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Seroconversion among rituximab-treated patients following SARS-CoV-2 vaccine supplemental dose

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ABSTRACT

Rituximab (RTX) is a very effective treatment for autoimmune rheumatic diseases (AIRD), but it increases infection risk and impairs vaccine responses. Herein we evaluated the antibody response of RTX-treated patients to the supplemental COVID-19 vaccine. After the supplemental dose, 53.1% of patients had detectable antibody titers. Only 36% of patients who did not mount an antibody response after the original vaccine series *did* have detectable antibodies after the supplemental dose (seroconversion). Patients with undetectable $CD20^{+}$ cell levels did not seroconvert while hypogammaglobulinemia was associated with a 15-times decrease in the likelihood of seroconversion. Although we noted 11 COVID-19 infections after the supplemental dose, no patients who received monoclonal antibodies pre-exposure prophylaxis had COVID-19 afterwards. We propose that patients receiving RTX should continue to be prioritized for prophylaxis measures and that vaccination should be timed after B cell recovery wherever possible.

1. Introduction

Rituximab (RTX) is widely used for the treatment of several autoimmune rheumatic diseases (AIRD), including Rheumatoid Arthritis (RA), ANCA-associated Vasculitis (AAV) and a variety of Connective Tissue Diseases (CTD). It a chimeric monoclonal antibody that targets CD20 on B-lymphocytes and induces B cell apoptosis. [1] Although RTX does not directly affect plasma cells, it has been associated with secondary hypogammaglobulinemia [2]. Given its mode action, RTX significantly increases risk of infections including reactivation of hepatitis B, and impairs responses to vaccines [3].

Patients receiving B-cell depleting therapies, such as RTX, have been shown to be vulnerable to COVID-19 and to have poor responses to COVID-19 vaccination [4,5]. Prior studies from our group and others showed that many patients receiving RTX have poor humoral immune responses after vaccination with 2 doses of the BNT162b2 or mRNA-1273 vaccines or 1 dose of Ad26.COV2.SCOVID-19 vaccine. Specifically, we have shown that only a third of rituximab treated patients with AIRD developed measurable titers of IgG anti-SARS-CoV-2 spike antibody after vaccination with the initially recommended doses. One of the main predictors of poor antibody response to anti-SARS-CoV-2 vaccination in that study, was pre-existing hypogammaglobulinemia. [6] Jyssum et al. also showed that most RTX-treated patient did not have an antibody response after 2 vaccine doses. A third dose increased percentages of patients with a serological response, but still less than half responded after 3 doses. T-cell responses though were similar among rituximab and non-rituximab treated patients [7].

On August 13, 2021, the Centers for Disease Control and Prevention (CDC) recommended that immunocompromised individuals receive a supplemental dose (additional primary dose) of COVID-19 vaccine [8]. Herein, we sought to evaluate the effect of the supplemental dose on AIRD patients treated with RTX in relation to vaccine timing, immunological status, infection history and concomitant treatments.

2. Materials and methods

2.1. Study design

We conducted an observational cohort study on adult patients with AIRD treated with RTX at Beth Israel Deaconess Medical Center (BIDMC) in Boston, MA. We measured timing of vaccine administration through chart review and telephone calls to patients. Additional details were also collected regarding disease treatment, COVID-19 infection, demographics and immunologic parameters. The project was approved by

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the BIDMC Institutional Review Board.

2.2. Study population

Participants were adult patients (age ≥ 18 years). All participants were treated with RTX for an established AIRD, including but not limited to Rheumatoid Arthritis (RA), Antineutrophil Cytoplasmic Antibody Associated Vasculitis (AAV), IgG4-related disease and various connective tissue diseases (CTD, including Systemic Lupus Erythematosus, Mixed Connective Tissue Disease, Anti-synthetase Syndrome). Included patients received at least one dose of Rituximab from January 2020 through to February 2021. Most received subsequent doses during this study.

2.3. Data collection

Medications, indication for RTX by disease, date of last RTX infusion, type of COVID-19 vaccine received, and dates of vaccine administration were collected from a combination of medical records review and patient telephone calls. Post-vaccination serum IgG antibody levels against SARS-CoV-2 spike protein S1 receptor binding domain (RBD), absolute $CD19^+$ and $CD20^+$ cell counts within 2 months of supplemental dose, and quantitative immunoglobulin levels within one year of supplemental dose were collected from chart review. Documentation of prior SARS-CoV-2 infection and whether requiring hospitalization or intensive care unit level of care was recorded. Hypogammaglobulinemia was defined as laboratory evidence of serum levels of IgG, IgA, or IgM less than the lower limit of normal within 1 year of vaccination date. A prior SARS-CoV-2 infection was determined by either medical record review or by patient reported positive SARS-CoV-2 PCR or rapid test.

2.4. Outcome measures

The primary outcome measure was the proportion of patients receiving RTX treatment who had detectable levels of the anti-spike IgG (seropositive) after vaccination with the supplemental dose of any of BNT162b2 mRNA (manufactured by BioNtech/Pfizer), mRNA-1273 (manufactured by Moderna), and Ad26.COV2.SCOVID-19 (manufactured by Janssen/Johnson & Johnson). Major secondary outcomes include proportion of seropositive patients after vaccination in relation to demographics, immunological parameters at time of vaccination including B-cell counts and immunoglobulin levels, and concomitant medication use. Additional outcomes included incidence of SARS-CoV-2 infection and uptake of pre-exposure prophylaxis.

2.5. Immunogenicity of the vaccine

Serum IgG antibody levels against SARS-CoV-2 spike protein S1 receptor binding domain were measured using anti-spike IgG enzyme immunoassay (Attelica IM COV2G or ADVIA Centaur COV2G, Siemens, Healthineers), which were the tests used at our institution during the study period. The tests were performed via Quest Diagnostics Laboratory. The sensitivity and specificity of these assays are >99%. An Index Value greater than or equal to 1.00 was considered as positive, according to the manufacturer's instruction.

2.6. Statistical analysis

Categorical variables are presented as proportions and continuous variables as median (interquartile range [IQR]). Between group comparisons were done using the chi-square test or Fisher's exact test for categorical variables and the Mann Whitney test to compare continuous variables. Analysis was performed using STATA.

3. Results

3.1. Cohort of rituximab-treated patients with autoimmune rheumatic diseases

In Table 1, we show the demographics, disease status and immunologic profile of the patients that were included in the study. 72 patients

Table 1
Patient demographics, clinical, and immunologic data of autoimmune rheumatic disease patients receiving rituximab.

Patient characteristics	
Demographics	
Age (years), median [IQR], $N = 72$	63 [54.8 71]
Gender	
	48 (66.7)
• Female, n (%)	24 (33.3)
• Male, n (%)	
Underlying disease:	
	30 (41.7)
• Rheumatoid arthritis, n (%)	18 (25)
• ANCA-associated vasculitis, n (%)	21 (29.2)
• Connective tissue disease*, n (%)	3 (4.2)
• IgG4-related disease, n (%)	
Received Supplemental Dose COVID-19 Vaccine# n, (%)	52 (72.2)
Supplemental Dose Type	
	23 (44.2)
• BNT162b2 mRNA, n (%)	19 (36.5)
• mRNA-1273, n (%)	1 (1.9)
• Ad26.COV2.SCOVID-19, n (%)	9 (17.3)
• Unknown, n (%)	
Documented history of COVID-19 infection, n (%)	19 (26.4)$
COVID-19 infections leading to hospitalization, n (%) (Total $N = 21$)	5 (23.8)
COVID-19 infections leading to ICU admission, n (%) (Total N = 21)	3 (14.3)
COVID-19 infections after supplemental dose, n (%) (Total N = 21)	11 (21.2)
Received monoclonal Ab Pre-exposure prophylaxis, n (%)	20 (28.6)
Immunological Parameters	
B cell counts (measured in $N = 16$):	
Absolute CD19+ count (#/uL), median [IQR]	0 [0, 10.7]
Absolute CD20+ count (#/uL), median [IQR]	0 [0, 9.9]
Hypogammaglobulinemia in the past year n, (%), (measured in $N = 35$)	20 (57.1)
• IgM hypogammaglobulinemia n, (%)	16 (45.7)
	12 (34.3)
• IgG hypogammaglobulinemia n, (%)	
• Immunoglobulin M (mg/dL), median [IQR]	48 [22.5,70]
• Immunoglobulin G, median [IQR]	834 [621.5, 1146.5]
Time between supplemental dose and SARS-CoV-2 Spike protein IgG measurement in weeks, median [IQR] (measured in $N = 32$ patients)	9 [4.8, 12.3]
SARS-CoV-2 Spike protein IgG (positive) after supplemental dose, n (%) (measured in N = 32 patients)	17 (53.1)
SARS-CoV-2 Spike protein IgG changed from negative to positive after supplemental dose, n (%)	8/22 (35.4)
Medications at the Time of Supplemental Dose ($N = 52$)	
Any Steroids at time of supplemental dose n, (%)	13 (25)
Steroids ≥10 mg/day, n (%)	2 (3.8)
Concomitant DMARD, n (%)	28 (53.8)
• Mycophenolate, n (%)	9 (17.3)
	7 (13.5)
• Hydroxychloroquine, n (%)	6 (11.5)
• Methotrexate, n (%)	
Weeks from last Rituximab, median [IQR]	24 [18.5, 31]

* The connective tissue disease group is composed of systemic lupus erythematosus, inflammatory myopathies, anti-synthetase syndrome, overlap syndromes, and mixed connective tissue disease patients.

3rd doses for patients who received mRNA vaccines or 2nd doses for patients who received JNJ

$ 2 patients were infected twice so there were a total of 21 infections in the cohort documented.

(median [IQR] age, 63 [54.8, 71] years) were included. The most common indication for RTX treatment was RA followed by AAV and CTD. 72.2% patients received a supplemental COVID-19 vaccine from August 2021 to May 2022. Most of the supplemental doses were either the BNT162b2 mRNA vaccine 23 (44.2%) or the mRNA-1273 vaccine 19 (36.5%). One person received Ad26.COV2.SCOVID-19 vaccine as the supplemental dose and 9 have documentation of receiving a supplemental dose but it is unknown which one.

Of the patients who received the supplemental dose, 25% were on steroids and 53.8% were on a concurrent Disease Modifying Anti-Rheumatic Drug (DMARD) at the time of the dose. The median [IQR] time from pre-vaccination RTX infusion to vaccination was 24 [18.5, 31] weeks.

Absolute $CD19^+$ and $CD20^+$ counts were measured in 16 patients within 2 months of the supplemental dose. Most of the patients (56.3%) had undetectable levels of $CD19^+$ and $CD20^+$ measured.

Thirty-five patients had gamma globulins measured within a year of the supplemental dose. 57.1% of patients had hypogammaglobulinemia (low IgG, low IgM or both); 45.7% had IgM hypogammaglobulinemia and 34.3% had IgG hypogammaglobulinemia.

3.2. Antibody response to the vaccine

From August 2021 to May 2022, 32 patients out of 52 (61.5%) had anti-spike antibody serologies measured after receiving the supplemental dose. The median [IQR] time from the supplemental dose to the SARS-CoV-2 spike protein IgG lab draw was 9 [4.8, 12.3] weeks. (Table 1).

Of the 32 patients who had anti-spike antibody serologies measured after the supplemental dose, 53.1% had detectable antibody titers (tested positive). Compared to patients who had positive titers, those who had negative titers had lower absolute $CD20^+$ levels (median [IQR] 10.17 [0, 10.71] versus 0 [0,0], $p = 0.034$). Out of 8 patients with undetectable $CD19^+$ and $CD20^+$ levels, only 2 had positive titers; whereas out of 5 patients with detectable $CD19^+$ and $CD20^+$ levels, 4 had positive antibody titers. The 2 patients with undetectable $CD19^+$ and $CD20^+$ levels but positive spike antibodies also had positive spike antibodies after the first 2 vaccines. Patients with negative titers were more likely to have hypogammaglobulinemia than patients with detectable anti-spike antibodies (85% versus 20%, $p = 0.002$). There was no difference in gender, age, indication for RTX or type of vaccine received between the patients who had positive titers and those who had negative titers. There was also no difference in corticosteroid use, concomitant DMARDs, time since last RTX dose or cumulative RTX dose. (Table 2).

3.3. Positive antibody response in patients who did not respond to the initial vaccination series (seroconversion)

29 patients had Anti-SARS-CoV-2 Spike Protein IgG measured after both the initial primary series and the supplemental dose. Only 24.1% of those patients had positive titers after the initial primary series. (Table 1) Of the patients who did not mount an antibody response after the original vaccine series, 36% had positive antibodies (seroconverted) after the supplemental dose (Table S1). Patients who seroconverted had higher absolute $CD20^+$ vs the ones who did not mount a detectable antibody response (median [IQR] 10.64 [9.7, 12.42] vs 0 [0,0], $p = 0.007$). None of the patients with undetectable $CD19^+$ and $CD20^+$ levels seroconverted after the supplemental dose; whereas, 50% of patients with detectable levels *did* seroconvert. There was a trend toward patients who seroconverted having higher overall IgM levels (76 [52.5, 102.5] versus 34.5 [9.5, 59], $p = 0.089$) and IgG levels (1179.5 [822.5, 1671.5] versus 694 [538.5, 806.5], $p = 0.090$). Importantly, patients who did not seroconvert were more likely to have IgM hypogammaglobulinemia vs. patients who seroconverted (58% versus 0%, $p = 0.042$]. There was no difference in vaccine type, history of COVID-19 infections, indication for RTX or concomitant rheumatologic medications between the group that seroconverted and the group that did not (Table S1).

Table 2
Comparisons of patients with positive versus negative titer of Anti-SARS-CoV-2 Spike Protein IgG after the supplemental vaccine dose.

Factor	Spike Titer Negative [1]	Spike Titer Positive [1]	p-value[2]
	$N = 15$	$N = 17$	
Demographics			
Male Gender, n (%)	7 (47%)	6 (35%)	0.51
Age in years, median, [IQR]	68 [55, 76)]	68 [56, 71]	0.98
Indication for Rituximab, n (%)			
• Rheumatoid Arthritis	6 (40%)	7 (41%)	0.46
• Vasculitis	5 (33%)	3 (18%)	
• Connective Tissue Disease	4 (27%)	5 (29%)	
• IGG4	0 (0%)	2 (12%)	
Initial COVID vaccine received, n (%)			
• BNT162b2	9(64%)	10 (59%)	0.92
• mRNA-1273	4 (29%)	6 (35%)	
• Ad26.COV2.SCOVID-19	1 (7%)	1 (6%)	
Supplemental COVID vaccine received, n (%)			
• BNT162b2	8 (53%)	10 (59%)	0.11
• mRNA-1273	3 (20%)	6 (35%)	
• Ad26.COV2.SCOVID-19	0 (0%)	1 (6%)	
• Unknown	4 (27%)	0 (0%)	
Immunological Parameters			
$CD20^{+3}$, median [IQR]	0 [0,0]	10.17 [0, 10.71]	0.034
Hypogammaglobulinemia,[4] n (%)	11 (85%)	2 (20%)	0.002
• Low IgM, n (%)	8 (62%)	1 (10%)	0.012
• Low IgG, n (%)	6 (46%)	2 (20%)	0.19
• IgM level, median [IQR]	32 [10, 54]	69 [53, 106]	0.022
• IgA level, median [IQR]	170.5 [93, 242]	303 [153, 423]	0.099
• IgG level, median [IQR]	702 [546, 834]	1179.5 [724, 1250]	0.013
Spike Ab titer positive after initial series,[5,6] n (%)	0 (0%)	7 (47%)	0.003
Spike titer level after initial series,[5,6] median [IQR]	0 [0, 0]	0 [0,20]	0.004
Medications at the Time of Supplemental Dose			
Steroids, n (%)	6 (40%)	3 (18%)	0.16
Any Concomitant DMARD, n (%)	8 (53%)	8 (47%)	0.72
• Mycophenolate, n (%)	4 (27%)	2 (12%)	0.28
• Hydroxychloroquine, n (%)	1 (7%)	1 (6%)	0.93
• Methotrexate, n (%)	1 (7%)	1 (6%)	0.93
Weeks from last rituximab, median [IQR]	22 [17, 28]	27 [17, 46]	0.42
Rituximab Cumulative Dose, mg, median [IQR]	8570 [5000, 10,000]	6000 [4000, 8000]	0.31

[1] Median (IQR) or n(%).
[2] Mann Whitney or chi-square tests.
[3] Within 2 months of supplemental dose if no rituximab in the interim.
[4] Within 12 months of supplemental dose.
[5] 2 doses of the BNT162b2 mRNA or mRNA-1273 vaccines or 1 dose of the Ad26.COV2.SCOVID-19 vaccine.
[6] Index <1.00 negative, >/= 1.00 positive).

These data show that patients who did not respond to the initial vaccine series were 15.2 times less likely to seroconvert if they were hypogammaglobulinemic. IgM hypogammaglobulinemia in particular was found to be a significant predictor of booster vaccine effectiveness when this is measured by spike antibody levels.

3.4. SARS-CoV-2 infections

In our cohort, there have been 21 infections in 19 patients since the beginning of the pandemic, including 11 infections after the supplemental dose. Five patients (26%) required hospitalization for their COVID-19 infection, including 2 after receiving the supplemental dose. Three of the hospitalized patients (60%) were treated in an ICU. There were no deaths. (Table 1).

The 11 patients with COVID-19 infections after the supplemental

dose were compared to the 41 patients without a COVID-19 infection. There were no differences in RTX indication, type of vaccine received, hypogammaglobinemia or concomitant steroids or DMARDs. Importantly, there were no differences in spike Ab positivity or titer between the group infected after the third dose versus the non-infected group, with the caveat that the time the patients followed after the supplemental dose may not have been sufficient to detect such differences.

3.5. Pre-exposure prophylaxis

In our center, we started using Evusheld (tixagevimab co-packaged with cilgavimab) monoclonal antibodies for pre-exposure prophylaxis in late January 2022. From January through May 2022, 28.6% of RTX-treated patients had received Evusheld and none have had COVID-19 after the prophylaxis. In that same time period, there were 4 COVID-19 infections among the patients that did not receive Evusheld. Patients who received Evusheld and those who did not, were equally likely to have detectable antibody titers after the supplemental dose (46% versus 58%, $p = 0.51$).

4. Discussion

We report the results of a single center observational cohort study on SARS-CoV-2 supplemental dose vaccination rates and immunogenicity in adult patients with AIRD treated with RTX. Most patients have received the supplemental dose, which for the majority of patients was their third dose. Approximately half (53.1%) of the patients in our study were positive for anti-spike IgG antibodies after the supplemental dose. Other studies have shown that the initial series of one or two doses resulted in seropositivity of about a third. [5,6,9] The supplemental dose has generally been associated with an increase in seropositivity. A recent meta-analysis showed that patients on anti-$CD20^+$ therapy had a much lower rate of seroconversion following the booster dose compared to patients receiving non-anti-$CD20^+$ therapy (25% vs 81%). [10] In our study, approximately one third of the patients who did not initially mount an antibody response to COVID-19 vaccination, were positive after the supplemental dose. This again supports an increase in seroconversion with additional doses, albeit lower than in patients not on RTX.

We found that hypogammaglobulinemia was a strong negative predictor of seroconversion after the supplemental dose. RTX therapy is associated with hypogammaglobulinemia, and this complication has previously been associated with an absence of seropositivity following vaccination and increased rates of serious infection [6,11,12].

Additionally, we found patients with negative spike protein antibody titers had lower absolute $CD20^+$ counts. Many patients in this study had undetectable B-cell levels, and those patients were very likely to not respond to the supplemental dose. The B-cell depletion therefore caused by RTX negatively affects antibody responses to vaccinations, as has also been suggested by prior studies. [5,9,13,14] Mrak et al. found that patients with no measurable peripheral B-cells did not develop antibodies after SARS-CoV-2 vaccination during the initial series, but some patients with repopulated B-cells did mount antibody responses. [5] The optimal timing of COVID-19 vaccination in patients treated with rituximab is unclear, but patients may have a better response when they have recovery of B-cell levels. Our study suggests that since none of the patients with undetectable $CD20^+$ levels developed new spike protein antibodies following the supplemental dose, those patients may benefit from waiting for B-cell recovery prior to receiving vaccine doses.

Breakthrough infections occurred despite vaccination. Patients with rheumatic diseases have a higher risk of developing SARS-CoV-2 infection and a higher risk of having a poor outcome compared to the general population. [15] Further, patients on B-cell depleting therapy have been shown to be at increased risk of COVID-19-related hospitalization compared with the general population, although subsequent ICU admission or death were infrequent in one study. [16] Another study found that RTX was associated with an increased risk for in-hospital death with COVID-19. [17] While there were no deaths in our cohort, hospitalization including ICU level care for COVID-19, were not uncommon.

Even after infection and vaccination not all patients seroconverted. Prior studies have indicated that patients can recover from COVID-19 infection in the absence of a humoral immune response [18]. Discordant B- and T- cell responses to infection with COVID-19 have been documented. [7] Multiple aspects of the immune system including memory $CD4^+$, $CD8^+$ T cells, memory B cells and antibodies contribute to long term immunity against SARS-CoV2. [19] Painter et al found that vaccination induced rapid antigen-specific $CD4^+$ T cell responses in COVID-19 naive subjects [20]. In patients undergoing B-cell depleting therapy, it is possible that these additional aspects of the immune system may be driving recovery from the infection despite the apparent absence of a humoral response.

-Because of the poor antibody generation, additional strategies are necessary to protect these vulnerable RTX treated patients from COVID-19. One such strategy is monoclonal antibody pre-exposure prophylaxis. Approximately a quarter of RTX-treated patients in this study have received monoclonal antibodies pre-exposure prophylaxis which to date has been highly efficacious in preventing infection. For patients receiving RTX, particularly those with hypogammaglobulinemia or undetectable levels of $CD20^+$ cells, pre-exposure prophylaxis can be a good bridge to protect from COVID-19.

This study has several limitations. First, although vaccination status and infection history were identified using multiple data sources, some vaccinations and infections among patient receiving rituximab may have been missed. This could lead to misclassification. Second, prior SARS-CoV-2 infections may influence the captured spike protein percentage. Nucleocapsid antibodies were not measured, so it is possible some of the positive spike antibodies are a response to infection instead of vaccine. Third, the data is obtained from a single health care system which may limit generalizability. Finally, many patients did not receive antibody testing and the timing was inconsistent in the cohort. We do not know the infection prevention behaviors of the patients included.

Despite these limitations, these findings can inform strategies to prevent COVID-19 in patients receiving RTX for autoimmune rheumatic diseases. Following the supplemental dose, additional patients developed antibodies to the spike protein but patients who had hypogammaglobulinemia and/or undetectable B-cell counts oftentimes did not seroconvert. We propose wherever it is feasible to time the vaccination to COVID-19 not only to RTX infusion but most importantly to B cell recovery. In addition, patients who are hypogammaglobulinemic should be strongly considered for pre-exposure prophylaxis. Finally, although B cell depletion impairs vaccine effectiveness, T cell responses are as important: measuring T cell responses to COVID-19 vaccination in patients who are B cell depleted, in a standardized fashion will further assist in risk stratification.

Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

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