

LETTERS

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Low levels of anti-SARS-CoV-2 antibodies after vaccination in rituximab-treated patients: comment on the article by Simon et al

To the Editor:

We read with great interest the report of the study by Dr. Simon and colleagues, in which impaired humoral immune responses, but not T cell immune responses, were observed after vaccination against SARS-CoV-2 in patients with immune-mediated inflammatory diseases (IMIDs) treated with rituximab (RTX) (1). The authors reported that none of the 8 vaccinated RTX-treated patients developed IgG antibodies against the spike S1 and nucleocapsid proteins of SARS-CoV-2. Moreover, Boyarsky et al recently reported increased rates of undetectable titers of anti-SARS-CoV-2 antibodies in patients treated with RTX ($P = 0.04$) (2). In patients with hematologic malignancies treated with RTX, only 0–14% developed a serologic response to the BNT162b2 messenger RNA (mRNA) vaccine when RTX was administered within the 12 months before vaccination (3).

On this basis, we examined antibody responses after 2 doses of the SARS-CoV-2 vaccine in 11 patients treated with RTX. Seven patients (63.6%) were female, 9 had a diagnosis of rheumatoid arthritis, 1 had a diagnosis of dermatomyositis, and 1 had a diagnosis of cryoglobulinemic vasculitis. Patients with a history of SARS-CoV-2 infection or low IgG levels were excluded. Patients had received a mean \pm SD of 5.5 ± 3.9 RTX cycles before SARS-CoV-2 vaccination, and the first dose of the vaccine was administered a mean \pm SD of 20.4 ± 13.4 weeks after the last RTX cycle. All patients except 1 were vaccinated with the BNT162b2 mRNA SARS-CoV-2 vaccine. We used a quantitative chemiluminescence microparticle immunoassay (Abbott) to detect IgG antibodies against the SARS-CoV-2 spike protein. Consistent with the aforementioned studies, only 2 (18.2%) of 11 patients had antibody levels above the cutoff value of 50 arbitrary units (AU)/ml; the median level of anti-SARS-CoV-2 antibodies was 21.3 AU/ml (interquartile range 4–28).

Our results confirm those from earlier studies showing reduced antibody response after COVID-19 vaccination in patients with IMIDs receiving RTX therapy (1,2,4). RTX treatment has been associated with worse COVID-19 outcomes, such as more severe disease and increased duration of hospitalization (5). Given that vaccination against SARS-CoV-2 has been highly effective in preventing the development of pneumonia associated with COVID-19 (6), it is considered essential for patients treated with RTX to be vaccinated. Nevertheless, RTX treatment has been associated with reduced antibody response after flu and

pneumococcal vaccination (7). Based on these data, the American College of Rheumatology recommends that patients being treated with RTX should optimally be vaccinated against COVID-19 4 weeks before the next scheduled cycle and that RTX administration should be withheld for 2–4 weeks after the second vaccine dose (8).

However, we observed low levels of anti-SARS-CoV-2 antibodies even though the first vaccine dose was administered a mean of 5 months after the last RTX cycle. Mrak et al also reported inadequate antibody development when the first vaccine dose was administered \sim 6.9 months after the last RTX cycle (4). Indeed, the time from the last RTX cycle correlated with peripheral B cell counts and anti-SARS-CoV-2 antibody levels, and the percentage of peripheral B cells was associated with antibody development in vaccinated patients (4). These data imply that the time interval between the last RTX administration and the first vaccine dose should possibly be reconsidered. As RTX-treated patients seem to exhibit T cell immune responses to SARS-CoV-2 vaccination (1,4), the clinical significance of impaired humoral responses after vaccination in these patients remains unclear.

Author disclosures are available at <https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fart.42011&file=art42011-sup-0001-Disclosureform.pdf>.

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Reply


To the Editor:

We appreciate the comments from Dr. Evangelatos and colleagues on our study of SARS-CoV-2 vaccine responses in RTX-treated patients. The authors briefly reviewed current evidence on the reduced rates of response to SARS-CoV-2 vaccines among patients undergoing B cell depletion therapy with RTX and provided novel data on this topic. In a series of 11 patients with immune-mediated inflammatory diseases treated with RTX, only 2 patients developed detectable levels of IgG antibodies against SARS-CoV-2 spike protein after vaccination with the BNT162b2 mRNA SARS-CoV-2 vaccine. This finding supports observations from other studies (1,2), including our own, in which we showed that humoral but not T cell-mediated responses to SARS-CoV-2 vaccination are reduced in patients treated with RTX.

These findings are highly relevant to the estimated 700,000 patients with hematologic malignancies (3) and 900,000 patients with immune-mediated inflammatory diseases (4) treated with RTX worldwide. Of note, RTX-treated patients show an increased risk of severe COVID-19 (5). Therefore, in light of the impaired humoral immune response to SARS-CoV-2 vaccination, new vaccination strategies and careful monitoring of vaccine efficacy are needed for this patient population, as urged by Evangelatos et al. For RTX-treated patients who have not been vaccinated, RTX therapy and vaccination regimens should be aligned. Thus, RTX administration can be time-adjusted, as also recommended in the American College of Rheumatology guidelines (vaccination

4 weeks before RTX administration [6]), or it could be administered depending on the grade of repopulation of peripheral B cells. The latter approach is reasonable, since adequate humoral immune responses are more likely if at least some B cells are detectable in the peripheral blood (1). However, further studies are needed to determine the effect of B cell repopulation and the best timing of vaccination.

Of note, T cell responses to SARS-CoV-2 vaccination have been shown to be intact in RTX-treated patients, and they have also been shown to support defense against infection and the development of severe COVID-19 (1). Therefore, patients treated with RTX should receive SARS-CoV-2 vaccination even in the absence of B cells. Furthermore, humoral immune responses should be assessed in RTX-treated patients who have received a full SARS-CoV-2 vaccination regimen. Fully vaccinated individuals who do not respond could benefit from additional boosters to achieve a protective humoral response (7). In this context, the observation that SARS-CoV-2 infection can mobilize tissue B cells and trigger protective antibody formation in RTX-treated patients without peripheral B cells is interesting and may support the use of booster vaccinations. When the standard vaccination regimen has failed, a humoral immune response may be mobilized by the timely administration of booster vaccines and by cross-vaccinating with different vaccine agents.

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