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LETTER TO THE EDITOR

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Late and booster anti-SARS-CoV-2 humoral responses in nonresponder vaccinated patients with rheumatic diseases receiving mycophenolate or rituximab: comment on the article by XXX et al

To the Editor:

Patients with systemic autoimmune rheumatic diseases (SARD) receiving immunosuppressive treatment with mycophenolate mofetil (MMF) or rituximab (RTX) exhibit altered antibody responses to SARS-CoV-2 vaccination (1–4). Such patients seem to adequately respond to a third dose, except from those treated with RTX (5,6).

Among vaccinated patients with SARD of the outpatient clinic of the Pathophysiology Department, National and Kapodistrian University of Athens, Greece (2), we identified 23 patients with SARD undergoing MMF/RTX-based treatments who had not seroconverted 1 month after the second messenger RNA (mRNA)-based SARS-CoV-2 vaccine dose (time point 1), and these patients were prospectively recruited for assessment of antibody responses before (time point 2) and after (time point 3) the administration of a third mRNA-based vaccine dose. All 23 patients undergoing MMF or RTX treatment withheld their treatment modalities following the updated American College of Rheumatology (ACR) treatment modification recommendations (7). Assessment of anti-SARS-CoV-2 S1 protein immunoglobulin G (IgG) antibodies and neutralizing activity was conducted using enzyme-linked immunosorbent assays (ELISA) from Euroimmun and GenScript Biotech, respectively (2). Characteristics of patients with SARD and time intervals between vaccine dose administration and RTX infusion are summarized in Supplementary Table 1. Of note, no patient was receiving tumor necrosis factor inhibitors, which have been shown to interfere with the antibody neutralizing activity among the different SARS-CoV-2 variants (8).

Interestingly, 3 of 23 patients with SARD (13%) showed delayed anti-SARS-CoV-2 antibody seroconversion before the third dose (late responders), whereas 20 of 23 (87%) remained seronegative up to revaccination (nonresponders). All three late responders belonged to the MMF-only group and displayed a rise in anti-SARS-CoV-2 antibodies and neutralizing activity after the third dose. Of 20 nonresponder patients with SARD, 15 (75%) developed antibodies after the third vaccine dose. Seroconversion rates across the treatment subgroups were 88.9% (eight of nine), 75% (three of four), and 57.1% (four of seven) in the MMF-only, MMF and RTX, and RTX-only subgroups, respectively (Figure 1). Neutralizing activity was above cutoff levels in 13 of 15 (87%) seropositive patients with SARD after the third vaccine dose. In an attempt to investigate the effect of IgG concentration in patients treated with RTX, different serum dilutions corrected for total IgG were applied in anti-SARS-CoV-2 assays, but variations were less than 10% (data not shown). Adverse events after the third vaccine dose were mild and transient compared with

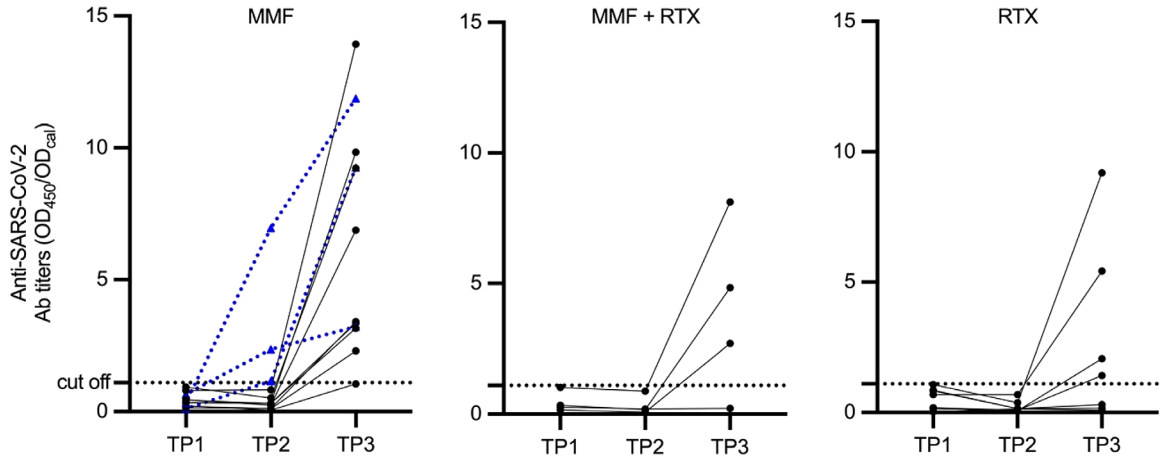

Figure 1. Antibody kinetics in patients with systemic autoimmune rheumatic disease before and after the third messenger RNA–based vaccine dose. y-Axis: optical density (OD) index corresponding to anti-SARS-CoV-2 S1 protein immunoglobulin G antibody titers; x-axis: time point antibodies were assessed after the two-dose vaccination (TP1), time point antibodies were assessed before the third dose (TP2), and time point antibodies were assessed after the third dose (TP3); black circle dots correspond to nonresponders until revaccination, and blue triangles correspond to late responders until revaccination; horizontal dotted lines indicate the predefined cutoff values. Ab, antibody; MMF, mycophenolate mofetil; RTX, rituximab.

those observed during the initial vaccination schedule. The most frequently reported side effects were pain at the injection site (56.5%), fatigue (21.7%), headache (13%), and fever (8.7%).

In accordance, Frey et al (9) reported that a small proportion of patients treated with conventional synthetic disease-modifying antirheumatic drugs, including MMF, showed delayed antibody responses over a 3-month period. In another study, nonresponder patients with SARD not previously exposed to RTX achieved an 80% seroconversion rate after a third dose without any treatment modifications, as opposed to only 18% among RTX-treated patients (5). In our study, though, the seroconversion rate in the RTX group was higher compared with the previous study, but our patients were vaccinated at least 6 months after the last RTX administration and in longer intervals from the second vaccine dose. Among the parameters defining the humoral responses after two-dose SARS-CoV-2 vaccination, only B-cell reconstitution and longer RTX-to-vaccination time periods have been found clinically significant (10).

Taken together and despite the very small number of patients included in the study, revaccination against SARS-CoV-2 seems to be efficacious for developing humoral immune responses in patients with SARD who had not previously responded to two-dose vaccination. Our findings are in line with the ACR recommendations for treatment adjustments during booster vaccination (7), and patients might benefit if (re)vaccinated at least 6 months after the last RTX treatment (7,11).

The authors declare no conflict of interest or any relationship relevant to this article that requires disclosure. All patients provided written informed consent prior to participation in the study. The study complied with the principles of the Declaration of Helsinki and the GDPR of the European Union and was approved by the Ethics Committee of the School of Medicine, National and Kapodistrian University of Athens, Greece (protocol No. 456).

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