Rheumatology Advances in Practice, 2023, **7(3)**, rkad097
https://doi.org/10.1093/rap/rkad097
Advance access publication 11 November 2023
Original Article

British Society for Rheumatology
RHEUMATOLOGY ADVANCES IN PRACTICE
OXFORD

Clinical science

Antibody response to four doses of SARS-CoV-2 vaccine in rare autoimmune rheumatic diseases: an observational study

Leher Gumber [1,2], Hannah Jackson[3], Nancy Gomez[3], Georgina Hopkins[3], Davis Tucis[3], Mithun Chakravorty[1], Patrick Tighe[3], Matthew J. Grainge [2], Megan Rutter [1,2], Alastair Ferraro[4], Sheila Power[5], Marie-Josèphe Pradère[5], Peter C. Lanyon[1,2,6], Fiona A. Pearce [1,2,6,*], Lucy Fairclough[3]

[1]Department of Rheumatology, Nottingham University Hospitals NHS Trust, Nottingham, UK
[2]Lifespan and Population Health, School of Medicine, University of Nottingham, Nottingham, UK
[3]School of Life Sciences, University of Nottingham, Nottingham, UK
[4]Department of Nephrology, Nottingham University Hospitals NHS Trust, Nottingham, UK
[5]Research & Innovation, Nottingham University Hospitals NHS Trust, Nottingham, UK
[6]NIHR Nottingham Biomedical Research Centre, Nottingham, UK

*Correspondence to: Fiona A. Pearce, City Hospital, Clinical Sciences Building, Nottingham NG5 1PB, UK. E-mail: fiona.pearce@nottingham.ac.uk

Abstract

Objective: Antibody responses to coronavirus disease 2019 (COVID-19) vaccines are reduced among immunocompromised patients but are not well quantified among people with rare disease. We conducted an observational study to evaluate the antibody responses to the booster SARS-CoV-2 vaccine in people with rare autoimmune rheumatic diseases (RAIRD).

Methods: Blood samples were collected after second, before third, after third and after fourth vaccine doses. Anti-spike and anti-nucleocapsid antibody levels were measured using an in-house ELISA. Logistic regression models were built to determine the predictors for non-response. Results were compared with age- and sex-matched healthy controls.

Results: Forty-three people with RAIRD were included, with a median age of 56 years. Anti-spike seropositivity increased from 42.9% after second dose to 51.2% after third dose and 65.6% after fourth dose. Median anti-spike antibody levels increased from 33.6 (interquartile range 7.8–724.5) binding antibody units after second dose to 239.4 (interquartile range 35.8–1051.1) binding antibody units after the booster dose (third dose, or fourth dose if eligible). Of the participants who had sufficient antibody levels post-second dose, 22.2% had insufficient levels after the booster, and 34.9% of participants had lower antibodies after the booster than the lowest healthy control had after the second dose. Rituximab in the 6 months prior to booster ($P = 0.02$) and non-White ethnicity ($P = 0.04$) were associated with non-response. There was a dose–response relationship between the timing of rituximab and generation of sufficient antibodies ($P = 0.03$).

Conclusion: Although the booster dose increased anti-spike IgG and seropositivity rates, some people with RAIRD, particularly those on rituximab, had insufficient antibody levels despite three or four doses.

Lay Summary

What does this mean for patients?

People living with rare autoimmune rheumatic illnesses, such as vasculitis, lupus, myositis and scleroderma, can have a weakened immune system because of their illness or its treatment. They might not respond to coronavirus disease 2019 (COVID-19) vaccinations as effectively as healthy people. Forty-three people with a rare autoimmune rheumatic illness took part (30 had vasculitis, 8 systemic lupus erythematosus and 5 myositis). We used a questionnaire to collect health information including diagnosis, treatments, age, sex, ethnic origin and details about COVID-19 vaccination and infection. We collected blood samples after the first booster vaccine, which was the third or fourth COVID-19 vaccine. We looked for anti-spike antibodies in the blood samples (a sign of response to the vaccine). We used the lowest level of antibodies produced by a group of healthy people to define having enough antibodies. We found that: 65% of people living with a rare autoimmune disease made enough antibodies after their first booster dose of vaccine; more vaccines increased the chance of having protective antibodies (enough antibodies were found in 43% of people after their second dose, 51% after their third dose and 66% after their fourth dose); and having a drug called rituximab in the 12 months before vaccination and being from a non-White ethnic background reduced the chance of producing enough antibodies.

Keywords: rare autoimmune rheumatic diseases, SARS-CoV-2, vaccination, antibody, rituximab

Received: 22 July 2023. **Accepted:** 20 October 2023

Key messages

- Despite additional doses, individuals with RAIRD had lower antibodies than lowest healthy control.
- Antibodies diminish over time, and rituximab treatment in the 6 months prior to the booster and non-White ethnicity were predictors of poor response.
- Individual risk assessments in all immunocompromised patients on rituximab should be conducted, and additional strategies will be necessary to provide protection.

Introduction

Coronavirus disease 2019 (COVID-19) vaccination programmes have been effective at reducing the severity of COVID-19 infection [1, 2]; however, it remains important for future pandemic planning to gain a better understanding of the immune response to vaccination of people who are immunocompromised, for whom vaccination might be less effective. Among immunosuppressed groups, people with the rare autoimmune rheumatic diseases (RAIRD; vasculitis, lupus, scleroderma and myositis) are at greater risk of COVID-19 infection and associated mortality compared with both the general population and those with other types of inflammatory rheumatic diseases [3–7]. They are also more likely to have a weakened response to vaccination compared with healthy individuals of a similar age and sex [8–11]. In addition, those with rare diseases are also harder to recruit to research, and there is less evidence available on their vaccine antibody responses than for people with more common diseases. The aim of this study was to conduct a prospective cohort study to evaluate antibody responses to third and fourth severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination in people with rare autoimmune rheumatic diseases.

Methods

Study design and participants

People aged ≥18 years with a diagnosis of RAIRD (vasculitis, SLE, myositis and scleroderma) were recruited from outpatient rheumatology and renal clinics in Nottingham University Hospitals NHS Trust from March to December 2021. People were not eligible if they were <18 years of age, ineligible to receive a SARS-CoV-2 vaccination, unable to provide blood samples, unable to travel to the hospital for study visits, unable to consent or had low English proficiency. All participants provided written informed consent and completed a questionnaire on demographic and clinical information.

All participants received SARS-CoV-2 vaccination as part of the UK vaccination programme. They received two primary doses 3–12 weeks apart [12] plus a booster dose 6 months later [13], or three primary doses plus a booster dose 6 months later if they were immunocompromised [14].

Patients and members of the public were involved at all stages of the study design and conduct. The study proposal was peer reviewed by people with vasculitis and other RAIRD, and their feedback was incorporated into the study design. Findings will be disseminated to patients and the public through the Vasculitis UK website and newsletters.

Ethical approval

The study was approved by the West Midlands–Black Country Research Ethics Committee (REC reference: 21/WM/0097).

Sample collection

Whole blood samples were collected at five time points during the study period: (i) prior to the second SARS-CoV-2 vaccination dose; (ii) 4 weeks (or 3 months if unable to attend sooner) after the second dose; (iii) 1–2 weeks before the third dose (which was given ∼6 months after the second dose in most people); (iv) 4–6 weeks after the third dose; and (v) 2 weeks after the fourth dose in the immunocompromised group. All samples were collected in accordance with national regulations and requirements.

Serological measurements

Heparinized whole blood was centrifuged at 300***g*** for 8 min to separate the plasma. Plasma was tested for nucleocapsid and spike-specific antibodies in two separate ELISAs. Briefly, 384-well Maxisorp (NUNC) assay plates were coated with 20 µl per well of 1 µg/ml of either Wuhan strain SARS-CoV-2 full-length spike protein or Wuhan strain SARS-CoV-2 nucleocapsid protein. Plates were sealed with foil film and incubated overnight at 4°C. Plates were then washed three times with PBS with 0.05% Tween 20 (PBS-T) using a Biochrom ASYS Atlantis plate washing robot with 16-channel head. Wells were immediately filled with 100 µl of blocking solution and 0.01% EDTA and blocked overnight at 4°C. Plates were washed a further three times, and serum samples were diluted to 1:200. SARS-CoV-2 antibody-positive and -negative serum controls were obtained from the National Institute of Biological Standards and Controls (NIBSC, UK). Each assay contained a 12-point standard dilution of NIBSC 20/162 calibration standard diluted 2-fold from 1:200, two negative controls from the NIBSC assay verification panel, and the NIBSC QC standard (20/764), all also diluted at 1:200. Twenty microlitres of γ-chain-specific anti-human IgG horseradish peroxidase conjugate (Sigma; A0170) was added per well at a dilution of 1:30 000. This was incubated for a further 30 min and subjected to a final three washes. Forty microlitres of ultra-TMB (ThermoFisher; catalogue no. 34028) was added per well and incubated for 20 min, then the reaction stopped by the addition of 40 µl of 2 N H_2SO_4 to each well and absorbance read at 450 and 600 nm using an EPOCH microplate reader (BioTek, UK). Data were presented as a conversion of the change in optical density (from 450 to 600 nm) into binding antibody units (BAU). All assays were performed on Opentrons OT-2 liquid-handling robots.

Statistical analysis

We performed a complete case analysis on all participants who provided samples after the third and/or fourth dose, using 5% as the significance level. Missing data were assumed to be missing at random, and no imputations were performed. Descriptive statistics were used to identify any differences in demographics and clinical characteristics. In the

immunogenicity analysis, we compared anti-spike protein IgG responses after the second dose, before the third dose, after the third dose and after the fourth dose. No analysis was conducted on anti-nucleocapsid responses. We also calculated the percentage change for each participant at three time points: after the third dose compared with after the second dose; after the fourth dose compared with after the third dose; and after the booster compared with after the second dose. A detectable response was defined as an IgG spike protein antibody level >10 BAU, and a sufficient response (responder) was defined as an IgG level above the lowest healthy control subject after two doses of vaccine (>80.585 BAU). Owing to the large variation in antibody responses, absolute levels have been summarized as the medians and interquartile ranges. Fisher's exact test (appropriate owing to cell counts less than five) was used to determine the predictors for non-response after two doses and booster doses, and logistic regression models were built adjusted for age, sex and rituximab treatment as a priori confounders, because these have previously been suggested to influence antibody levels [15–17]. Variables that were statistically significant in the univariate analysis were incorporated as additional confounding factors. All statistical analyses were performed using Stata v.14, Prism and Microsoft Excel.

Study outcomes

The primary outcome was to assess the antibody response after the booster dose (defined as third dose, or fourth dose if eligible for third primary dose owing to immunosuppressive treatment) given routinely in the UK SARS-CoV-2 vaccination programme.

Results

Among 102 RAIRD patients identified, 52 were enrolled into the study, of whom 43 provided a blood sample after their third and/or fourth dose and are included in this analysis (Fig. 1). Thirty-two people were eligible for a third primary dose and 11 were not. The median age of the cohort was 56.0 years [interquartile range (IQR) 47.0–64.0 years; Table 1]. The majority of participants were female (67%) and of White ethnicity (88%). Diagnosis was ANCA-associated vasculitis in 24 participants (56%), SLE in 8 (19%), another type of systemic vasculitis in 6 (14%) and myositis in 5 (12%). Most of the cohort had a history of treatment with rituximab ($n = 35$, 81%). The median intervals between rituximab infusion and the third dose and fourth dose were 251.0 (IQR 145.0–421.0) days and 121.5 (IQR 54.0–481.0) days, respectively. Eighteen (42%) participants were taking CSs, and 14 (33%) participants were taking oral immunosuppressants other than CSs or rituximab. The median intervals between the date of the third and fourth doses and sample collection were similar (31.0 *vs* 30.5 days, respectively). During the study, 8 (19%) participants self-reported COVID-19 infection and 32 (74%) had a rise in their nucleocapsid antibodies suggesting COVID-19 infection. It is noteworthy that natural COVID-19 infection will also increase spike antibody levels. All participants survived their infection. We did not collect data on COVID-19 treatment. We excluded four participants from the analysis because they had immunoglobulin therapy during the study. Their median age was 33.0 (IQR 28.7–36.2) years, three were female and all were of White ethnicity. Three had a diagnosis of ANCA-associated vasculitis and previous rituximab treatment, and one had a diagnosis of SLE. Their anti-spike IgG concentration measured at four time points ranged from to 2.6 to 288.5 BAU.

An increasing proportion of people with RAIRD developed sufficient antibody responses after each of the second dose, third dose and fourth dose (42.9, 51.2 and 65.6%, respectively), as shown in Table 2. However, after the booster dose (defined as third dose, or the fourth dose if eligible for third primary dose owing to immunosuppressive treatment), 34.9% of people with RAIRD still had lower antibodies than the lowest healthy control did after the second dose. Antibody levels waned over time, and having antibodies after the second dose did not guarantee having them after the third dose or fourth dose; of the 18 people who had sufficient

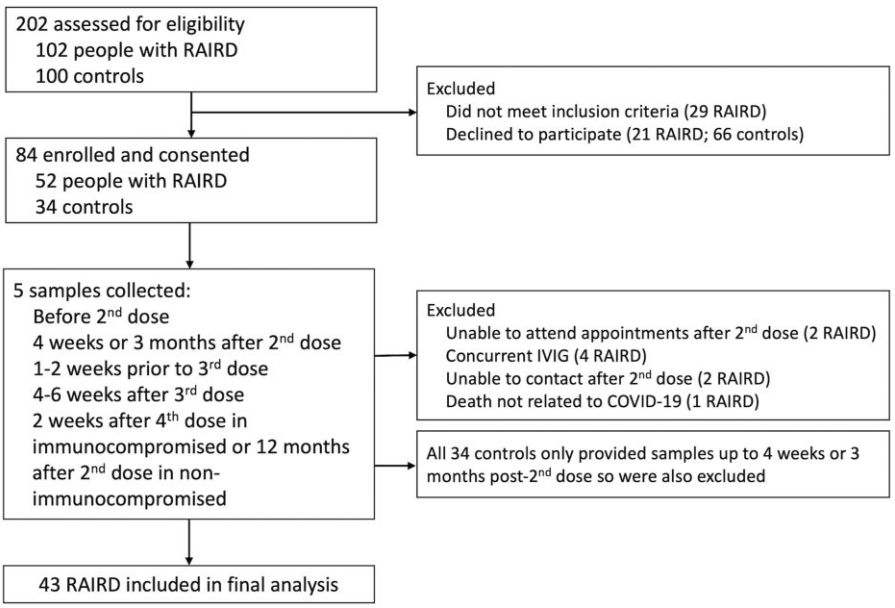

Figure 1. Flowchart of the study

Table 1. Baseline characteristics of participants with rare autoimmune rheumatic diseases

Characteristic	RAIRD ($n = 43$)
Age, *n* (%), years	
Median (IQR)	56.0 (47.0–64.0)
18–49	14 (32)
50–64	20 (47)
≥65	9 (21)
Sex, *n* (%)	
Female	29 (67)
Male	14 (33)
Ethnicity, *n* (%)	
White	38 (88)
Non-White	5 (12)
Diagnosis, *n* (%)	
ANCA-associated vasculitis	24 (56)
SLE	8 (19)
Other systemic vasculitis[a]	6 (14)
Myositis	5 (12)
Current immunosuppression, *n* (%)	
CSs	18 (42)
Other oral immunosuppressant[b]	14 (33)
Rituximab timing, median (IQR), days	
Before second dose ($n = 32$)	198.5 (165.0–502.0)
Between second and third dose ($n = 27$)	251.0 (145.0–421.0)
Between third and fourth dose ($n = 22$)	121.5 (54.0–481.0)
Rituximab ever, *n* (%)	35 (81)
Vaccine, *n* (%)	
Oxford-AstraZeneca	22 (51)
Pfizer-BioNTech	21 (49)
Interval between dose and sample, median (IQR), days	
After second ($n = 42$)	35.5 (11.0–96.0)
Before third ($n = 33$)	8.0 (1.0–72.0)
After third ($n = 41$)	31.0 (12.0–51.0)
After fourth ($n = 32$)	30.5 (12.0–74.0)

Data are the median (IQR) or *n* (%).
[a] Other systemic vasculitis included GCA and relapsing polychondritis.
[b] Other oral immunosuppressants included MTX, MMF and HCQ.
IQR: interquartile range; RAID: rare autoimmune rheumatic diseases.

Table 2. Antibody responses

Parameter	*n* (%)	SARS-CoV-2 anti-spike protein IgG concentration, BAU
After the second dose ($n = 42$)		33.6 (7.8–724.5)
Responder	18 (42.9)	783.2 (386.1–1050.0)
Non-responder	24 (57.1)	9.2 (0.5–18.7)
Before the third dose ($n = 34$)		7.8 (3.3–55.2)
After the third dose ($n = 41$)		111.0 (16.8–529.4)
Responder	21 (51.2)	529.4 (206.0–885.4)
Non-responder	20 (48.8)	14.7 (0.3–45.0)
Percentage change (after third *vs* after second dose)	+2.3%	
After the fourth dose if eligible ($n = 32$)		249.5 (34.3–920.0)
Responder	21 (65.6)	695.5 (259.5–2042.8)
Non-responder	11 (34.4)	3.4 (0–39.5)
Percentage change (after fourth *vs* after third dose)	+1.2%	
After booster dose (either third or fourth vaccine depending on eligibility) ($n = 43$)		239.4 (35.8–1051.1)
Responder	28 (65.1)	784.0 (249.5–1737.8)
Non-responder	15 (34.9)	12.6 (0–39.5)
Percentage change (after booster *vs* after second dose)	+6.1%	

Data are expressed as the median (interquartile range).
[a] Responder was defined as IgG above the lowest healthy control (>80.585 BAU).
BAU: binding antibody units.

antibodies after the second dose, 4 or 18 (22.2%) did not after their booster (Fig. 2). Thirteen (54%) of the non-responders to the second dose mounted a sufficient IgG response after the booster dose, whereas 11 (46%) did not respond to the second dose or the booster dose (Supplementary Table S1, available at *Rheumatology Advances in Practice* online). Additionally, antibody levels were significantly lower in individuals who had had rituximab, after both the second dose and the booster dose (Supplementary Figure S1, available at *Rheumatology Advances in Practice* online). Non-responders to the fourth dose were more likely to be female, of non-White ethnicity, have myositis and have received rituximab in the 6 months before their fourth dose. Oral immunosuppression did not have a significant effect on response to the fourth dose (Supplementary Table S2, available at *Rheumatology Advances in Practice* online).

The median anti-spike IgG concentration after the second dose was 33.6 (IQR 5.5–724.5) BAU, which increased to 111.0 (IQR 16.8–529.4) BAU after the third dose and 249.5 (IQR 34.3–920.0) BAU after the fourth dose, a fold change of 2.3 and 1.2%, respectively. Fifty-eight percent of RAIRD participants had IgG levels below the lowest healthy control after the second dose (median IgG, 8.1 BAU), which reduced to 34% after the fourth dose (median IgG, 3.4 BAU). The median anti-spike IgG concentration after the booster dose was 239.4 BAU, which represented a 6.1% increase from the median IgG concentration after the second dose (Table 2).

We have previously published the antibody responses to the first and second doses, as part of a more detailed study including cellular responses [18]. Given that the cohort differs slightly in this study, because not every patient gave a blood sample at every time point, we have repeated the post-second dose analysis, which can be found in the Supplementary Table S3 (available at *Rheumatology Advances in Practice* online). The findings were in line with the previous paper.

After the booster dose, non-White ethnicity and treatment with rituximab were significantly associated with non-response to vaccination on univariable testing using Fisher's exact test. There was a dose–response relationship with sufficient antibodies to the booster dose found in 8 of 8 (100%) of those who had never had rituximab, 8 of 10 (80.0%) who had last had rituximab >12 months ago, 6 of 11 (54.5%) who had rituximab 6–12 months ago, and 6 of 14 (42.9%) who had rituximab in the last 6 months. On multivariable regression analysis, including age and sex as a priori confounders, and ethnicity and timing of rituximab (<6 months, 6–12 months or >12 months/never), only timing of rituximab remained significantly associated with response to vaccination after the booster dose (Table 3).

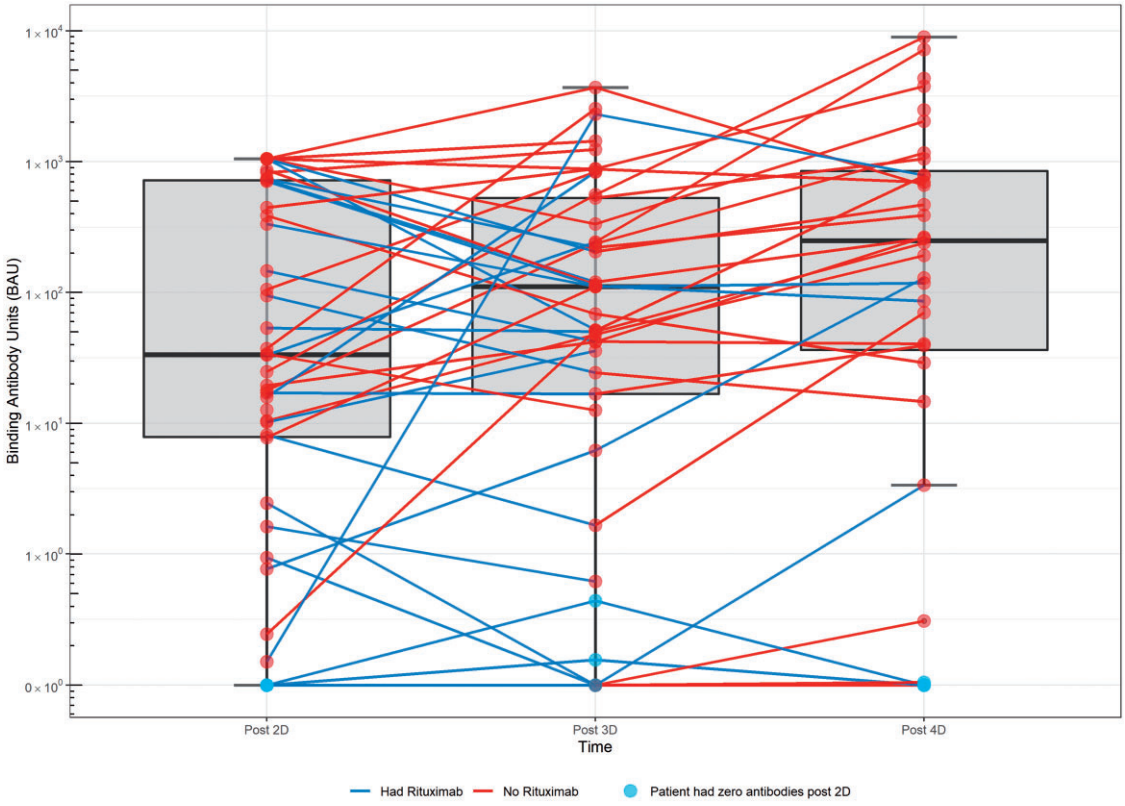

Figure 2. Antibody responses and rituximab timing for each dose of SARS-CoV-2 vaccine

Table 3. Predictors of response after the SARS-CoV-2 booster vaccine

Predictor	Responder ($n = 28$)	Non-responder ($n = 15$)	Fisher's exact test	Multivariate logistic regression	
	n (%)	*n* (%)	*P*-value	Odds ratio (95% CI)	*P*-value
Age, years (for each additional year)				0.99 (0.94–1.05)	0.76
18–49	7 (50.0)	7 (50.0)	0.32		
50–64	15 (75.0)	5 (25.0)			
≥65	6 (66.7)	3 (33.3)			
Sex			0.31		
Female	17 (58.6)	12 (41.4)		1 (reference)	
Male	11 (78.6)	3 (21.4)		0.36 (0.07–1.86)	0.22
Ethnicity			0.043*		
White	25 (65.8)	13 (34.2)		1 (reference)	
Non-White	3 (60.0)	2 (40.0)		8.46 (0.44–163.26)	0.16
Diagnosis			0.27		
ANCA-associated vasculitis	14 (58.3)	10 (41.7)			
SLE	5 (62.5)	3 (37.5)			
Other systemic vasculitis	6 (100.0)	0			
Myositis	3 (60.0)	2 (40.0)			
Current oral immunosuppression	10 (71.4)	4 (28.6)	0.74		
Rituximab timing			0.027*		
<6 months	6 (42.9)	8 (57.1)		9.70 (1.37–68.82)	*P*-trend
6–12 months	6 (54.5)	5 (45.5)		6.92 (0.94–50.62)	0.03*
>12 months	8 (80.0)	2 (20.0)		1 (reference)	
Never	8 (100.0)	0		1 (reference)	

Data are expressed as *n* (%).
* Statistically significant *P*-value.

Discussion

We present data on the antibody response following three and four doses of SARS-CoV-2 vaccines in people with RAIRD in the UK. There was an increase in the proportion of people responding to vaccination after each subsequent dose. However, 35% of participants were still non-responders after the booster, which we defined as having lower antibodies than the lowest healthy control after the second dose.

Antibody levels wane over time, and we found that having antibodies after the second dose did not guarantee having them after the third or fourth dose (22% of people who responded to the second dose did not respond to their booster dose). We observed that having had rituximab and the timing of rituximab treatment were significantly associated with reduced response to both the second and booster dose, but no other factors were statistically significant in this small study.

It is difficult to study vaccine responses in people with rare diseases, because it is difficult to recruit enough people. Each study of people with RAIRD, such as vasculitis, SLE and myositis, typically includes <50 people. This means each study is underpowered to report all clinically significant associations with vaccine response. One important aspect of publication of this and other studies in rare groups is enabling future pooled analyses of the findings, which will enable more granular risk stratification by demographics, disease and treatment groups.

Our most statistically significant finding was the detrimental impact of rituximab on antibody response to SARS-CoV-2 vaccines, which corroborates the findings of other studies [8, 10, 17, 19]. We demonstrated that antibody responses were significantly diminished in people receiving rituximab, and we found a dose–response relationship between the timing of rituximab before vaccine administration. People who had received rituximab in the 6 months before their booster dose were most at risk of non-response. A study on people with ANCA-associated vasculitis also found that cumulative dose and administration of rituximab in the 6 months before vaccination were important predictors of poor antibody response following the first vaccine. Vaccine administration >6 months after the last rituximab dose was associated with a 7-fold increase in the odds of seroconversion, in line with our findings. Interestingly, they identified that CD19 count was the strongest predictor of seroconversion [20]. However, given that data on reconstitution of B cells are not collected routinely in clinical practice in the UK, we were not able to identify the effect of this in our study. A blunted immune response that persists for ≤6 months after rituximab treatment has also been found in studies on other vaccines, such as *Haemophilus* influenza B, *Pneumococcus* and hepatitis B [21]. More recently, an open-label trial on rituximab-treated patients found that the proportion of participants who seroconverted increased from 33 to 58% following the fourth dose of COVID-19 vaccine. However, that study had a small number of RAIRD patients and did not look at the effects of rituximab timing on antibody response [22].

Our study also brings to light new findings about the relationship between ethnicity and response to vaccination. We observed that individuals from a non-White ethnic background were less likely to mount an antibody response, despite additional booster doses, than their White counterparts. However, this association was not sustained after adjustment for age and sex. Although several studies have shown that individuals from a minority ethnic background have a higher risk of SARS-CoV-2 infection and mortality [23, 24], less evidence is available on ethnic differences in immunogenicity. A small association was observed in the OCTAVE study, where patients of Asian ethnicity had a slightly higher odds of adequate serological response after two doses compared with White ethnicity [25]. However, the study was not adequately powered for a subset analysis on ethnicity; it included only a small number of patients with RAIRD and did not assess whether responses were sustained after booster doses. Further research from pooled data might help to clarify whether there are true ethnic differences in immunogenicity.

Our findings highlight the need for continued caution among people with RAIRD with the emergence of new strains of SARS-CoV-2. Seven (16.3%) participants had no measurable antibodies after a booster dose, and 15 (34.9%) had lower antibody levels than healthy controls after two doses. For individuals requiring maintenance rituximab, shared decision-making and risk assessments should be conducted by clinicians to review the timing of rituximab in relationship to future vaccinations, for example timing rituximab infusions ≥2 weeks after vaccination if clinically reasonable.

Strengths and limitations

The strengths of this study include the broad inclusion criteria, and adjustment for age and sex in our analyses as potential confounders. This study has several limitations, including small sample size, resulting in wide 95% confidence intervals for some of the analyses, and lack of data on the cellular response and reconstitution of B cells. Although we did not measure neutralizing antibodies, spike antibodies have been shown to correlate well with neutralizing antibody levels [26] and we think are therefore a reasonable surrogate.

Conclusions

This study reports COVID-19 antibody responses after three or four vaccine doses among 43 people with rare autoimmune rheumatic diseases. Our most significant finding was the detrimental impact of rituximab on the antibody response to SARS-CoV-2 vaccines, which corroborates the findings of other studies. We also found that non-White ethnicity was a predictor of non-response, but this was not sustained after adjustment. Publication will make the results available for future meta-analyses, which might identify associations that individual studies of rare diseases are underpowered to find.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

Owing to the nature of the research and ethical restrictions, the data are not publicly available. Please contact the corresponding author should you wish to access the data.

Contribution statement

The study was conceived by L.F., F.A.P. and P.C.L. L.G. did the entire data analysis and wrote up the final manuscript. F. A.P. also contributed to the data analysis. M.C., A.F., S.P., M.-J.P. and M.R. were involved in recruitment of participants and data collection. N.G., G.H., D.T., H.J. and P.T. contributed to the antibody analysis. All authors contributed to the manuscript.

Funding

This study was funded by Vasculitis UK. M.R. is supported by a Versus Arthritis Clinical Research Fellowship [Grant 22727], and F.A.P. is a National Institute for Health Research (NIHR) Advanced Fellow [NIHR300863]. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR, NHS or the UK Department of Health and Social Care or any other organization.

Disclosure statement: F.A.P. and P.C.L. are recipients of an investigator-led research award from Vifor pharma for another project unrelated to COVID-19 or vaccination. None of the other authors has any competing interests.

Acknowledgements

We would like to thank all the study participants.

References

1. Agrawal U, Bedston S, McCowan C *et al.* Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30 million individuals in England, Northern Ireland, Scotland, and Wales. Lancet 2022;400:1305–20.
2. Nab L, Parker EPK, Andrews CD *et al.* Changes in COVID-19-related mortality across key demographic and clinical subgroups in England from 2020 to 2022: a retrospective cohort study using the OpenSAFELY platform. Lancet Public Health 2023; 8:e364–77.
3. Peach E, Rutter M, Lanyon P *et al.* Risk of death among people with rare autoimmune diseases compared with the general population in England during the 2020 COVID-19 pandemic. Rheumatology (Oxf Engl) 2021;60:1902–9.
4. Rutter M, Lanyon PC, Grainge MJ *et al.* COVID-19 infection, admission and death among people with rare autoimmune rheumatic disease in England: results from the RECORDER project. Rheumatology (Oxf Engl) 2022;61:3161–71.
5. Strangfeld A, Schäfer M, Gianfrancesco MA *et al.*; COVID-19 Global Rheumatology Alliance. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2021;80:930–42.
6. Kroon FPB, Najm A, Alunno A *et al.* Risk and prognosis of SARS-CoV-2 infection and vaccination against SARS-CoV-2 in rheumatic and musculoskeletal diseases: a systematic literature review to inform EULAR recommendations. Ann Rheum Dis 2022; 81:422–32.
7. Gianfrancesco MA, Leykina LA, Izadi Z *et al.*; COVID-19 Global Rheumatology Alliance. Association of race and ethnicity with COVID-19 outcomes in rheumatic disease: data from the COVID-19 Global Rheumatology Alliance Physician Registry. Arthritis Rheumatol (Hoboken NJ) 2021;73:374–80.
8. Prendecki M, Clarke C, Edwards H *et al.* Humoral and T-cell responses to SARS-CoV-2 vaccination in patients receiving immunosuppression. Ann Rheum Dis 2021;80:1322–9.
9. Lee ARYB, Wong SY, Chai LYA *et al.* Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis. BMJ 2022;376:e068632.
10. Furer V, Eviatar T, Zisman D *et al.* Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. Ann Rheum Dis 2021;80:1330–8.
11. Fagni F, Simon D, Tascilar K *et al.* COVID-19 and immune-mediated inflammatory diseases: effect of disease and treatment on COVID-19 outcomes and vaccine responses. Lancet Rheumatol 2021;3:e724–36.
12. Department of Health and Social Care. Joint Committee on Vaccination and Immunisation: advice on priority groups for COVID-19 vaccination, 30 December 2020. GOV.UK. 2020. https://www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-30-december-2020/joint-committee-on-vaccination-and-immunisation-advice-on-priority-groups-for-covid-19-vaccination-30-december-2020 (25 July 2022, date last accessed).
13. Department of Health and Social Care. Joint Committee on Vaccination and Immunisation (JCVI) advice on third primary dose vaccination. GOV.UK. 2021. https://www.gov.uk/government/publications/third-primary-covid-19-vaccine-dose-for-people-who-are-immunosuppressed-jcvi-advice/joint-committee-on-vaccination-and-immunisation-jcvi-advice-on-third-primary-dose-vaccination (4 May 2022, date last accessed).
14. Joint Committee on Vaccination and Immunisation Updated JCVI guidance for vaccinating immunosuppressed individuals with a third primary dose. https://www.gov.uk/government/publications/third-primary-covid-19-vaccine-dose-for-people-who-are-immunosuppressed-jcvi-advice/joint-committee-on-vaccination-and-immunisation-jcvi-advice-on-third-primary-dose-vaccination (24 November 2023, date last accessed).
15. Simon D, Tascilar K, Schmidt K *et al.* Humoral and cellular immune responses to SARS–CoV-2 infection and vaccination in autoimmune disease patients with B cell depletion. Arthritis Rheumatol 2022;74:33–7.
16. Walsh EE, Frenck RW, Falsey AR *et al.* Safety and immunogenicity of two RNA-based covid-19 vaccine candidates. N Engl J Med 2020;383:2439–50.
17. Bingham CO, Looney RJ, Deodhar A *et al.* Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis Rheum 2010;62:64–74.
18. Gumber L, Gomez N, Hopkins G *et al.* Humoral and cellular immunity in patients with rare autoimmune rheumatic diseases following SARS-CoV-2 vaccination. Rheumatology (Oxford) 2023; 62:2294–2303.
19. Mehta P, Porter JC, Chambers RC, Isenberg DA, Reddy V. B-cell depletion with rituximab in the COVID-19 pandemic: where do we stand? Lancet Rheumatol 2020;2:e589–90.
20. Floyd L, Elsayed ME, Seibt T *et al.* SARS-CoV-2 vaccine response in patients with antineutrophil cytoplasmic autoantibody-associated vasculitis. Kidney Int Rep 2022;7:629–32.
21. Rondaan C, Furer V, Heijstek MW *et al.* Efficacy, immunogenicity and safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases: a systematic literature review for the 2019 update of EULAR recommendations. RMD Open 2019; 5:e001035.
22. Mrak D, Simader E, Sieghart D *et al.* Immunogenicity and safety of a fourth COVID-19 vaccination in rituximab-treated patients: an open-label extension study. Ann Rheum Dis 2022;81:1750–6.
23. Sze S, Pan D, Nevill CR *et al.* Ethnicity and clinical outcomes in COVID-19: a systematic review and meta-analysis. EClinicalMedicine 2020;29:100630.
24. Mathur R, Rentsch CT, Morton CE *et al.*; OpenSAFELY Collaborative. Ethnic differences in SARS-CoV-2 infection and COVID-19-related hospitalisation, intensive care unit admission, and death in 17 million adults in England: an observational cohort study using the OpenSAFELY platform. Lancet 2021;397:1711–24.
25. Barnes E, Goodyear CS, Willicombe M *et al.*; OCTAVE Collaborative Group CONSENSUS. SARS-CoV-2-specific immune responses and clinical outcomes after COVID-19 vaccination in patients with immune-suppressive disease. Nat Med 2023; 29:1760–74.
26. Lustig Y, Sapir E, Regev-Yochay G *et al.* BNT162b2 COVID-19 vaccine and correlates of humoral immune responses and dynamics: a prospective, single-centre, longitudinal cohort study in health-care workers. Lancet Respir Med 2021;9:999–1009.