Rituximab, but not other antirheumatic therapies, is associated with impaired serological response to SARS- CoV-2 vaccination in patients with rheumatic diseases

There is a paucity of data on the effect of antirheumatic drugs on serological responses to COVID-19 vaccines. Anti-CD20 therapies deplete B-cells, with reconstitution often not beginning for 6–9 months after infusion, resulting in diminished humoral immune responsiveness to recall antigens.[1–6] We retrospectively assessed response to COVID-19 vaccination in rheumatic disease patients treated with a variety of antirheumatic medications including rituximab.

A retrospective chart review of adult patients from one rheumatology practice who received at least one dose of a COVID-19 vaccine was performed. Data were collected from patients who had a clinic visit from 24 February 2021 to 8 April 2021 and were serologically screened for antibodies to the SARS-CoV-2 Spike protein.

Serological response to vaccination was assessed using a semi-quantitative anti-SARS-CoV-2 enzyme immunoassay.

Vaccination responsiveness was compared between patients receiving various antirheumatic medications. In patients treated with rituximab time between most recent administration of drug and vaccination was recorded. Exposure to rituximab was defined as having ever been treated, however, all patients were within 4.5 years (median (IQR) 0.70 (0.41–1.74)) years of last exposure. B-cell reconstitution at time of anti-SARS-CoV-2 antibodies measurement was documented, when available, for rituximab-treated patients.

Primary outcome was the presence of a serological response to COVID-19 vaccination. Descriptive statistics, box plots and bivariate comparisons using Fisher's exact test, Student's t-test and Wilcoxon rank sum tests were performed. An alpha of 0.05 was used to assess statistical significance.

Eighty-nine patients met criteria for inclusion. Eighty-three subjects (93.26%) had received both doses of a COVID-19 vaccine at the time of immunoassay. Thirty patients (34%) were treated with rituximab. Thirty-five patients (39%) were taking more than one antirheumatic medication at time of assessment (table 1).

A majority of the serologically negative results were among patients using rituximab (20/21), with the only other serologically negative patient having been treated with belimumab.

Among rituximab users, there was a significant difference in the number of days between those with a positive serological response (median, IQR 704.5 (540–1035) days) compared with those with a negative response (median, IQR 98 (64-164) days) ($p<0.001$) (figure 1A). B-cell reconstitution was available for 11 patients and there was a significant difference among those with a positive serological response (N=7) compared with those with a negative response, (N=4) ($p=0.026$) (figure 1B). When B-cell reconstitution is dichotomised, there is a statistical significance among those with a positive serological response (N=7) compared with those with a negative response ($p=0.024$).

In this study, all patients who did not demonstrate a positive serological response had been treated with rituximab, with the exception of one patient that was treated with belimumab, another B-cell targeting strategy. Longer duration from most recent rituximab exposure was associated with a greater likelihood of response. The results suggest that time from last rituximab exposure is an important consideration in maximising the likelihood of a serological response, but this likely is related to the substantial variation in the period of B-cell depletion following rituximab. In many cases, the duration of B-cell depletion and observed lack of vaccine responsiveness was longer than what is recommended in some current guidelines, and longer than the traditional interval between rituximab doses in remission maintenance regimens in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, or in the treatment of rheumatoid arthritis. Confirming B-cell reconstitution before vaccination may increase the likelihood of a positive serological response.

Patients who had even weak levels of B-cell reconstitution had higher rates of seropositive responses to vaccines, while B-cell depleted patients invariably demonstrated a negative serological response to vaccination. Importantly, absence of a detectable antibody response to COVID-19 vaccines does not imply absence of improved immunity relative to prior to vaccination in those patients, recognising that other facets of immunity may be enhanced by vaccination.[5]

Strengths of our study include the largest cohort of rituximab treated patients in whom vaccine responsiveness was assessed reported to date. Limitations of the study include small sample size and being retrospective.

These data, if confirmed in larger cohorts, could have important clinical implications regarding timing of vaccination in rituximab exposed patients. In communities with limited access to COVID-19 vaccines, confirming B-cell reconstitution prior to vaccine administration may be prudent.

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Table 1 Bivariate comparisons of serological responsiveness to the COVID-19 vaccine

	Overall	Negative for antibody response	Positive for antibody response	
Factor	**N (%)**	**N (%)**	**N (%)**	**P value***
N	89	21	68	
Age, mean (SD)	61.3034 (16.081)	65.4286 (15.0916)	60.0294 (16.2692)	0.18†
Sex				0.38
Female	68 (76%)	18 (86%)	50 (74%)	
Male	21 (24%)	3 (14%)	18 (26%)	
Race				0.19
White	84 (94%)	19 (90%)	65 (96%)	
Black or African American	2 (2%)	0 (0%)	2 (3%)	
Asian	3 (3%)	2 (10%)	1 (1%)	
Primary diagnosis				
RA	23 (26%)	2 (10%)	21 (31%)	0.084
Systemic lupus erythematosus	9 (10%)	2 (10%)	7 (10%)	1.00
Sjogrens syndrome	10 (11%)	3 (14%)	7 (10%)	0.69
Systemic sclerosis	5 (6%)	3 (14%)	2 (3%)	0.083
Psoriatic arthritis	6 (7%)	0 (0%)	6 (9%)	0.33
Granulomatosis with polyangiitis	12 (13%)	6 (29%)	6 (9%)	0.031
Giant cell arteritis	2 (2%)	0 (0%)	2 (3%)	1.00
Polymyalgia rheumatica	3 (3%)	1 (5%)	2 (3%)	0.56
Microscopic polyangitis	4 (4%)	2 (10%)	2 (3%)	0.24
IgG4 disease	1 (1%)	1 (5%)	0 (0%)	0.24
Behcet's disease	2 (2%)	0 (0%)	2 (3%)	
Dermatomyositis	1 (1%)	0 (0%)	1 (1.5%)	
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	1 (1%)	0 (0%)	1 (1.5%)	
Familial mediterranean fever	1 (1%)	0 (0%)	1 (1.5%)	
Mixed connective tissue disease	1 (1%)	0 (0%)	1 (1.5%)	
Osteoarthritis	1 (1%)	0 (0%)	1 (1.5%)	
Relapsing polychondritis	2 (2%)	1 (5%)	1 (1.5%)	
Retinal vasculitis	2 (2%)	0 (0%)	2 (3%)	
Systemic lupus erythematosus/rheumatoid arthritis overlap syndrome	1 (1%)	0 (0%)	1 (1.5%)	
Undifferentiated connective tissue disease	2 (2%)	0 (0%)	2 (3%)	
Vaccine type				1.00
Pfizer	51 (57%)	12 (57%)	39 (57%)	
Moderna	38 (43%)	9 (43%)	29 (43%)	
COVID-19 antibody assay				
Roche elecsys anti-SARS-CoV-2	84 (94.38%)	–	–	
Siemens healthineers SARS-CoV-2 Total Assay Atellica IM or ADVIA Centaur XP/XPT‡	5 (5.62%)	–	–	
Days from last rituximab exposure to assay among Rituximab treated patients, median (IQR), (n=30)	212 (122, 599)	153 (114, 212)	762 (599, 1064)	<0.001
Days from last rituximab exposure to second dose of COVID-19 vaccine among rituximab-treated patients, median (IQR), (n=30)	167 (79, 540)	102 (66, 167)	705 (540, 1035)	<0.001
Time from last rituximab exposure to second dose of COVID-19 vaccine among Rituximab treated patients (n=30)§				
<6 months	16 (53%)	16 (80%)	0 (0%)	<0.001
6–12 months	4 (13%)	3 (15%)	1 (10%)	
>12 months	10 (33%)	1 (5%)	9 (90%)	
Prior documented COVID infection	2 (2%)	–	–	
Medications ¶	Number and percentage of overall group	Number and percentage of group negative for antibody response	Number and percentage of group positive for antibody response	
Patients with rituximab exposure in combination with other therapy	15 (17%)	10 (48%)	5 (7%)	1.00
Patients without rituximab exposure treated with two or more medications	20 (22%)	1 (4%)	19 (28%)	0.34
Patients on two or more medications	35 (39%)	11 (52%)	24 (35%)	0.20
Non-Steroidal Anti-inflammatory Drugs	6 (7%)	0 (0%)	6 (9%)	0.33
Corticosteroids	17 (19%)	5 (24%)	12 (18%)	0.54
Non-biological DMARD **				
Sulfasalazine	1 (1%)	0 (0%)	1 (1%)	1.00
Leflunomide	3 (3%)	1 (5%)	2 (3%)	0.56

Continued

Table 1 Continued

Factor	Overall N (%)	Negative for antibody response N (%)	Positive for antibody response N (%)	P value*
Hydroxychloroquine	19 (21%)	2 (10%)	17 (25%)	0.22
Azathioprine	3 (3%)	0 (0%)	3 (4%)	1.00
Upadacitinib	2 (2%)	0 (0%)	2 (3%)	1.00
Methotrexate	13 (15%)	1 (5%)	12 (18%)	0.29
Apremilast	1 (1%)	0 (0%)	1 (1%)	1.00
Mycophenolate mofetil	7 (8%)	3 (14%)	4 (6%)	0.35
Tofacitinib	4 (4%)	0 (0%)	4 (6%)	0.57
Colchicine	3 (3%)	0 (0%)	3 (4%)	1.00
Biological DMARDs				
Adalimumab	8 (9%)	0 (0%)	8 (12%)	0.19
Secukinumab	2 (2%)	0 (0%)	2 (3%)	1.00
Mepolizumab	1 (1%)	0 (0%)	1 (1%)	1.00
Tocilizumab	2 (2%)	1 (5%)	1 (1%)	0.42
Etanercept	1 (1%)	0 (0%)	1 (1%)	1.00
Abatacept	1 (1%)	0 (0%)	1 (1%)	1.00
Belimumab	2 (2%)	1 (4.76%)	1 (1.47%)	0.42
Rituximab	30 (34%)	20 (95%)	10 (15%)	<0.001
Antibody concentration (U/mL) in rituximab-treated patients (n=30), median (IQR)	–	0 (0, 0)	251 (169, 251)	<0.001††

*All p values were calculated from a Fisher's exact test unless otherwise indicated.
†T-test was used.
‡Roche Elecsys Anti-SARS-CoV-2, specificity 99.8% sensitivity 99.5%, or a Siemens Healthineers SARS-CoV-2 total (COV2T) Assay Atellica IM, specificity 99.82% sensitivity 100% or ADVIA Centaur XP/XPT, specificity 99.81% sensitivity 100%.
§Among the four people who were negative, the specific number of days from last infusion to first vaccination were 188, 229, 230, 415.
¶Medications are not mutually exclusive. 35 (39%) patients are taking two or more medications.
**Includes both conventional and targeted synthetics.
††Wilcoxon rank sum test was used.
DMARDS, disease modifying antirheumatic drugs.

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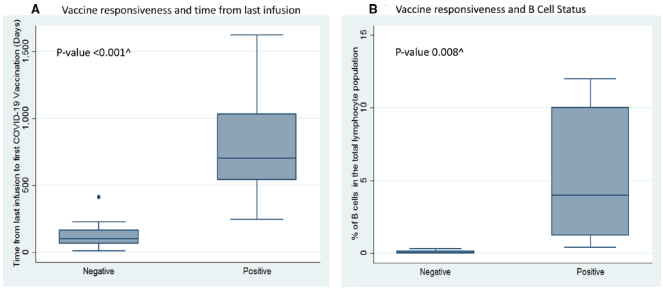

Figure 1 (A) Among patients treated with rituximab with a negative serological response (N=20), the median IQR of days from last infusion to first vaccination was 98 (64–164) days. Patients with a positive serological response (N=10) had a median IQR of 704.5 (540–1035) days. Wilcoxon rank sum test was used to calculate the p value. (B) Among N=11 people with % B-cells available, four were serologically negative and seven were serologically positive. The percentage of B-cells among the negative serological response median IQR=0 (0–0.15). Among the positive serological vaccine response group, the median (IQR) is 4 (1.2–10). The p value is from the Wilcoxon rank sum test. The y-axis is the percentage of B-cells in the total lymphocyte population as measured by flow cytometry.

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