre of 252 U/ml (28, 1426.6 U/ml); this included six participants with anti-RBD titre above the assay ceiling (2500 U/ml). At median (IQR) 26 (17, 34) days post-D5, all participants were seropositive. Among the 11 tested on assay with ceiling 2500 U/ml, five resulted >2500 U/ml, with median (IQR) titre of 371.5 U/ml (136.6, 1018.5) among the remainder. The six participants with response below assay ceiling were older [median (IQR) 59 (52,67) vs 49 (40,67)] and more commonly reported MMF use (4/6 vs 2/5). Among the five tested on expanded assay (25 000 U/ml), one tested above ceiling, with median (IQR) titre of 13 691 U/ml (8567, 18 553) among the remainder. The most common post-vaccination reactions were injection

Fig. 1 Serial Anti-SARS-CoV-2 anti-RBD responses after 5 SARS-CoV-2 vaccine doses



Each line denotes an individual participant

site pain (12/16) and myalgia (8/16); most reactions were mild without any severe reactions. There were no reports of breakthrough COVID-19 or disease flare at 30 days post-D5.

This is the first report of safety and immunogenicity of a fifth SARS-CoV-2 vaccine dose in immunosuppressed patients with autoimmune diseases. D5 boosted antibody response in all participants and induced a robust anti-spike antibody response in many. However, some participants continued to have antibody response below the threshold based on proposed minimum levels required for neutralization vs Omicron despite additional doses [1, 7], specifically those reporting use of regimens containing MMF, which has previously been associated with blunted immunogenicity [2]. D5 was well tolerated; no participant reported a flare requiring treatment post-D5, and most reported mild reactogenicity.

This study is limited by small sample size, lack of granularity on baseline disease, ceiling of anti-RBD assay and lack of formal neutralizing titres or cellular analyses; B-cell reconstitution can predict the likelihood of humoral responses among those treated with B-cell depleting agents [8]. We did not assess baseline immunoglobulin or lymphocyte subsets, nor can we exclude asymptomatic SARS-CoV-2 infections given lack of anti-nucleocapsid antibody testing.

Our findings support the administration of additional vaccine doses to augment waning or suboptimal immune response in persons with autoimmune disease, which is critical to counteract the increased immune escape of the now-dominant Omicron variant and its sublineages. Confirmation of safety, as well as durability of booster response, warrants additional evaluation in larger cohorts. While additional insights into the cellular response following booster vaccination is needed, serologic testing may provide insights into personal risk, namely identifying persons for whom additional risk mitigation interventions might be prioritized.

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## Data availability statement

The data that support the findings of this study are not publicly available due to privacy or ethical reasons.

## Supplementary data

Supplementary data are available at *Rheumatology* online.

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