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ORIGINAL ARTICLE

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Rituximab-to-vaccine interval on SARS-CoV-2 immunogenicity in children: The potential role of prior natural infection

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Abstract

Background: Treatment with anti-CD20 antibodies (rituximab) is used in both adults and children to treat various autoimmune and oncological diseases. Rituximab depletes B CD20+ cells and, thereby, antibody response to vaccines. This study aimed to examine the antibody response to mRNA-based COVID-19 vaccines in children aged 5–18 years undergoing rituximab treatment compared to healthy matched children.

Methods: Between 31 January and 18 July 2022, we conducted a prospective observational study at the Geneva University Hospitals, enrolling children aged 5–18 years under rituximab treatment who had received two mRNA-based SARS-CoV-2 vaccine doses. Controls were healthy volunteers with no significant medical conditions. Exclusion criteria included a recent SARS-CoV-2 infection. Blood samples were collected at day 60 (±30) and day 270 (±90) after the second vaccination.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; GMC, geometric mean concentration; IQR, interquartile range; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Results: The rituximab-treated group exhibited significantly lower levels of antibodies specific to the anti-receptor binding domain (RBD) of the SARS-CoV-2 spike (S) protein than healthy controls at 60 (±30) days after the second vaccine dose (geometric mean concentration: 868.3 IU/mL in patients and 11,393 IU/mL in controls; $p = .008$). However, patients with a rituximab-to-vaccine interval shorter than 6 months and with evidence of a past infection (based on positive anti-N antibody levels) had a high level of anti-RBD antibodies.

Conclusion: A past infection with SARS-CoV-2 may induce anti-RBD-specific memory B cells that can be re-activated by SARS-CoV-2 vaccination, even after rituximab-induced B-cell depletion. This suggests that it is possible to vaccinate earlier than 6 months after rituximab to develop a good antibody response, especially in the case of past SARS-CoV-2 infection.

KEYWORDS
B-cell depletion, immunocompromised children, rituximab, SARS-CoV-2 mRNA-based vaccines, vaccine immunogenicity

1 | INTRODUCTION

Rituximab, an anti-CD20 therapy, is used in both adults and children to treat various autoimmune and oncological diseases. Rituximab depletes B cells expressing the CD20 surface marker, mainly in peripheral blood and secondary lymphoid tissues[1] and thereby reduces the antibody response to vaccines.[2,3] The detrimental effect of rituximab on vaccine immunogenicity has already been established for numerous vaccines.[4–6] In addition, the infection with SARS-CoV-2 has been shown to be more severe in immunocompromised patients treated with rituximab.[7–9] Due to this heightened risk, vaccination against SARS-CoV-2 has been prioritized for this vulnerable population according to national and international recommendations.[10,11]

Several studies have shown that treatment with rituximab can lead to a reduced humoral immune response against SARS-CoV-2-mRNA vaccines.[12–14] This highlights the need for careful vaccine scheduling of vaccination in anti-CD20 treated patients and adaptation of vaccine strategies for these patients. The timing of rituximab treatment relative to vaccination appears to be crucial. Indeed, after rituximab, B-cell counts decrease and become undetectable in peripheral blood. They usually begin to recover between 6 and 9 months after the last dose of rituximab, reaching normal levels between 9 and 12 months post-rituximab treatment.[15] Therefore, many authors and guidelines strongly suggest that non-live vaccines should be administered at least 6 months after the last dose and/or 4 weeks prior to the next dose of rituximab to achieve the best immunogenicity.[16–18]

Ensuring strict adherence to this schedule in the routine clinical setting can present difficulties, particularly when factoring in the varied clinical scenarios and potential urgent requirements associated with rituximab therapy across different diseases, while at the same time, it can be an urgent need to vaccinate vulnerable patients, to protect them against a pandemic virus.

Key message

The findings reveal a notable decrease in vaccine immunogenicity in rituximab-treated patients, with the interval between rituximab treatment and vaccination playing a pivotal role. Interestingly, natural infection prior to vaccination may induce memory B cells that can be re-activated rapidly by vaccination, despite the B-cell-depleting effect of rituximab. These insights are critical in guiding clinicians to personalize vaccination strategies for rituximab-treated patients and emphasize the necessity of further research.

Adult populations have been the primary focus of many initial studies, but pediatric patients have unique physiological and immunological characteristics that warrant separate studies and specific considerations.

In this study, we investigated the antibody response to SARS-CoV-2 mRNA-based vaccines in immunocompromised children treated with rituximab compared to healthy children.

2 | METHODS

2.1 | Study design and participants

Between 31 January and 18 July 2022, we conducted a prospective observational study at the Children's Hospital part of the Geneva University Hospitals (Geneva, Switzerland) among children aged between 5 and 18 years who had received a primary vaccination with an SARS-CoV-2 mRNA-based vaccine within the past 8 weeks. In accordance with the national vaccination guidelines in place at the

time of the study, a primary vaccination was defined as two doses of the BNT162b2 (Pfizer-BioNTech) vaccine administered at a minimum interval of 21 days apart or two doses of the mRNA-1273 (Moderna) vaccine administered at a minimum interval of 28 days apart.[11] During this period, the predominant SARS-CoV-2 variants in circulation were Omicron subvariants 21K, 21L, and 22B.[19]

The study was performed according to the principles of good clinical practice and approved by the Geneva Cantonal Ethics Commission (no. 2021-02478). Informed consent was obtained from the guardians of all participants. Patients undergoing rituximab treatment at our institution were eligible for inclusion if the last dose had been administered within the 12 months prior to the first dose of the SARS-CoV-2 vaccine. The control group consisted of healthy, age-matched volunteers with no major medical conditions and no immunosuppressive treatment. Participants with a documented SARS-CoV-2 infection <3 months prior to inclusion were excluded. Participants were actively monitored for signs of SARS-CoV-2 infection through regular symptom reporting throughout the study duration. If participants exhibited symptoms indicative of SARS-CoV-2, RT-PCR testing was to be conducted. Baseline data collected were: demographic and disease information; vaccine type (BNT162b2 [Pfizer-BioNTech] or 12 mRNA-1273 [Moderna]); anti-CD20 dose and date of last treatment; concomitant medications with other immunomodulatory treatments; and history of previous infections, including COVID-19. Blood samples were collected at 60 (±30) days after the second dose of vaccination for the patients and controls and at 270 (±90) days only for the patients.

2.2 | Endpoints

The primary endpoint was the quantification of anti-receptor binding domain (RBD) antibodies of the SARS-CoV-2 spike (S) protein 60 (±30) days after the second vaccine dose. The primary objective was to assess and compare the serological immune response in immunocompromised children and healthy children 60 (±30) days after their second dose of COVID-19 vaccine. Secondary objectives focused on comparison of antibodies specific for SARS-CoV-2 nucleoprotein (anti-N total antibodies) at 60 (±30) days between patients and controls on the persistence of these antibodies at 270 (±90) days post-vaccination in the patient group.

Given the exploratory nature of this study, aimed at investigating the serological immune response to mRNA-based SARS-CoV-2 vaccines in immunocompromised children during the initial vaccination campaign, we did not calculate a target sample size based on formal hypotheses. Instead, the sample size was primarily based on the feasibility of recruitment within the constrained available timeframe.

2.3 | Laboratory assessments

Anti-N antibodies and anti-RBD antibodies were measured in sera using the Elecsys® Anti-SARS-CoV-2 immunoassay (Roche Diagnostics, Rotkreuz, Switzerland) on the Cobas e801 Analyzer (Roche Diagnostics). This assay quantifies total antibodies against the SARS-CoV-2 S glycoprotein utilizing recombinant SARS-CoV-2 S RBD antigens, predominantly capturing anti-SARS-CoV-2 S immunoglobulin G (IgG), as well as IgA and IgM.[20] Although its performance is suboptimal for Omicron variants,[21] it effectively detects antibodies induced by active immunization from vaccinations with BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna).[20]

Results are reported as numeric values in form of an index (signal sample/signal calibrator) for anti-N assay and as concentration (IU/mL) for the quantitative anti-RBD assay.

Seroconversion was defined as anti-RBD antibodies >0.9 IU/mL and anti-N antibodies >1.1 as previously reported.[22]

2.4 | Statistical analysis

All analyses were performed using Stata version 17 (2021; StataCorp, College Station, TX). All associated graphs were produced using GraphPad Prism version 10.0.2 for Windows (GraphPad Software, San Diego, CA; www.graphpad.com). Continuous data were presented when appropriate as median and interquartile ranges (IQRs) (for age) or geometric mean concentrations (GMC) with the 95% Cis (for anti-RBD and anti-N antibodies levels). Categorical data were presented as frequencies and percentages. Mann–Whitney U test was used to compare anti-RBD and anti-N antibody levels between the rituximab-treated group and the control group at 60 (±30) days and anti-RBD antibody levels at 60 (±30) and 270 (±90) days in the patient group. To examine the correlation between anti-RBD antibody levels and the rituximab-to-vaccination interval we employed the Kendall's correlation test. For all tests and analyses, a p-value of less than 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Study participants

Twenty participants were enrolled in the study, comprising nine patients under rituximab treatment and 11 healthy controls, who came to receive the SARS-CoV-2 vaccine and agree to have a blood sampling after vaccination (Table 1). Among the controls, 4 (36%) were male, compared to 5 (55%) in the patient group. The mean age of the patients was balanced between the groups. Among the patients, 3 (33%) had nephrotic syndrome, 3 (33%) had neurological autoimmune diseases, and 3 (33%) had post-transplant lymphoproliferative disorder (PTLD). Two children in each group had RT-PCR-confirmed pauci-symptomatic SARS-COV-2 infection prior to vaccination.

All patients were vaccinated with two doses (children between 5 and 11 years: 10 μg/dose; children >12 years: 30 μg/dose) of BNT162b2 according to national guidelines available at that time.[11] Regarding concomitant medication, one patient, diagnosed with

multiple sclerosis, received additional immunosuppressive treatment (prednisone 0.5 mg/kg/day). The median time interval between rituximab administration and vaccination was 210 days [IQR 115–322], although four patients received the SARS-CoV-2 vaccine relatively soon (between 74 and 146 days) after the last dose of rituximab (Table 2). Throughout the study, no participants exhibited symptoms that necessitated RT-PCR testing for SARS-CoV-2 infection.

TABLE 1 Demographic and clinical characteristics of nine patients treated with rituximab compared to 11 healthy controls.[a]

	Patients	Controls
Participants, *n*	9	11
Male, *n* (%)	5 (55)	4 (36)
Age, years, mean [IQR]	14 [7.5–18.0]	10 [6.5–14.5]
Ethnicity		
Caucasian, *n* (%)	7 (78)	10 (99)
African, *n* (%)	1 (11)	1 (1)
Asian, *n* (%)	1 (11)	0
History COVID-19 (RT-PCR), *n* (%)	2 (22)	2 (18)
Positive anti-N serology, *n* (%)	4 (44)	6 (55)
Disease		
Nephrotic syndrome, *n* (%)	3 (33)	NA
PTLD, *n* (%)	3 (33)	NA
Neurological diseases[b]	3 (33)	
Rituximab		
375 mg/m^2	6 (67)	NA
750 mg/m^2	2 (22)	NA
1000 mg	1 (11)	NA

Abbreviations: COVID-19 (RT-PCR), coronavirus disease 2019 reverse transcription polymerase chain reaction – confirmed infection; PTLD, post-transplant lymphoproliferative disorder.

[a]Continuous data are presented as median with the interquartile range [IQR] and categorical data as numbers and percentages.

[b]Others: multiple sclerosis, $n=1$ (this patient received additional immunosuppressive treatment—prednisone 0.5 mg/kg/day); anti-MOG demyelinating disease of the central nervous system, $n=1$; Neuromyelitis Optica Spectrum Disorder with aquaporin-4 antibody positivity, $n=1$.

3.2 | Specific humoral response

In the patient group, the GMC of anti-RBD levels was 868 IU/mL (95% CI 112 to 6685), and in the control group, it was 11,393 IU/mL (95% CI 5291–24,529). The level of anti-RBD antibodies was significantly lower in patients than in controls ($p=.008$; Figure 1). No significant difference was found in anti-N antibody levels between patients and controls (GMC: 0.98 index in the patient group; 3.35 index in the control group). Further data collected at 270 (±90) days post-vaccination showed that the GMC for anti-RBD antibodies in patients was 667 IU/mL (95% CI: 42–10,610) and 1.56 index (95% CI: 0.22–11.12) for anti-N antibodies (Table S1). There was no significant difference in anti-RBD antibody levels in the patient group between days 60 (±30) and 270 (±90).

3.3 | Impact of Rituximab-to-vaccine interval on SARS-CoV-2 immunogenicity

The relationship between the interval from rituximab treatment and vaccination and the SARS-CoV-2 antibody levels was assessed in nine patients (Figure 2; Table 2). Four patients (patients 1, 2, 3, and 9) showed detectable anti-N antibody levels (index > 1.1) and a GMT of anti-RBD antibody levels of 4735 IU/mL (95% CI 256–87,387). Among these, three patients (patients 1, 2, and 3) who had received the vaccine within a time interval of less than 6 months from the last dose of rituximab had a GMT of anti-RBD antibody levels of 2333 IU/mL (95% CI 67 to 80,219). Among them, only patients 1 and 3 had a history of RT-PCR-confirmed SARS-CoV-2-symptomatic infection.

TABLE 2 Rituximab-to-vaccination interval and SARS-CoV-2 antibody levels in patients.

Patient	Rituximab-to-vaccination interval (days)	SARS-CoV-2 anti-RBD Ab (IU/mL)	SARS-CoV-2 anti-N Ab (index)
1	74	10,660	11.00
2[a]	98	633	3.86
3	133	1881	12.10
4	146	5	0.79
5	196	71	0.24
6	235	754	0.08
7	300	585	0.08
8	344	3505	0.08
9	365	39,598	16.6

Abbreviations: anti-N Ab, anti-SARS-CoV-2 nucleoprotein antibody; anti-RBD Ab, antibodies specific to the anti-receptor binding domain (RBD) of the SARS-CoV-2 spike protein.

[a]This patient received additional immunosuppressive treatment (prednisone 0.5 mg/kg/day).

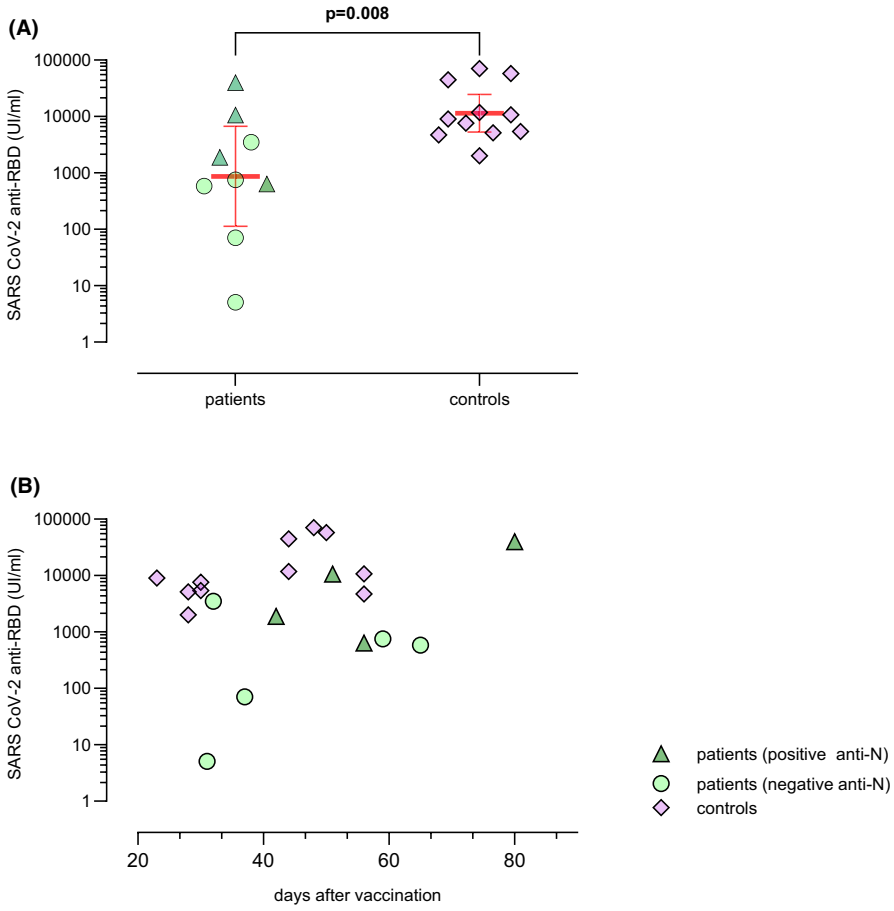

FIGURE 1 Levels of anti-RBD antibodies in patients and controls 60 (±30) days after second vaccine dose. (A) Geometric mean concentration and 95% confidence Intervals are displayed with groups compared using the Mann–Whitney Test. (B) Exact time interval in days between vaccination and blood sample collection represented on the *X*-axis.

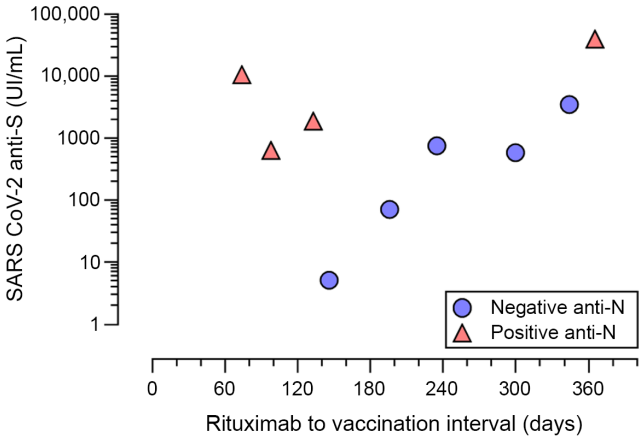

FIGURE 2 Anti-RBD antibody levels in patients relative to the time interval between the last rituximab dose and vaccination. Patients with positive anti-N in red and patients with negative anti-N in blue.

The remaining five patients had undetectable anti-N antibody levels and showed GMT of anti-RBD antibody levels of 222 IU/mL (95% CI 9.5–5196). The Kendall correlation test between anti-RBD antibody levels and the rituximab-to-vaccination interval showed Kendall's tau-a and tau-b coefficient of 0.8, indicating a strong positive correlation but with a *p*-value of .08.

4 | DISCUSSION

This study underscores the importance of strategically orchestrating SARS-CoV-2 vaccination to maximize vaccine immunogenicity among patients receiving rituximab or other B-cell-depleting therapies. Our findings reveal a notable reduction in humoral immunity induced by mRNA-based COVID-19 vaccines in pediatric patients undergoing rituximab therapy. These outcomes parallel analogous observations in the adult patient population.[23–27] Our research unveiled a noteworthy aspect: among patients who received the vaccine at a shorter interval than the recommended 6 months post-rituximab treatment, those showcasing detectable anti-N antibodies—signifying a past natural infection—displayed considerable levels of anti-RBD antibodies. These levels were lower than those observed in the control group but markedly higher than those in patients with negative anti-N antibodies. A possible explanation for these observations could be that rituximab treatment leads to a significant depletion of B cells expressing CD20 that are present in circulation and secondary peripheral lymphoid organs. However, memory B cells may be less affected as they typically have lower levels of CD20 expression compared to naïve B cells. Furthermore, long-lived plasma cells (LLPCs) in the bone marrow do not express CD20. Therefore, after a booster dose of vaccination, memory B cells and LLPCs play a critical role in the secondary immune response, as they can induce a rapid and

effective antibody response to re-exposure to the antigen. This could explain why patients with evidence of past infection or past exposure to the SARS-CoV-2 (as indicated by anti-N antibodies) exhibited a relatively better response to vaccination. However, it is expected that the induction of antibodies following primary vaccination with the SARS-CoV-2 mRNA vaccine may be more severely impacted, likely due to the depletion of naive B cells necessary for initiating new immune responses. It is paramount, however, to approach this finding with the utmost caution, as the sample size is limited to only the three patients who were vaccinated less than 6 months after the last dose of rituximab and had positive anti-N antibodies. Further research with larger cohorts is essential to explore and confirm these preliminary observations.

In patients with negative anti-N antibody levels, we observed a strong positive correlation between the increase in the rituximab-to-vaccine interval and the levels of anti-RBD antibodies, which was not statistically significant ($p = .08$), likely due to the small sample size. This correlation, similar to those observed in previous studies,[28–31] may reflect the gradual reconstitution of CD20+ B cells following a dose of rituximab. It should be recognized that the absence of anti-N antibody does not totally exclude a past infection, as patients may not have mounted an anti-N antibody response. Furthermore, we observed that patients under rituximab sustained stable antibody levels 270 days (±90) post-primary vaccination, albeit at low level, suggesting a good long-term maintenance of specific antibodies following mRNA-based COVID-19 vaccination in children receiving rituximab.

Our study has several significant limitations that must be carefully considered. The most notable is the small sample size, which impacts the generalizability of our findings. Additionally, there is uncertainty regarding the baseline antibody levels in patients with a previous SARS-CoV-2 infection before vaccination, which could significantly influence the observed immune responses. Despite these limitations, this investigation provides important, albeit very preliminary, insights that could help clinicians in considering a vaccination timeframe shorter than the conventional 6 months following the last rituximab dose, particularly in situations where seroprevalence of natural SARS-CoV-2 infection is high.

In summary, while these insights necessitate further validation through more extensive and comprehensive studies, they contribute to enhancing existing guidelines, by suggesting that, in epidemic contexts, vaccination could be considered earlier than the conventional 6 months after rituximab treatment, particularly for patients who have evidence of prior SARS-CoV-2 infection. These findings provide medical professionals with additional perspectives for tailoring vaccination protocols for patients undergoing rituximab treatment.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest to disclose as described by *Pediatric Allergy and Immunology*.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/pai.14161.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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