

## LETTER

# Very low rate of humoral response after a third COVID-19 vaccine dose in patients with autoimmune diseases treated with rituximab and non-responders to two doses

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Patients with autoimmune diseases (AIDs) treated with rituximab (RTX) are at increased risk of death from COVID-19 infection. They have a diminished humoral response despite a preserved T-cell response to two doses of mRNA COVID-19 vaccines.<sup>1 2</sup> It is currently not established how efficient the third dose is in this population. The objective of this study was to assess the effect of a third dose of COVID-19 vaccine on the anti-spike (anti-S) response in patients with AID treated with RTX and non-responders to two doses.

This bicentric observational real-life study included patients with AID treated with RTX having no anti-S response after two doses between March and October 2021. Response was defined as anti-S of  $\geq 49$  binding antibody units (BAU)/mL, the threshold being associated with a detectable neutralising response.<sup>1</sup> Anti-S response was measured using various ELISA kits, but all results were expressed in BAU/mL, which means that the technique has been calibrated with WHO standards. Some provided results with an upper quantification limit of 243; we thus applied this threshold for all. Responders and non-responders were compared to identify factors associated with response to the third dose. Some patients without response to a third dose had a fourth dose. Patients were not involved in the conduct of this study.

We included 62 patients with AID, previously treated with RTX, who had no response to two doses of COVID-19 vaccine. Only 9/62 (14.5%) patients responded to a third dose. Responders and non-responders after three

doses had similar demographic characteristics (table 1). Detectable anti-S following two doses, but below the neutralising threshold ( $< 49$  BAU/mL), were significantly more frequent in responders (4/8 (50%)) than non-responders (2/48 (4%)) ( $p=0.0025$ ) after the third dose. There was a positive correlation between anti-S levels after dose 3 and time between second and third doses ( $r=0.39$ ,  $p=0.001$ ; online supplemental figure 1). Likewise, the median time between the second and third doses was numerically, but not significantly, higher in responders than in non-responders (129 vs 84 days,  $p=0.30$ ). There was a trend towards a correlation between the anti-S levels after the third dose and the time between the last RTX infusion and the third dose ( $r=0.23$ ,  $p=0.07$ ; online supplemental figure 2). There was a similar proportion of responders (28%) and non-responders (33%,  $p=0.71$ ) that received an infusion of RTX between the second and third vaccine doses. Numerically, more non-responders received methotrexate comedication (62%) than responders (33%,  $p=0.15$ ). Overall, seven patients (including five (71%) having undetectable and two (29%) having  $< 49$  BAU/mL anti-S titers after the third dose) received a fourth dose and 4 (57%) responded. The antinucleocapsid (N) status was available for all patients at baseline, and in 54/62 (87%) after third dose. All samples were negative for anti-N, except in one patient who was positive since baseline but did not have anti-S response to the third dose.

**Table 1** Characteristics of patients without response after the second dose of vaccine treated with RTX for AIDs according to their seroconversion after the third dose

	Non-responders (n=53)	Responders (n=9)	P value
Age (years), median (IQR)	61 (45–69)	58 (52–72)	0.31
Female sex, n (%)	44 (83)	6 (67)	0.36
Underlying disease, n (%)			
Rheumatoid arthritis	37 (70)	5 (56)	0.45
Other AID	16 (30)	4 (44)	
<b>RTX treatment</b>			
Received an RTX infusion between doses 2 and 3, n (%)	15 (28)	3 (33)	0.71
Time between the last RTX infusion and the third dose of vaccine (days), median (IQR)	165 (124–252)	187 (150–360)	0.19
Less than 3 months between the last RTX infusion and the third dose of vaccine, n (%)	10 (19)	1 (11)	0.99
Previous number of RTX injections, median (IQR)	7 (4–10)	6 (4–11)	0.66
<b>Antispikes response to the second dose</b>			
Detectable but below 49 BAU/mL, n/n (%)	2/48 (4)	4/8 (50)	0.0025
<b>Antispikes response to the third dose</b>			
Undetectable, n (%)	36 (68)	0	NA
Detectable but below 49 BAU/mL n (%)	17 (32)	0	NA
>49 and <243 BAU/mL, n (%)	0	2 (22)	NA
>243 BAU/mL, n (%)	0	7 (78)	NA
<b>Vaccination scheme</b>			
Time between the third dose and serological assessment (days), median (IQR)	49 (21–90)	54 (19–97)	0,9
Interval between second and third vaccine dose in days, median (IQR)	84 (46–204)	129 (96–182)	0.41
<b>Comedications</b>			
Corticosteroids n (%)	20 (38)	3 (33.3)	0.99
Prednisone equivalent dose per day (mg), median (IQR)	5 (5–6)	5 (5–10)	0.48
Methotrexate, n (%)	33 (62)	3 (33)	0.15
Results are expressed as median and were compared using Fisher exact test for categorical variables and Mann-Whitney for continuous variables.			
AID, autoimmune disease; BAU, binding antibody unit; NA, not applicable; RTX, rituximab.			

Few data exist on response to a third vaccine dose in RTX-treated patients having no response after two doses.<sup>3,4</sup> We here observe a very low response rate to a third dose of COVID-19 vaccine (14.5%) compared with a 44% rate of response in solid organ transplant recipients after a third dose in patients without response to two doses<sup>5</sup> or compared with a previously published report of 17 patients with rheumatoid arthritis where all but 2 patients responded.<sup>4</sup> However, none of these patients received RTX. Also, compared with this previous report, our definition of non-response to two doses was more stringent according to our previous findings.<sup>1</sup> Finally, our results are in line with the very low response rate observed with RTX in a small previous study.<sup>3</sup> This reinforces our finding that having a detectable response, even low, to

two doses predicts the response to the third dose. Also, we observed that longer intervals between the second and third doses might be associated with better response, as previously observed in patients on dialysis not treated with RTX.<sup>6</sup>

As a limitation, we did not assess circulating B cells at the time of vaccine injections, which might influence humoral response. However, time since the last RTX could be a proxy of B-cell repopulation. Also, we did not assess the T-cell response, which is, however, less impacted by RTX.<sup>1</sup>

In conclusion, a third dose of COVID-19 vaccine led to only 14,5% of response in RTX-treated AID patients non-responding to two doses. A detectable anti-S response after second dose, even below the neutralising threshold,

might positively influence response to a third COVID-19 vaccine. This suggests that, in case of total absence of humoral response after the second dose, the expected response rate of a third dose is very low. Now, alternatives to vaccination such as prophylactic anti-S antibodies exist<sup>7</sup> and could be useful approaches that should be evaluated in this context.

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