DEAR EDITOR, Rituximab (RTX) is associated with reduced humoral response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA-based vaccine [1, 2]. A recent study has shown that a single dose of SARS-CoV-2 mRNA-based vaccine was sufficient to obtain a robust humoral response in immunocompetent individuals with a previous history of coronavirus disease 2019 (COVID-19) [3]. While research has demonstrated that immunodeficient kidney transplant recipients (KTRs) who received mRNA-based vaccines show low immunization rates, KTRs with previous exposure to SARS-CoV-2 exhibited a marked increase in antibody titre, even after a single dose of vaccine [4]. Whether this also applies to RTX-treated patients with a history of COVID-19 is unknown. Our aim was to depict the results of immunization after 1–3 doses of mRNA-based SARS-CoV-2 vaccine in RTX-treated patients with previous symptomatic COVID-19 infection.

We conducted an observational prospective usual-care study including consecutive patients with inflammatory rheumatic diseases in maintenance therapy with RTX. All patients were closely followed up by the department, including the use of RT-PCR for SARS-CoV-2 detection in case of any symptoms. All patients received a 1–3-dose regimen of mRNA-based COVID-19 vaccination (BNT162b2 Pfizer/BioNTech or mRNA-1273, Moderna). Serum IgG antibody levels against SARS-CoV-2 spike proteins were measured at the time of the following RTX infusion. The LIAISON® SARS-CoV-2 S1/S2 IgG immunoassay (DiaSorin) was used for the quantitative determination of antibodies to the receptor-binding domain of the viral spike (S) protein. Seropositivity was defined as SARS-CoV-2 Spike antibodies measured at >15 arbitrary Units (AU)/ml. The protocol and the informed consent document received Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval before initiation of the study (Comité de Protection des Personnes Paris Ile de France I, No. CPPIDF-DAP13). All patients agreed to participate in this study and provided written informed consent, which was recorded in the medical source file.

All data were expressed as median values with 95% CIs or as number and percentage (%) for continuous and categorical variables, respectively. Statistical analysis was performed using GraphPad Prism (v9.1.2) and Medcalc (v18.9.1). We used the Mann–Whitney U test and the Kruskall–Wallis test for variance on ranks for continuous variables. The $\chi^2$ test was used to test for differences in frequency (categorical variables).

We included 69 patients (60 females, median age 63 years, 95% CI 56–68 years) on maintenance therapy with RTX, including 13 with previous symptomatic COVID-19, all proven by RT-PCR (10 females, median age 58 years, 95% CI 47–70 years, of whom 3 had severe disease, defined by the need of hospitalization and/or oxygen requirement) (Supplementary Table S1, available at Rheumatology online).

Symptomatic COVID-19 occurred between March 2020 and May 2021. The median interval between the last RTX infusion and COVID-19 was 83 days (95% CI 44–179 days), and the median interval between COVID-19 and the next RTX infusion was 131 days (95% CI 114–267 days). The median interval between COVID-19 and the first dose of vaccine was 262 days (95% CI 151–365 days), and the serological response was assessed after a median of 58 days (95% CI 32–151 days) from the last dose of vaccine (third dose for 3 patients, second dose for 6 patients and first dose for 4 patients) (Fig. 1A). The 56 patients with no history of symptomatic COVID-19 infection all received three doses of vaccine (median time between the RTX infusion and the first dose of vaccine: 145 days, 95% CI 126–180 days). The serological response was assessed after a median of 59 days (95% CI 50–76 days) from the third dose of vaccination. These patients did not differ from those with a history of symptomatic COVID-19 with respect to age, gender, underlying disease, disease duration, associated CSs or DMARDs, RTX cumulative dose, or CD19 counts (Supplementary Table S1, available at Rheumatology online). The seropositivity rate was significantly higher in RTX-treated patients with previous symptomatic COVID-19 infection (11/13, 85% vs 15/56, 27%, $P < 0.001$). SARS-CoV-2 spike antibodies were also markedly increased in patients with previous symptomatic COVID-19 infection (median 119 AU/ml, 95% CI 16–400 AU/ml vs 3.80 AU/ml, 95% CI 3.80–4.81 AU/ml $P < 0.001$) (Fig. 1B). SARS-CoV-2 spike antibody titres did not significantly differ in the 26 seropositive patients according to history of COVID-19 (median 328 AU/ml, 95% CI 66–400 AU/ml vs 178 AU/ml, 95% CI 49–400 AU/ml $P = 0.44$) (Supplementary Fig. S1, available at Rheumatology online).
Antibody titres did not differ in patients with a history of symptomatic COVID-19 according to the severity of previous COVID-19 infection (severe: median 100 AU/ml, 95% CI 5.28–400 AU/ml, vs non-severe: 223 AU/ml, 95% CI 16–400 AU/ml, \(P = 0.81\)) or the number of doses of vaccine (a single dose: median 260 AU/ml, 95% CI 4.81–400 AU/ml, two doses: median 214 AU/ml, 95% CI 5.28–400 AU/ml, three doses: 71 AU/ml, 95% CI 66–400 AU/ml, \(P = 0.97\)). A trend was observed for higher antibody titres in patients with detectable B cells (CD19 < 18/μl 66 AU/ml, 95% CI 4.81–400 AU/ml vs 364 AU/ml, 95% CI 16–400 AU/ml, \(P = 0.12\)).

Despite their immunodepression burden, RTX-treated patients with previous symptomatic COVID-19 displayed increased seropositivity and antibody titres after mRNA-based SARS-CoV-2 vaccination, even after a single dose of vaccine. This response was dramatically different from that observed for SARS-CoV-2-naïve RTX-treated patients who received three doses of SARS-CoV-2 mRNA-based vaccination, but may vary depending on the period of time between the last RTX infusion and vaccination. A pre-existent B cell memory in recovered subjects may be implicated in this phenomenon [5, 6]. A potential clinical implication might be to increase antibody response through an additional dose of vaccine following an exposure to SARS-CoV-2 in RTX-treated patients with absent or insufficient post-vaccination antibody response.

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**Data availability statement**

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.
Supplementary data

Supplementary data are available at Rheumatology online.

Jérôme Avouac1, Roba Ghossan1, Omar Al Tabaa1, Alice Combier1, Alexia Steelandt1, Marion Thomas1, Olivier Fogel1, Alice Andrée Mariaggi2, Jean-François Meritet2, Flore Rozenberg2, Anna Molto1, Corinne Miceli-Richard1 and Yannick Allanore1

1Service de Rhumatologie and 2Service de Virologie, Hôpital Cochin, AP-HP.CUP, Université de Paris, Paris, France
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Correspondence to: Jérôme Avouac, Service de Rhumatologie, Hôpital Cochin, AP-HP.CUP, Université de Paris, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France. E-mail: jerome.avouac@aphp.fr

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