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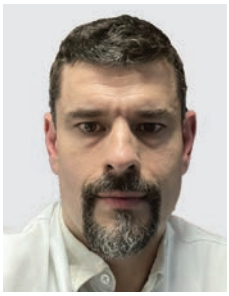
Editorial

Importance of SARS-CoV-2 Spike Antibodies and B Cell Reconstitution to Optimize the Prevention Strategy of COVID-19



Marion Thomas[1] and Jérôme Avouac[1]

Several lines of evidence have shown that rituximab (RTX)-treated patients are at high risk of severe coronavirus disease 2019 (COVID-19).[1] Thus, health authorities have considered patients receiving RTX as extremely high priority for anti-SARS-CoV-2 vaccination. However, a major issue relates to the high risk of reduced vaccination efficacy in these patients.[2] Indeed, a metaanalysis conducted in 2021 showed an overall low rate of humoral response of 0.40 (95% CI 0.35-0.47) after a predominantly 2-dose vaccination course. Moreover, humoral response was highly heterogeneous in the 23 included studies, with a rate of responders ranging from 0 to approximately 80%.[3] These results must be put in perspective with the probable conservation of a functional T cell response in RTX-treated patients. However, further work is warranted to determine the clinical protection granted by a functionally active T cell response.[4]

Given the heterogeneity of antibody response, patients with a treatment history of RTX therapy should be individually assessed for a personalized vaccination strategy against SARS-CoV-2. To that end, it is crucial to identify factors associated with response to vaccination. Three main factors have been identified. First, B cell reconstitution has a critical role in influencing the response to the vaccine. The degree of B cell recovery has been shown to correlate with the extent of SARS-CoV-2 spike antibody levels, suggesting the development of humoral immune response once peripheral B cells are repopulated.[2] Second, the time from last RTX infusion needs to be considered, with a longer time allowing an increased chance of B cell repopulation. Finally, concomitant treatment with methotrexate may further decrease the possibility of seroconversion.[5-7]

[1]*M. Thomas, MD, J. Avouac, MD, PhD, Service de Rhumatologie, Hôpital Cochin, AP-HP. Centre - Université Paris Cité, 75014, Paris, France.*

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Address correspondence to Prof. J. Avouac, Service de Rhumatologie, Hôpital Cochin, Université Paris Descartes, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France. Email: jerome.avouac@aphp.fr.

The majority of these data were obtained from patients after 2 doses of the vaccine, whereas booster doses of the SARS-CoV-2 vaccines have since emerged as an important strategy for containing the pandemic. The majority of patients have now received 3 to 4 doses of vaccine, and a fifth dose may even be discussed in severely immunocompromised patients. However, there is still a paucity of data regarding factors associated with a serologic response to COVID-19 vaccine boosters in RTX-treated patients who were initially seronegative.

In this issue of *The Journal of Rheumatology*, Schultz et al assessed in a retrospective study factors associated with humoral response to the COVID-19 booster vaccine in patients with autoimmune rheumatic disease treated with RTX who were previously serologically unresponsive to the initial vaccine series.[8] Among the 31 included patients, 68% seroconverted following a booster of the COVID-19 vaccine. This percentage of positive serological response was higher than those observed in previous series, including the largest of 62 patients, in which only 9 (14.5%) patients seroconverted following a third dose.[9-11] Several factors may at least partly explain these discrepancies, including a population that had a majority of patients being treated for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, whereas most other studies had a majority of patients with rheumatoid arthritis (RA). The standard treatment for RA often includes the concomitant use of methotrexate, whereas ANCA-associated vasculitis does not. Therefore, these results may be less affected by this confounding variable than those of other studies. The extent of B cell reconstitution and time from last RTX may also account for these differences, but, unfortunately, these parameters were often not measured or discussed in the different studies.

In the study of Schultz et al,[8] the higher percentage of patients who were able to seroconvert after a booster dose allowed for more accurate associations than what other studies have been able to accomplish with their low numbers of seroconverted patients. The authors confirmed that detectable B cells and

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time from last RTX exposure > 6 months were also strongly associated with a positive response following a booster vaccine. Interestingly, demographic characteristics, corticosteroid use, and RTX dosage were not associated with seroconversion. This is consistent with results from previous studies that also showed that gammaglobulin levels or cumulative RTX dose did not influence antibody response.[2] Altogether, these results strongly support including the assessment of B cell reconstitution and SARS-CoV-2 spike antibodies into clinical decisions on timing of booster doses in RTX-treated patients, although it is still not currently incorporated into European Alliance of Associations for Rheumatology or American College of Rheumatology guidelines (Figure). In seronegative patients with detectable B cells, a booster dose of the vaccine should be administered, given the higher chances of seroconversion. In seronegative patients with undetectable B cells, 2 strategies may be considered. The first would be to postpone RTX therapy to improve immunogenicity, if the last RTX infusion was ≥ 6 months and in cases of stable and quiescent disease. This approach still needs to be formally demonstrated and may increase the risk of disease flare and/or progression. The second would be to apply a preexposure prophylaxis with anti–SARS-CoV-2 monoclonal antibodies. The monoclonal antibody combination tixagevimab/cilgavimab consists of 2 Fc-modified fully human monoclonal antibodies administered by intramuscular injection. It has been shown to be effective for the prevention of COVID-19 in patients with moderate-to-severe immunodeficiency who are unlikely to mount an adequate immune response to COVID-19 vaccination.[12] The first real-world experience in 412 patients undergoing B cell–depleting therapies for immune-mediated inflammatory diseases who received tixagevimab/cilgavimab as a preexposure prophylaxis was encouraging, as it revealed that of 12 breakthrough infections, disease was mild in 11, with only a single patient experiencing severe disease.[13] A low rate of infections and severe illnesses has also been observed among 1112 severely immunocompromised patients, including those treated with RTX, treated with tixagevimab/cilgavimab.[14]

It is becoming more and more evident that multiple strategies including vaccination and monoclonal antibodies are required to prevent COVID-19 in immunosuppressed patients. Several questions are still pending and will need to be considered. The course of antibody titers following vaccination in RTX-treated patients needs to be precise because it may influence the time of vaccine booster. The optimal antibody level required to protect patients from severe clinical outcomes according to the type of variant, as well as the involvement of T cell response in vaccination efficacy, have not been clearly identified. The incidence and severity of breakthrough infection in vaccinated patients treated with RTX is also largely unknown. The combined effects of vaccination and natural immunity following infection have also been scarcely studied, as patients with a history of symptomatic COVID-19 are usually excluded from studies related to vaccination and anti-N antibody testing is not routinely performed in all centers. A first clinical experience showed increased antibody response in RTX-treated patients following a symptomatic COVID-19 infection.[15] Finally, in patients receiving monoclonal antibodies, the efficacy may largely vary according to the variants, and the optimal dose and timing of reinjection are not firmly established.

Vaccination against SARS-CoV-2 has been a major step forward to protect immunocompromised patients from severe clinical outcomes. We are now at a crossroads, with an epidemic whose contagiousness and severity have become disparate due to the different variants that can modify sensitivity to vaccines. To contain the pandemic, selecting the correct vaccine and defining the precise timing of booster vaccinations are now the challenge of the next months.

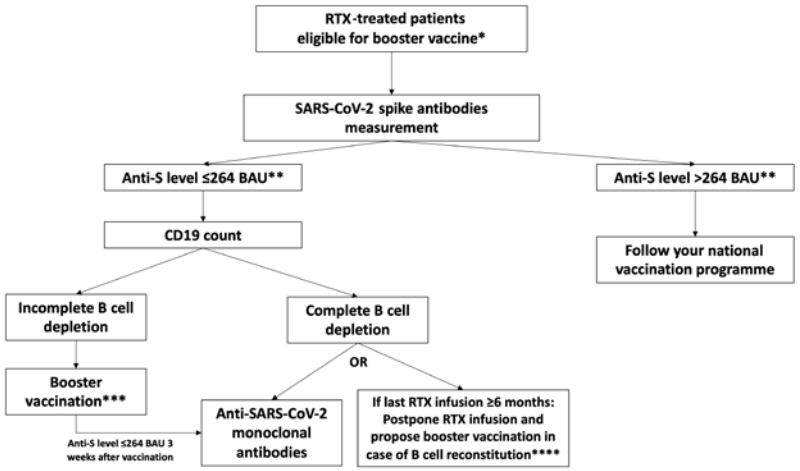

Figure. Algorithm integrating SARS-CoV-2 spike antibodies and B cell reconstitution to optimize the prevention strategy of COVID-19. * 3 to 6 months following the last dose of vaccine. ** Considered as protective level.[16] *** Hold RTX for at least 2 weeks after vaccination if disease activity allows (ACR guidelines[17]). **** In case of stable and quiescent disease. ACR: American College of Rheumatology; BAU: binding antibody unit; COVID-19: coronavirus disease 2019; RTX: rituximab.

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