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Letter to the Editor (Other)

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COVID-19 mRNA vaccine booster in patients with autoimmune rheumatic diseases

Rheumatology key messages

- Booster doses of COVID-19 vaccination are of crucial importance in patients with autoimmune rheumatic diseases.

Dear Editor, The COVID-19 pandemic continues to be a global problem and mass vaccination has been crucial for decreasing morbidity and mortality from SARS-CoV-2 infection.

It is still a matter of debate whether patients with autoimmune rheumatic diseases (ARDs) are at increased risk for adverse COVID-19 outcomes because of the underlying chronic disease, ongoing immunosuppressive treatments and comorbid conditions [1, 2]. In those patients a reduced immunogenicity of anti-SARS-CoV-2 vaccine compared with healthy controls has been observed, especially in the presence of certain concomitant therapies (i.e. rituximab, abatacept, methotrexate, mycophenolate mofetil, high doses of glucocorticoids) [3, 4].

Administration of a booster dose of the vaccine could be particularly important in these patients, but data on its efficacy and tolerability in ARDs patients are limited [5].

Fragoulis *et al.* recently reported that COVID-19-related hospitalizations and deaths were less common in booster-vaccinated than in fully vaccinated or unvaccinated patients with systemic rheumatic diseases [6].

We performed a prospective observational study at the Rheumatology Unit of the University of Pisa, Italy, to assess the antibody response to a booster dose of mRNA SARS-CoV-2 vaccine in patients with ARDs.

Consecutive patients with an established diagnosis of ARD undergoing SARS-CoV-2 vaccination were enrolled from January 2021 and clinically monitored at 4, 12 and at a later time-point between 24 and 36 weeks after the first vaccination cycle (W4, W12, W24-36) and 4 weeks after the booster dose (W4pB), with the latest evaluations carried out in February 2022. At the same time-points, blood samples were collected and IgG antibodies to SARS-CoV-2 receptor-binding domain (RBD) and neutralizing antibodies inhibiting the interaction between RBD and angiotensin converting enzyme 2 (ACE2) were evaluated using the SPIA kit (DiaMetra Srl, Immunodiagnostics System, Spello, Perugia, Italy) as previously described [4].

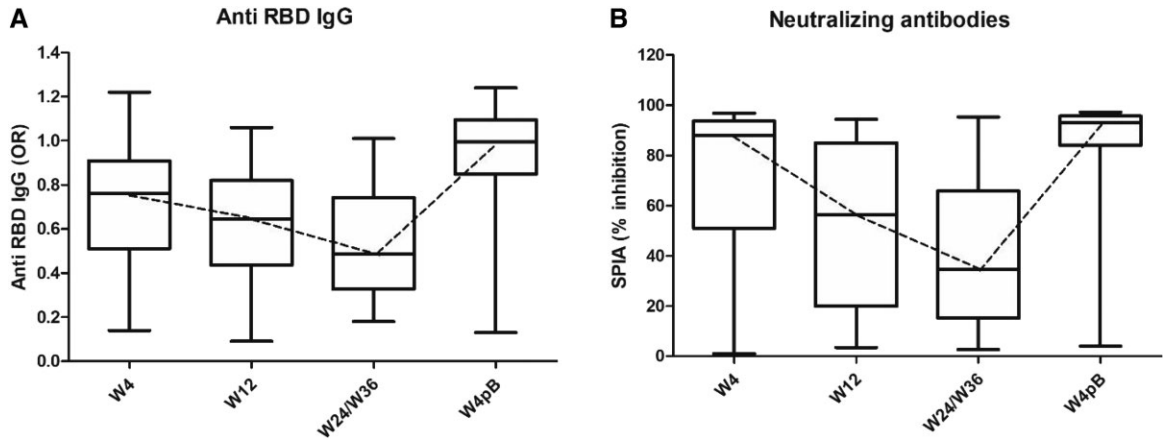
We recruited 91 patients [female : male ratio 80 : 11, mean age 55.8 (±14.2) years, mean disease duration 13.5 (±10.4) years] with the following ARDs: 64 CTD (70.3%), 20 inflammatory arthritis (22.0%), seven systemic vasculitis (7.7%). The most frequent diagnoses were SLE ($n = 30$, 33.0%), RA ($n = 14$, 15.4%), SSc ($n = 11$, 12.1%) and SS ($n = 10$, 11.0%). Nine patients had concomitant hypogammaglobulinemia (9.9%), four had SARS-CoV-2 infection before the vaccination (4.4%). For more details about diagnosis and baseline features of the whole cohort, see Supplementary Table S1, available at *Rheumatology* online.

At the time of the first vaccination cycle, 38 patients (41.8%) were on systemic glucocorticoids (GCs, median daily dose 4 mg, IQR 2–5 mg), 35 (38.5%) were on conventional synthetic DMARDs (csDMARDs), 26 (28.6%) were on biological drugs (bDMARDs) and one (1.1%) was on targeted synthetic DMARDs (tsDMARDs).

After the first vaccination cycle (W4), 86 (94.5%) and 82 (90.1%) patients were positive, respectively, for anti-RDB IgG and neutralizing antibodies. The majority of patients maintained a satisfactory serological response through W12 and W24-36; however, the antibody titres significantly decreased starting from W12 for both anti-RDB IgG and neutralizing antibodies (Fig. 1). Interestingly, for both anti-RBD IgG and neutralizing antibodies, titres were restored after the third dose ($P < 0.0001$, as compared with W24-36) (Fig. 1).

Overall, nine patients (9.9%) did not respond at W4 for anti-RBD and/or neutralizing antibodies. Their diagnosis was CTD in 77.8% of cases. Five out of nine (55.6%) were on combination therapy (GCs + csDMARDs and/or bDMARDs), three (33.3%) were on monotherapy (1/3 low dose of GCs, 2/3 csDMARDs), while one patient (11.1%) was off treatment. Hypogammaglobulinemia was present in two out of nine patients (22.2%). Comparison of baseline characteristics between responder and non-responder patients is reported in Supplementary Table S2, available at *Rheumatology* online. After the booster dose, 5/9 patients (55.6%) developed adequate titres for both anti-RBD and neutralizing antibodies. Of note, two out of the five seroconverted patients reduced the dosage or discontinued treatment with mycophenolate mofetil between the primary vaccination cycle and the administration of the booster dose and one out of five discontinued treatment with azathioprine. On the other hand, four patients (44.4%) were still non-responders even after the booster dose. All persistently non-responders were on combination therapy (3/4; all on low doses of GCs in association with mycophenolate mofetil in one case, with abatacept in one case and with methotrexate plus infliximab in the other one) or presented concomitant hypogammaglobulinemia (2/4). Clinical data of non-responders patients are detailed in

Fig. 1 Serological responses over time for anti-RBD IgG (**A**) and neutralizing antibodies (**B**) in ARDs patients



Results of anti-RBD are expressed as odds ratio of a positive internal control (OR); results of neutralizing antibodies as the percentage of inhibition of the binding of labelled ACE2 receptor to RBD coated plates. ACE2: angiotensin converting enzyme 2; ARDs: autoimmune rheumatic diseases; RBD: receptor-binding domain.

Supplementary Table S3, available at *Rheumatology* online.

Our data suggest that the administration of a booster dose of the COVID-19 vaccine is of particular importance in ARDs patients to restore a protective antibody titre after the expected time-dependent decrease. Booster dose is also crucial in non-responders to the first vaccination cycle in order to secure a higher seroconversion rate. In patients who do not respond to the third dose, different vaccination strategies should be implemented, as well as, when compatible with disease control, spacing of certain immunosuppressive drugs, as recently demonstrated for methotrexate [7].

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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