RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Antibody response to the COVID-19 ChAdOx1nCov-19 and BNT162b vaccines after temporary suspension of DMARD therapy in immune-mediated inflammatory disease: an extension study (RESCUE 2)

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To cite: Tran AP, Tassone D.F, Ding NS, *et al*. Antibody response to the COVID-19 ChAdOx1nCov-19 and BNT162b vaccines after temporary suspension of DMARD therapy in immune-mediated inflammatory disease: an extension study (RESCUE 2). *RMD Open* 2023;**9**:e002871. doi:10.1136/rmdopen-2022-002871

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2022-002871).

Received 16 November 2022
Accepted 1 February 2023

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ABSTRACT

The persistence of immunogenicity in patients with immune-mediated inflammatory diseases (IMID) on disease-modifying antirheumatic therapy (DMARD) has been less well studied. This extension study evaluates the SARS-CoV2 antibody decay kinetics 6 months following two doses of ChAdO1nCov-19 (AZ) and BNT162b (Pfizer) and subsequent response following an mRNA booster.

Results 175 participants were included. Six months after initial AZ vaccination, 87.5%, 85.4% and 79.2% (p=0.756) in the withhold, continue and control groups remained seropositive compared with 91.4%, 100% and 100% (p=0.226), respectively, in the Pfizer group. Both vaccine groups developed robust humoral immune responses following a booster with seroconversion rates being 100% for all three intervention categories. The mean SARS-CoV-2 antibody levels were significantly lower in the targeted synthetic DMARD (tsDMARD) group that continued therapy compared with the control (2.2 vs 4.8 U/mL, p=0.010). The mean time interval until loss of protective antibodies in the IMID group was 61 days for the AZ and 137.5 days for the Pfizer vaccine. Within each DMARD class the interval until loss of protective antibody titres in the csDMARD, bDMARD and tsDMARD groups were 68.3, 71.8 and 64.0 days in the AZ group and 185.5, 137.5 and 116.0 days in the Pfizer group, respectively.

Conclusion Antibody persistence was longer in the Pfizer group due to a higher peak antibody level following second vaccination with levels of protection in IMID on DMARD therapy similar to controls except in those on tsDMARDs where it was lower. A third mRNA vaccine booster can restore immunity in all groups.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The durability of humoral immunity following SARS-CoV2 infection is known to wane following natural infection and vaccination, however, there are limited data on rate of decay in patients with immune-mediated inflammatory diseases (IMID) on disease-modifying antirheumatic therapy (DMARD) therapy.

WHAT THIS STUDY ADDS

⇒ There is a significant drop in SARS-CoV-2 IgG Ab titres between the second vaccine dose and the 6-month booster dose in all study arms, however, the seroconversion rates remained similar to controls.
⇒ Patients with IMID on targeted synthetic DMARDs (tsDMARDs) who continued with therapy had the lowest SARS-CoV-2 IgG Ab titre.
⇒ The peak antibody level following the second vaccination is the most important factor in influencing the SARS-CoV2 level at 6 months.
⇒ Both vaccine groups developed robust humoral responses following the mRNA vaccine booster.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A third mRNA vaccine dose can restore immunity in all groups.
⇒ Withholding tsDMARD therapy specifically after SARS-CoV-2 vaccinations is a recommended strategy to improve antibody persistence.

INTRODUCTION

The Omicron variants during the SARS-CoV-2 pandemic has continued to pose a risk to patients with immune-mediated inflammatory disease (IMID) despite vaccination. Worldwide, the vaccine roll out continues and boosters have been administered to improve the durability of humoral immunity. There is growing evidence that patients with IMID on disease-modifying antirheumatic therapy (DMARD) mount a delayed and reduced immune response to COVID-19 vaccination which may result in breakthrough

infections.[1–3] Recent strategy studies show that the reduced vaccine antibody response can be mitigated by withholding DMARD therapy contemporaneous to COVID-19 vaccination or by the administration of additional vaccine booster doses.[4–8] Antibodies elicited by natural COVID-19 infection and via vaccination have been observed to decay rapidly in the first few months after infection in healthy individuals, however, the durability of humoral immunity after vaccination in patients with IMID on DMARD therapy remains less well studied.[9–11] We recently reported the results of a multicentre three-arm randomised clinical trial comparing the immunogenicity of the ChAdOx1nCov-19 (AZ) and BNT162b (Pfizer) vaccines in patients with IMID compared with controls. Here, we describe immunogenicity data six months post first vaccination and 4 weeks post booster (third) vaccination with the Pfizer or mRNA-1273 (Moderna) vaccine on participants in the same trial and in addition we aim to determine the duration of antibody persistence for each of the DMARD groups.

METHODS

The eligibility criteria and SARS-CoV-2 IgG assay evaluation have been previously reported.[6] Serum SARS-CoV-2 IgG detection and titres against the S1/2 proteins were measured at baseline, 3–4 weeks post first vaccination and 4 weeks post second vaccination. Participants with IMID were randomised to continue or withhold their DMARD in each of the vaccine groups following the first dose only and the same intervention was then applied following the third (booster) dose.[6] To summarise, in participants on weekly methotrexate, the vaccination was timed on the day the dose was due however the methotrexate dose was paused on the day of vaccination for two cycles. Participants on daily DMARDs withheld therapy for 1 week starting on the day of first vaccination. For those on bDMARDs, therapy was delayed by 1 week following their usual injection cycle (eg, for bDMARD administered every 2 weeks, the vaccination was timed at the end of the 2 weeks and then restarted 1 week later leaving an interval of 3 weeks). Participants who contracted COVID-19 infection prior to the third vaccine were excluded in the analysis. The participants were stratified according to the vaccine received and intervention group allocated during the first two vaccinations (table 1). The drugs used in each of the DMARD classes are listed in online supplemental table 1.

Statistical analyses and graphs were performed using either STATA 17.0 (StataCorp) or RStudio. Fisher's exact test was used to compare seroconversion rates between the various DMARD and control groups while the Wilcoxon-Mann-Whitney U test was used to compare antibody titres between the groups. We conducted univariate logistic regression to assess predictive factors for developing protective SARS-CoV2 IgG antibody titre levels. Multivariate logistic regression was then performed to generate adjusted estimates for factors, which were found to be significant on univariate analysis.

We conducted simple linear regression using log-transformed IgG titre levels as the outcome variable and time since second vaccine dose administration as the explanatory variable to investigate the rate of antibody decay among the cohort studied.

RESULTS

SARS-CoV-2 vaccination response in the AZ and Pfizer at 6 months and post booster dose

The final analysis included 175 (72.9%) of the initial 240 participants due to COVID-19 infection (n=7) or missing blood tests (n=58). After a median of 99 days (IQR 93–103) post second AZ vaccination or 6 months post first dose, 87.5%, 85.4% and 79.2% in the withhold, continue and control groups, respectively, remained seropositive (p=0.756) (table 2A). Following the booster vaccination with an mRNA vaccine (Pfizer or Moderna), 100% of patients in all of the groups seroconverted. The mean prebooster SARS-CoV-2 IgG Ab titres were 4.0, 3.0 and 2.4 U/L (p=0.344) in the withhold, continued and control groups, respectively, and rose to 92.0, 64.0 and 95.3 U/L (p=0.26) in the withhold, continued and control groups, respectively (table 2).

For the Pfizer vaccine, after a median of 148 days (IQR 129–158) post second dose (6-month post first dose), the seroconversion rates were 91.4%, 100% and 100% in the withhold, continue and control groups (p=0.226) and following the booster dose with an mRNA vaccine, the seroconversion rates were 100% for all three groups. The mean prebooster SARS-CoV-2 IgG Ab titres at 6 months were 9.3, 4.1 and 11.8 U/mL (p=0.001) while the mean post booster dose SARS-CoV-2 IgG titres increased to 118.1, 163.2 and 189.5 U/mL in the withhold, continue and control groups, respectively (p=0.235)

When examining the effect of the DMARD class at 6 months postvaccination, the group that continued DMARDs showed no significant difference in the seroconversion rates in each of the DMARD classes regardless of whether therapy was temporarily withheld (table 3). Seroconversion rates were 95.5%, 96.3% and 84.6% for patients continuing either conventinal synthetic DMARD (csDMARD), biological DMARD (bDMARD) and targeted synthetic DMARD (tsDMARD), respectively (p=0.311). Similarly, in the withhold group, there was also no significant difference in the seroconversion rates for each of the DMARD groups (p=0.476). The mean SARS-CoV-2 IgG Ab titres, however, were significantly lower in the tsDMARD group in the group that continued therapy compared with the control group (2.2 vs 4.8 U/mL, p=0.010) while it was not statistically significant in the withhold group (5.4 vs 4.8 U/mL, p=0.600). In both the csDMARD and bDMARD groups who continued with therapy, the mean SARS-CoV-2 IgG Ab titres were comparable to the controls being 5.3 vs 4.8 U/mL, p=0.798) and 3.7 vs 4.8 U/mL (p=0.357), respectively. Following

Table 1 Demographics and clinical characteristics of patients with autoimmune diseases and healthy controls

	Autoimmune disease group		Healthy controls	Total
Trial Arm	Withhold therapy	Continue therapy	Healthy controls	
N	82	99	59	240
Vaccine (first two doses)				
CHadOx1nCov-19 (Astra Zeneca)	34 (41.5)	47 (47.5)	31 (52.5)	112 (46.7)
BNT162b2 (Pfizer)	48 (58.5)	52 (52.5)	28 (47.5)	128 (53.3)
Vaccine (booster)				
CHadOx1nCov-19 (Astra Zeneca)	0 (0.0)	0 (0.0)	2 (7.4)	2 (1.1)
BNT162b2 (Pfizer)	53 (81.5)	68 (81.9)	15 (55.6)	136 (77.7)
mRNA-1273 (Moderna)	12 (18.5)	15 (18.1)	10 (37.0)	37 (21.1)
Sex				
Female	60 (73.2)	65 (66.3)	33 (59.6)	158 (66.4)
Male	22 (26.8)	33 (33.7)	25 (43.1)	80 (33.6)
BMI	29.2 (7.1)	28.8 (6.1)	26.2 (5.0)	28.3 (6.3)
Ethnicity				
African American or black	1 (1)	1 (1)	1 (1.7)	3 (1.3)
Arabic	0 (0)	1 (1)	0 (0)	1 (0.4)
Asian	8 (10)	8 (8)	14 (24.1)	30 (12.7)
Indian	2 (2.5)	3 (3)	1 (1.7)	6 (2.5)
Indigenous	2 (2.5	3 (3)	0 (0)	5 (2.1)
White	66 (82.5)	83 (84)	40 (69)	189 (79.8)
Other	1 (0)	0 (0)	2 (3.4)	3 (1.3)
Age	55.4 (12.6)	53.3 (14.4)	54.4 (12.6)	54.2 (13.3)
Smoking status				
Non-smoker	55 (67.1)	72 (73.5)	48 (84.2)	175 (73.8)
Current smoker	9 (11.0)	7 (7.1)	5 (8.8)	21 (8.9)
Ex-smoker	18 (22.0)	19 (19.4)	4 (7.0)	41 (17.3)
Medication class				
csDMARD	26 (31.7)	32 (32.3)	n/a	58 (32.0)
bDMARD	26 (31.7)	37 (37.4)	n/a	63 (34.8)
tsDMARD	30 (36.6)	30 (30.3)	n/a	60 (33.2)
Autoimmune disease				
Ankylosing spondylitis	6 (7.3)	13 (13.1)	n/a	19 (10.5)
Crohn's disease	1 (1.2)	1 (1.0)	n/a	2 (1.1)
Psoriatic arthritis	27 (32.9)	26 (26.3)	n/a	53 (29.3)
Rheumatoid arthritis	44 (53.7)	53 (53.5)	n/a	97 (53.6)
SLE/Sjogren's/CTD	3 (3.7)	2 (2.0)	n/a	5 (2.8)
Ulcerative colitis	0 (0)	2 (2.0)	n/a	2 (1.1)
Other	1 (1.2)	2 (2.0)	n/a	3 (1.7)

All data are n (%) or mean (SD) unless otherwise indicated.
SLE (Systemic lupus erythematosis), CTD (connective tissue disease), csDMARD (conventional synthetic disease modifying therapy), bDMARD (biological disease modifying therapy), tsDMARD (targeted synthetic disease modifying therpy.
BMI, body mass index; DMARD, disease-modifying antirheumatic therapy; n/a, not available; tsDMARD, targeted synthetic DMARD.

the booster dose the seroconversion rates were 100% for all DMARD classes in both the continue and withhold groups and including the control group (table 3). When comparing intervention within each of the DMARD classes, withholding tsDMARD resulted in a significantly higher mean SARS-CoV2 IgG ab titre at 6 months post first vaccination dose (online supplemental table 2).

Decay rate of SARS-CoV-2 IgG after vaccination in IMID and controls

The durability of humoral immunity after the second vaccine dose and just prior to the booster dose showed that the SARS-CoV-2 Ab titres were lower with the AZ compared with Pfizer vaccine in both the IMID and control groups. Using a SARS-CoV-2 Ab titre cut-off of 7.0 U/mL

Table 2 Immunological response in subjects who received Astra Zeneca

	Withhold therapy	Continue therapy	Healthy controls	Total
Detectable SARS-CoV2 IgG antibodies*				
Post second dose	27/27 (100)	36/43 (83.7)	22/22 (100)	85/92 (92.39)
6 months post (p=0.756)	21/24 (87.5)	35/41 (85.4)	19/24 (79.2)	75/89 (84.3)
Withhold versus continue (p=1.00)				
Withhold versus healthy controls (p=0.701)				
Continue vs healthy controls (p=0.517)				
Post booster vaccine dose	25/25 (100)	40/40 (100)	16/16 (100)	81/81 (100)
Median SARS-CoV2 IgG Ab titre†				
Post second dose	14.2 (4.3–48.4)	5.7 (1.5–20.8)	7.3 (4.4–15.9)	7.2 (2.3–23.2)
	11.7 (6.8–20.3)	5.7 (3.4–9.3)	7.3 (4.9–10.7)	7.6 (5.7–10.1)
6 months post (p=0.344‡)	3.3 (1.7–12.3)	2.3 (1.3–7.4)	2.3 (0.9–5.3)	2.6 (1.3–8.3)
Withhold versus continue (p=0.325)	4.0 (2.4–6.7)	3.0 (2.0–4.53)	2.4 (1.5–3.8)	3.1 (2.4–4.0)
Withhold versus healthy controls (p=0.143)				
Continue versus healthy controls (p=0.577)				
Post booster vaccine dose (p=0.226‡)	91.8 (58.9–229.1)	75.4 (39.0–114.4)	106.1 (53.5–212.5)	85.9 (46.4–162.6)
Withhold versus continue (p=0.134)	92.0 (51.7–163.8)	64.0 (44.6–91.9)	95.3 (48.2–188.4)	77.6 (58.9–102.3)
Withhold versus healthy controls (p=0.949)				
Continue versus healthy controls (p=0.203)				
Immunological response in subjects who received Pfizer				
Post second dose	37/44 (84.1)	31/48 (64.58)	27/27 (100)	95/119 (79.83)
6 months post (p=0.226)	32/35 (91.4)	34/34 (100)	18/18 (100)	84/87 (96.6)
Withhold versus continue (p=0.239)				
Withhold versus healthy controls (p=0.279)				
Continue versus healthy controls				
Post booster vaccine dose	34/34 (100)	38/38 (100)	20/20 (100)	92/92 (100)
Withhold versus continue				
Withhold versus healthy controls				
Continue versus healthy controls				
Mean SARS-CoV2 IgG Ab titre†				
Post second dose	77.8 (38.7–150)	60 (17.2–128.4)	66.7 (52.1–106.7)	68.4 (35.5–129.4)
	65.1 (43.8–96.7)	45.7 (31.4–66.7)	85.1 (65.5–117.8)	60.1 (48.1–75.0)
6 months post (p=0.001‡)	12.0 (3.9–35.1)	3.1 (2.0–8.8)	10.5 (8.0–17.0)	7.9 (2.7–15.9)
Withhold versus continue (p=0.005)	9.3 (5.8–15.0)	4.1 (2.8–5.9)	11.8 (8.1–17.3)	7.1 (5.5–9.2)
Withhold versus healthy controls (p=0.755)				
Continue versus healthy controls (p=0.000)				
Post booster vaccine dose (p=0.235‡)	103.5 (79.3–202.8)	154.5 (79.0–378.0)	254.8 (73.1–371.6)	147.7 (29.0–298.7)
Withhold versus continue (p=0.221)	118.1 (87.0–160.3)	163.2 (112.6–236.5)	189.5 (114.1–314.7)	149.2 (120.4–184.9)
Withhold versus healthy controls (p=0.092)				
Continue versus healthy controls (p=0.827)				

Data are presented as proportions (%) or median (IQR).
Geometric means and corresponding 95% CI are shown in blue.
*Using Fisher's exact test with significance cut-off 5%.
†Using Wilcoxon-Mann-Whitney test with significance cut-off 5%.
‡Using Kruskal-Wallis test with significance cut-off 5%.

as determined previously to equate to a neutralising antibody titre of 50 which was found to be the minimum correlate of protection against SARS-CoV-2 in rhesus macaques, the mean time interval until the loss of protection in the IMID group was 61 days [log10(7)−1.33/−0.008] for the AZ, and 137.5 days [log10(7)−1.67/−0.006] for the Pfizer vaccine[6 12] (figure 1a,b).[12] Within the intervention groups the durability of humoral response was best in the withhold group for the AZ vaccine (p=0.001) while it was better in the control group for the Pfizer vaccine (p=0.013). In the control group, the number of days before the antibody levels reached below 7.0 U/mL was longer at 62.1 days [log10(7)−1.51/−0.0107] and 209.7 days [log10(7)−1.60/−0.0036] for the AZ and

Table 3 Impact of class of immunosuppression on vaccine response in the IMID group

	csDMARDS	bDMARDS	tsDMARDS	Controls
Continue group				
Detectable SARS-CoV2 IgG antibodies*				
6 months postvaccination (p=0.311)	21/22 (95.5)	26/27 (96.3)	22/26 (84.6)	37/42 (88.1)
	p=0.320	p=0.392	p=0.723	
Postbooster vaccine dose	28/28 (100)	25/25 (100)	25/25 (100)	36/36 (100)
Median SARS-CoV2 IgG Ab titre†				
6 months postvaccination (p=0.030)	5.8 (2.3–13.0)	2.6 (1.4–9.4)	2.1 (1.0–4.1)	5.7 (1.8–10.6)
	5.3 (3.2–9.0)	3.7 (2.3–5.8)	2.2 (1.4–3.6)	4.8 (3.2–7.3)
	p=0.798	p=0.357	**p=0.010**	
Post booster vaccine dose (p=0.188)	129.5 (73.4–289.4)	93.2 (55.7–241.8)	74.7 (36.7–156.5)	199.9 (64.9–347.9)
	123.5 (77.2–197.6)	108.8 (65.6–180.5)	74.8 45.5–123.0)	139.6 (92.8–210.1)
	p=0.752	p=0.378	p=0.068	
Withhold group				
Detectable SARS-CoV2 IgG antibodies*				
6 months postvaccination (p=0.476)	13/13 (100)	18/21 (85.7)	22/25 (88.0)	37/42 (88.1)
	p=0.324	p=1.00	p=1.00	
Postbooster vaccine dose	15/15 (100)	19/19 (100)	24/24 (100)	36/36 (100)
Median SARS-CoV2 IgG Ab titre†				
6 months postvaccination (p=0.609)	10.1 (6.5–12.9)	7.7 (1.5–19.0)	3.9 (2.2–14.7)	5.7 (1.8–10.6)
	9.7 (4.7–20.1)	6.6 (3.3–13.1)	5.4 (3.1–9.6)	4.8 (3.2–7.3)
	p=0.091	p=0.337	p=0.600	
Postbooster vaccine dose (p=0.085)	196.8 (88.5–426.4)	96.1 (55.0–145.6)	97.8 (72.5–197.3)	199.9 (64.9–347.9)
	190.7 (119.7–303.8)	82.4 (52.3–129.8)	89.7 (51.4–156.7)	139.6 (92.8–210.1)
	p=0.406	p=0.110	p=0.240	

Data are presented as proportions (%) or median (IQR).
Geometric means and corresponding 95% CI are shown in blue.
Comparison of DMARD categories with healthy controls using Fisher's exact test or Wilcoxon-Mann-Whitney test as appropriate with significance cut-off 5%.
*Using Fisher's exact test with significance cut-off 5%.
†Using Kruskal-Wallis test among the immunosuppression groups only with significance cut-off 5%.
IMID, immune-mediated inflammatory diseases.

Pfizer vaccines, respectively. The number of patients within each DMARD class who had non protective antibody levels at 6 months post second dose was significantly higher in the tsDMARD group (p=0.026) (figure 2).

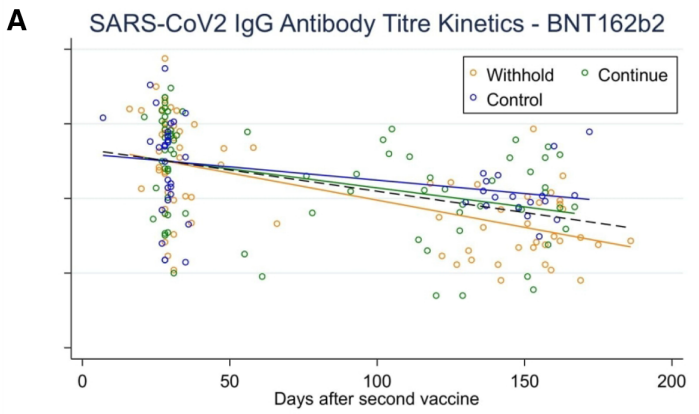
When stratified across the different DMARD groups, the AZ vaccine time interval following the second vaccination when the SARS-CoV-2 Ab titres dropped below 7.0 U/mL were 68.3, 71.8 and 64.0 days in the csDMARD, bDMARD and tsDMARD groups, respectively. For the Pfizer vaccine, it was 185.5, 137.5 and 116.0 days csDMARD, bDMARD and tsDMARD groups, respectively (table 4, online supplemental figure 1).

Factors associated with the magnitude of the humoral response to the AZ and mRNA vaccines

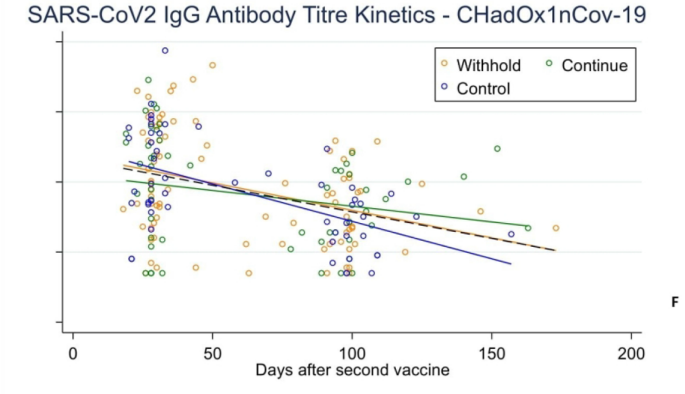
Multivariate modelling of SARS-CoV-2 IgG Ab titres at 6 months postvaccination show increasing age was associated with lower odds of having an IgG level >7.0 U/mL (OR 0.95 (95% CI 0.93 to 0.97), p=0.000). In addition, relative to csDMARDs, patients on tsDMARDs were at a lower odds of having an IgG level >7.0 U/mL at 6 months (OR of 0.38 (95% CI 0.17 to 0.88, p=0.023)). The Ab titres were higher in the group that withheld DMARD therapy (OR 2.89 (95% CI 1.42 to 5.87, p=0.003)) and in those who had the mRNA vaccines (OR 3.43 (95% CI 1.84 to 6.41), p=0.000). After adjusting for confounding, only the peak IgG antibody titre post second vaccination was significant in having an IgG level >7.0 U/mL at 6 months (OR 1.07 (95% CI 1.04 to 1.10), p=0.000)) (online supplemental table 3).

DISCUSSION

Our study shows that there is a significant drop in SARS-CoV-2 IgG Ab titres between the second vaccine dose and the 6 month booster dose in all study arms, however,



				Slope coefficient		
Group	**Vaccine**	**Model R^2**	**Intercept**	**Point estimate**	**95%CI**	**P value**
Withhold	AZ	0.13	1.38	-0.008	-0.012 to -0.004	**0.001**
Continue	AZ	0.06	1.10	-0.004	-0.010 to 0.001	0.081
Controls	AZ	0.31	1.50	-0.01	-0.013 to -0.006	**<0.001**
Overall	AZ	0.14	1.33	-0.008	-0.010 to -0.005	**<0.001**



				Slope coefficient		
Group	**Vaccine**	**Model R^2**	**Intercept**	**Point estimate**	**95%CI**	**P value**
Withhold	Pfizer	0.36	1.71	-0.007	-0.009 to -0.005	<0.001
Continue	Pfizer	0.15	1.65	-0.005	-0.007 to -0.002	**<0.001**
Controls	Pfizer	0.13	1.60	-0.004	-0.006 to -0.001	**0.013**
Overall	Pfizer	0.22	1.67	-0.006	-0.007 to -0.004	**<0.001**

Figure 1

the seroconversion rates remained similar to controls. Patients with IMID on tsDMARDS who continued with therapy, however, had a lower SARS-CoV-2 IgG Ab titre after 6 months compared with those who withheld therapy and the control group (p=0.010), which is in keeping with another study showing that JAK inhibitors result in a significantly reduced humoral response to vaccination.[13] Following the booster vaccination with an mRNA vaccine, the seroconversion rates were 100% in all groups with a corresponding rebound in SARS-CoV-2 IgG Ab levels that even exceeded levels following the second vaccine dose. This was especially in those who received the AZ vaccination initially suggesting that the biological ceiling had not yet been reached.[6] Both seroconversion rates and SARS-CoV-2 IgG Ab levels were higher in the Pfizer group for the 6 months and post booster doses. Subsequent vaccine dosing with an mRNA vaccine mitigated the effect of withholding or continuing therapy making it

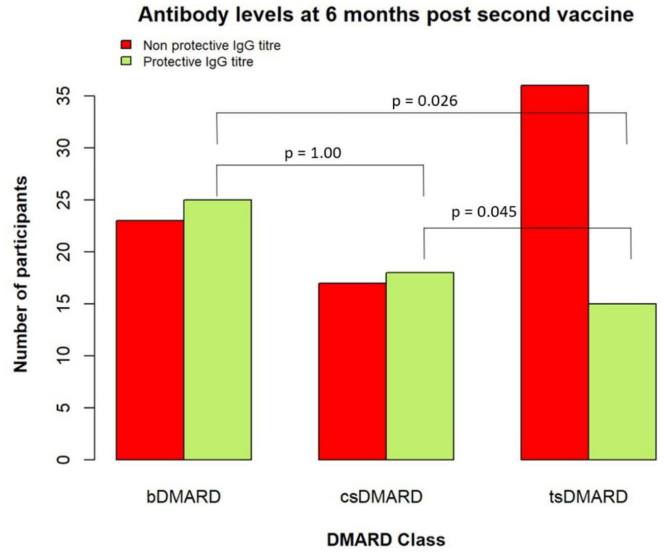


Figure 2

a less important factor in achieving an adequate humoral response which is consistent with previous studies.[14]

The most important factor in influencing the SARS-CoV2 level at 6 months was the peak antibody level following the second vaccination of the primary vaccine regimen. Studies examining the antibody decay kinetics in participants following COVID-19 infection showed that the height of the peak is dependent on disease severity with antibodies for IgG remaining above the positivity threshold for up to 500 days.[15–17] Following vaccination our study showed that SARS-CoV2-Ig Ab persistence (≥7.0 U/mL) was 62 days for the AZ and 210 days for the Pfizer vaccine. Although the antibody levels may persist for longer below 7.0 U/mL, this relative discrepancy suggests that vaccination provides a shorter duration of humoral coverage than natural infection which is consistent previous studies showing a higher risk for breakthrough infection in the vaccinated compared with natural infection.[18 19] For patients with IMID on DMARDs the SARS-CoV-Ig Ab persistence was even shorter which supports the need for regular boosting in this cohort especially for those on tsDMARDs.

Longitudinal vaccine responses following the Pfizer and Moderna vaccines have shown that the reduction in SARS-CoV2 IgG Ab to be relatively log-linear.[9 11] Although our study measured the SARS-CoV2 Ab levels at two time points only, we found the antibody decay rates to be highest in participants on tsDMARD with a larger gradient in both the AZ and Pfizer vaccines groups compared with patients on csDMARD and bDMARDs. The decay rates were also mostly higher in the Pfizer group on DMARD therapy compared with the AZ group on DMARD therapy. However, due to the higher initial SARS-CoV-2 IgG antibody titres in the Pfizer group, the time for the Ab level to fall below the cut-off was still longer in the Pfizer group. The SARS-CoV-2 IgG antibody reduction rate being dependent on the initial antibody level is supported by another study with higher initial values yielding faster decay rates.[20] This observation, however, was reversed in the control group whereby the decay rate was higher in the AZ group which suggests that either DMARD therapy or IMID may accelerate the Pfizer vaccine decay rate. Since an mRNA vaccine is preferred

Table 4 SARS-CoV-2 IgG titre decay rates in IMID versus controls

	Days for SARS-CoV-2 Ab titre to reach 7.0 U/mL	Days for SARS-CoV-2 Ab titre to reach 0 U/mL	Change after 90 days (%)	Slope coefficient	
				95% CI	P value
AZ vaccine					
csDMARD IgG titre=1.05–0.0034 (days after second vaccination) R∧2=2.8%	68.3	308.8	50.53	−0.010 to 0.003	0.313
bDMARD IgG titre=1.29–0.0062 (days after second vaccination) R∧2=9.0%	71.8	208.1	72.31	−0.012 to −0.00006	**0.048**
tsDMARD IgG titre=1.37–0.0082(days after second vaccination) R∧2=17.3%	64.0	167.1	81.70	−0.013 to −0.003	**0.001**
Pfizer vaccine					
csDMARD IgG titre=1.55–0.0038(days after second vaccination) R∧2=9.2%	185.5	407.9	54.51	−0.0078 to 0.0001	0.061
bDMARD IgG titre=1.56–0.0052(days after second vaccination) R∧2=20.7%	137.5	300.0	65.96	−0.0078 to −0.0026	**0.000**
tsDMARD IgG titre=1.97–0.0097(days after second vaccination) R∧2=46.3%	116.0	203.1	86.61	−0.013 to −0.007	**0.000**
AZ vaccine control					
IgG titre=1.51–0.0107(days after second vaccination) R∧2=30.9%	62.1	141.1	89.12	−0.0152 to −0.006	**0.000**
Pfizer vaccine control					
IgG titre=1.60–0.0036(days after second vaccination) R∧2=13.2%	209.7	444.4	52.57	−0.006 to −0.0007	**0.013**

Bold values are significant with p-value <0.05.
DMARD, disease-modifying antirheumatic therapy; IMID, immune-mediated inflammatory diseases; tsDMARD, targeted synthetic DMARD.

for booster doses in adults, these findings suggest that patients with IMID receive a booster dose approximately every 7, 5 and 4 months for those on csDMARD, bDMARD and tsDMARD, respectively.[21] This is in support of a recent study showing the risk of severe COVID-19 outcomes is increased after 10 weeks of completing primary vaccination dosing especially in those aged over 80 years, have a greater number of comorbidities, males or those receiving immunosuppressants.[22]

Our control group data are also in keeping with another study showing that the SARS-CoV-2 antibodies from vaccination waned over time resulting in an approximate 53% and 89% loss within 90 days of vaccination for the Pfizer and AZ vaccinations, respectively.[11] In addition, our longitudinal data showed that age had no difference in the SARS-CoV-2 ab titre decay rate.[11]

Heterogeneity in both the magnitude and decay rates have also been reported to other vaccines such as tetanus and measles where decay rates of 6.2%/year and 0.2%/year, respectively, have been reported, however, these decay rates are substantially lower than that following both AZ and Pfizer vaccination as calculated in our study.[23] This could be due to the different mechanisms of action, types of adjuvants used and patterns of loss of protective immunity elicited by the toxoid antigen (tetanus) and live attenuated vaccines (measles) versus viral vector (AZ) and messenger RNA vaccines (Pfizer and Moderna), which can influence the kinetics of antibody production and decay. Of interest, the SARS-CoV-2 Ab decay rate in the csDMARD group was not significantly different to both the AZ and Pfizer control groups. This could be due to the low mean age and dose of methotrexate in our study (54.2 years and 16.9 mg weekly, respectively).

In contrast to already published data which showed that immunogenicity to COVID-19 vaccines may be suboptimal or absent following the second and booster doses due to specific DMARDs such as corticosteroids, mycophenolate and rituximab, our study did not include these agents and hence a direct comparison cannot be made.[24 25] In addition, all subjects included in our study were in clinical disease remission and none had interstitial lung disease or renal involvement. Our study, however, observed a significantly diminished humoral response in the tsDMARDs when continued contemporaneous to vaccination.

The methodological limitations to our study have previously been discussed, however, there were additional limitations identified during the 6 months and post booster follow-up.[6] First, due to pandemic timelines and the government recommendation to have an earlier booster during the study, the interval from the second to third dose was shorter in some participants.[21] This consequently resulted in a number of participants missing their scheduled blood tests. The shortened timeline could also lead to higher residual antibody levels prior to the booster dose and hence under estimate the antibody decay rate. In addition, it also could potentially underestimate the peak antibody response following the booster as the shorter time interval may have an impact on T cells and immunological memory.

Second, the majority of included patients received an mRNA vaccine for the booster dose as this was the preferred vaccine schedule as per the Government guidelines during the study period and hence a homologous schedule for the AZ arm could not assessed.[21] A study has observed a 25–35 fold increase in the mean SARS-CoV-2 IgG antibody levels when AZ primed subjects were given a single booster with an mRNA COVID-19 vaccine compared with a three fold increase when AZ booster was used.[26] It has also been shown that a homologous Pfizer regime with a prolonged priming interval of 12 weeks instead of 4 weeks had a slightly reduced rate of antibody decay, however, the greater effect on immunogenicity was the choice of vaccine used.[27]

Third, antigen specific T-cells are also involved following COVID-19 vaccination and relying solely on humoral responses to determine booster timing in patients with and without IMID are not entirely accurate. Hence, reductions in the antibody titres may not translate to a clinically significant loss of protection, however, evaluating IgG levels is still clinically important as convalescent plasma therapy has demonstrated efficacy in critically ill patients with COVID-19 infection.[28]

Lastly, there is significant heterogeneity in our study population with different IMID's, DMARDs and COVID-19 vaccines with the assumption that all DMARDs and IMID's have the same impact on the vaccine response. Our study was, therefore, not adequately powered to examine the vaccine response in each of the IMID and DMARD groups.

CONCLUSION

Six months after standard vaccination regimens, patients with IMID had protective levels of SARS-CoV-2 IgG Ab similar to controls, except for those on tsDMARDs. Despite higher SARS-CoV-2 IgG Ab decay rates in the Pfizer group, antibody persistence was longer due to a higher peak antibody level following the second vaccination. Seroconversion following the booster dose was 100% across all categories illustrating that a third mRNA-based booster vaccine can restore humoral immunity in patients with IMID on DMARD therapies suggesting that subsequent boosters can elicit robust responses.

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Contributors All authors contributed to the intellectual content of the submission and preparation of the manuscript and all have approved the final version for submission. AT is responsible for the overall content as guarantor and accepts full responsibilty for the work and conduct of the trial.

Funding Australian Rheumatology Association Private Practice Grant.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by St John of God Murdoch ethics ID: 1809St Vincent's Hospital Melbourne ethics ID: 099/21. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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