



# Effectiveness of delayed second dose of AZD1222 vaccine in patients with autoimmune rheumatic disease

Pankti Mehta<sup>1</sup> · Aby Paul<sup>2</sup> · Sakir Ahmed<sup>3</sup> · Somy Cherian<sup>2</sup> · Ameya Panthak<sup>2</sup> · Janet Benny<sup>2</sup> · Padmanabha Shenoy<sup>2</sup>

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## Abstract

There is paucity of data on extended dosing interval between two doses of AZD1222 (AstraZeneca) in patients with Autoimmune Rheumatic Diseases (AIRD). We aimed to study the humoral response and rate of breakthrough infections between the two groups who had received the second dose of vaccine at 4 weeks (Group 1) and 10–14 weeks (Group 2). From established cohort [COVID-19 vaccination cohort from CARE(CVCC)] of vaccinated patients with AIRD, those who had received AZD1222 were included and divided into two groups. Anti-Receptor Binding Domain (RBD) antibodies (IU/ml) were measured 1 month after the second dose. Its predictors and rate of breakthrough infections were studied. Four hundred ninety-five patients with AIRD were included in this study. Group 2 had higher anti-RBD antibody titres [1310.6 ( $\pm$ 977.8) and [736 ( $\pm$ 864.7),  $p = 0.0001$ . On univariate analysis, presence of Diabetes Mellitus; use of Methotrexate, Sulfasalazine, and Mycophenolate Mofetil; and vaccine interval were significantly associated with anti-RBD antibodies. Diabetes Mellitus and vaccine interval were independent predictors on multivariate analysis. Breakthrough infections were higher in Group 1 numerically on survival analysis but the difference was not significant (7.5% and 4.5%; log rank test:  $p = 0.25$ ). In conclusion, increasing the gap between doses of the AZD1222 vaccine from 4 week to 10–14 weeks was found to be more beneficial in terms of antibody response in patients with AIRD. There was a trend towards higher breakthrough infections in the short interval group, supporting the antibody data.

## Key Points

- There is paucity of data on effectiveness of increased dosing interval from 4-6 to 10-14 weeks for AZD1222 in patients with AIRDs
- We observed a better humoral response with increased dosing interval with the interval and Diabetes Mellitus being independent predictors of the anti-RBD antibody levels
- Breakthrough infections were numerically higher in the short interval group but the difference wasn't significant

**Keywords** ChAdOx1 nCoV-19 · COVID-19 Vaccines · COVID-19 · Rheumatic Diseases

## Introduction

Patients with Autoimmune Rheumatic Diseases (AIRD) form a high priority group for vaccination against SARS CoV2. Despite exclusion of this group from vaccine trials and a questionable immunogenicity in immunocompromised individuals, they have proven to be safe and efficacious for patients with AIRDs [1, 2]. The proportion of population fully vaccinated against COVID-19 varies from 30 to 70% in majority of counties with poorer rates in some due to unavailability of vaccines. India is predominantly using AZD1222 (AstraZeneca, ChAdOx1 nCoV-19, 'covishield')

✉ Padmanabha Shenoy  
drdpshenoy@gmail.com

<sup>1</sup> Department of Clinical Immunology and Rheumatology, King George's Medical University, Lucknow, India

<sup>2</sup> Centre for Arthritis and Rheumatism Excellence, Nettor, Kochi, Kerala 682040, India

<sup>3</sup> Clinical Immunology and Rheumatology, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India

and BBV152 (Bharat Biotech, ‘covaxin’) for vaccination against SARS-CoV2. The extension of the interval between the two doses of AZD1222 from 4–6 weeks to 10–14 weeks had been shown to be more efficacious in healthy participants. This led to a change in policy by the Government of India (GOI) to use an extended gap dosing policy for AZD1222 [3, 4].

The effect of extended dose interval on immunogenicity of AZD1222 in patients with AIRD is unknown. Concerns about delay in the second vaccine dose in patients with AIRD are the need for rapid completion of vaccination schedule and avoid longer interruption of immunosuppressive therapy [5]. Thus, we conducted this study to assess real world effectiveness of the extended interval on the humoral immunogenicity as compared to the usual dosing schedule of AZD1222.

## Methods

An established cohort [COVID-19 vaccination cohort from CARE(CVCC)] of vaccinated patients with AIRDs are being followed at Centre for Arthritis and Rheumatism (CARE), Kochi, Kerala, India [6, 7]. Amongst those who received AZD1222 vaccine, patients were categorized into two groups based on the dosing interval of 4–6 weeks versus 10–14 weeks between the two doses of the AZD1222 vaccine. The two vaccines predominantly used in India are adenoviral vector-borne AZD1222 and the indigenous whole-virion  $\beta$ -propiolactone-inactivated BBV152. To avoid disparity due to different vaccines, we included patients who were administered AZD1222. Furthermore, BBV152 is administered uniformly at an interval of 4 weeks. Patients with prior COVID-19 infection were excluded.

## Participants

Patients were matched for confounding factors (age, gender and immunosuppressants) and grouped into two arms. The demographic, clinical, therapy and vaccination details of the patients were recorded. Additionally, their blood samples were drawn 4–6 weeks after the second dose for assessment of RBD (receptor binding domain of the spike protein) antibody titre. All sera were stored in aliquots at  $-80^{\circ}\text{C}$  until processing.

## Main outcome variable

Anti-RBD antibody titres were measured 1 month after the second dose using Elecsys Anti-SARS-CoV-2 Chemiluminescent assay (Roche, Switzerland).

## Other outcome variables

Predictors for anti-RBD antibody response were studied across the two groups. For the analysis, patients were classified based on their anti-SARS CoV 2S antibody titres into adequate responders (GR) ( $>212$  IU), inadequate responders (IR) (0.8–212 IU) and non-responders (NR) ( $<0.8$  IU). This was based on our previous work where a Receiver Operator Curve (ROC) had showed that antibody titres above 212 IU/ml predicted more than 30% neutralization by sera, with a sensitivity of 81.5% and a specificity of 83.6% [14].

Additionally, breakthrough infections detected by means of a positive RT PCR (Reverse Transcriptase Polymerase Chain Reaction) for SARS-Cov2 were compared between the two groups.

## Statistical analysis

Data is expressed as mean and standard deviation. The normality of data was checked by the Shapiro-Wilk test. The difference in proportions was tested by the Fisher Exact/Chi Square test and the difference in antibody titres was tested by Independent sample *t*-test. Variables significantly different between the two groups at baseline were included for multivariate analysis.  $P < 0.05$  was deemed as statistically significant. GraphPad prism v8.4.2 was used for statistical analysis.

## Results

Four hundred ninety-five patients with AIRD were included in this study, of whom 253 had received two doses of the vaccine 4 weeks apart (Group 1) while 242 had received the two doses at 12 weeks apart (Group 2). The mean age of the cohort was 56.5 ( $\pm 11.5$ ) years with 84% being women. The most common AIRD was Rheumatoid Arthritis (332, 67%) followed by Spondyloarthritis (39, 7.8%) with the most common comorbidity being Diabetes Mellitus (63, 12.7%).

Both the groups had similar baseline characteristics (Table 1) except that Group 1 had higher comorbidities (as those patients with comorbidities were vaccinated first with the older policy of shorter vaccine interval), more patients with Rheumatoid Arthritis and a higher prevalence of steroid use.

## Primary outcome measure

Group 2 had higher anti-RBD antibody titre [1310.6 ( $\pm 977.8$ )] IU/ml as compared to Group 1 [736 ( $\pm 864.7$ ), *p*

**Table 1** Baseline characteristics of the two groups

	Vaccine interval, 4–6 weeks, (n = 253)	Vaccine interval, 10–14 weeks, (n = 242)	<i>P</i>
Age	56.5(11.9)	56.5(11.2)	0.9
M:F	1:4.5	1:6.5	0.1
Comorbidity			
Overall	92(36.5)	53(21.9)	<b>0.0001</b>
Diabetes Mellitus	44(17.3)	19(7.8)	<b>0.0001</b>
Hypertension	34(13.4)	21(8.7)	<b>0.0001</b>
Others	14(5.5)	13(5.3)	0.2
Diagnosis			
Rheumatoid Arthritis	155(61)	177(73.1)	<b>0.005</b>
Spondyloarthritis	52(20.6)	34(14)	0.06
SLE	24(9.5)	15(6.2)	0.2
Vasculitis	15(6)	2(0.8)	0.5
CTD	1(0.6)	9(3.3)	0.2
Systemic Sclerosis	6(2.4)	5(2)	0.8
Drugs			
Methotrexate	149(58.8)	132(54.6)	0.4
Hydroxychloroquine	154(60.8)	160(66.1)	0.6
Sulfasalazine	66(26)	59(24.4)	0.6
Leflunomide	26(10)	18(7.4)	0.2
Tofacitinib	18(7)	19(7.8)	0.7
Mycophenolate Mofetil	11(4)	17(7)	0.2
Tacrolimus	1(0.3)	4(1.6)	0.4
Azathioprine	1(0.3)	1(0.4)	0.9
Rituximab	28(11)	18(7.4)	0.2
Anti-TNFs	2(0.7)	1(0.4)	0.6
Glucocorticoid	54(21.3)	28(11.5)	<b>0.004</b>

CTD, connective tissue disease other than SLE and Systemic Sclerosis; F, female; M, male; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor

Age, M:F, Comorbidity, Diagnosis and Drugs

= 0.0001]. Furthermore, an adequate response was seen in a greater proportion of Group 2 than of Group 1 (Fig. 1).

### Predictors of antibody titres

On univariate analysis, presence of Diabetes Mellitus (663.12 versus 1168.9,  $p = 0.0001$ ), the use of Methotrexate (1000.15 and 1154.2,  $p = 0.04$ ), Sulfasalazine (1187 and 955,  $p = 0.02$ ), or Mycophenolate Mofetil use (542 and 1042,  $p = 0.008$ ), and vaccine interval (602.71 and 1044;  $p = 0.03$ ) were significantly associated with anti-RBD antibody titre (Table 2).

Multivariate analysis was carried out using generalized linear modelling (GLM), with diabetes mellitus, hypertension, rheumatoid arthritis, vaccine interval and steroid use as predictors and anti-RBD antibody titres as the dependent variable. This showed that anti-RBD antibody titres were associated with presence of diabetes mellitus and the vaccine interval independently.

### Breakthrough infection in either group

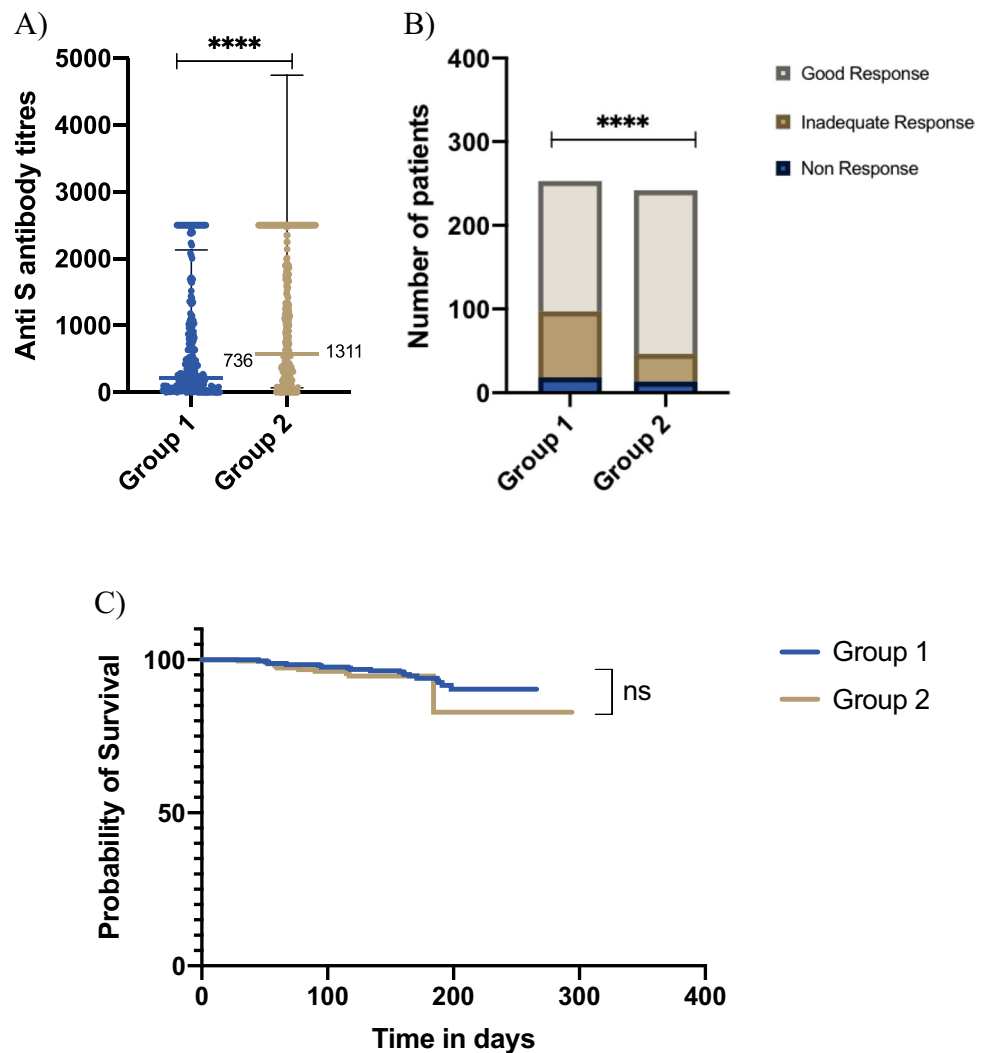
Breakthrough infections were higher in Group 1 numerically on survival analysis (Fig. 1C) but the difference was not significant (7.5% and 4.5%; log rank test:  $p = 0.25$ ).

### Discussion

Patients with AIRD whose second dose of AZD1222 was delayed by 10–14 weeks had higher antibody titres. Besides the vaccine interval, diabetes mellitus, use of methotrexate, sulfasalazine, or mycophenolate correlated with the antibody levels. In the multivariate analysis, the presence of diabetes and the vaccine gap were independent predictors of antibody titres. We also report a numerically higher rate of breakthrough infections in those who had the vaccine at 4 weeks gap.

Studies in healthy subjects have shown that longer interval between doses of AZD1222 resulted in higher antibody

**Fig. 1** Anti Spike(S) antibodies between the two groups (A), difference in the type of antibody response when stratified into adequate, inadequate and non-responders (B), survival difference between the two groups with breakthrough infection as the event



levels [4], higher seropositivity and reduced ICU admissions [8]. Better antibody and antiviral T cell response were observed with mRNA vaccines as well when studied in health care workers and paramedics [9–11]. At the population level, on the background of vaccine scarcity, number of severe COVID-19 cases would be expected to be significantly lower if more people receive the first dose rather than a smaller proportion receiving both the doses [12]. Modelling studies have also suggested a decreased mortality with delayed second doses with partial protection offered by one dose of the vaccine at least for individuals younger than 65 years [13, 14].

Anti-RBD antibody titres are an important correlate of protection against breakthrough COVID-19 infections in healthy individuals and patients with AIRDS. Increasing the interval of AZD1222 vaccination increases the anti-RBD antibody response by two-fold. Thus, it is desirable to have a higher antibody response to vaccination especially in patients with AIRDs, this could be even more valuable in

patients who have not been infected with COVID-19 naturally [6, 7].

The novelty of the study lies in the fact that this concept has been proven in a cohort of patients with AIRD who are on different immunomodulatory drugs. Both due to the underlying disease as well as the immunomodulators, their immune response may be different to that of healthy volunteers [15, 16]. People with AIRD, especially the elderly, have reduced immunogenicity with COVID-19 vaccines [17]. It is important to optimize the vaccination schedule for such patients since they tend to have more vaccine hesitancy [18]. It has been shown previously that withholding methotrexate for a week after each dose of the influenza vaccine was beneficial and the same has been recommended for COVID-19 vaccination [19, 20]. Similar results have been shown with COVID-19 vaccines as well [21].

The strengths of our study include a large prospectively enrolled cohort of vaccinated patients with AIRDs. They have been equally divided into two groups by matching for

**Table 2** Difference between anti-Spike antibody titres across various subgroups

	Yes	No	<i>P</i>
Female	1000.25 ± 963.1	1108.3 ± 973.5	0.36
Comorbidity	903.6 ± 968.2	1064.4 ± 960.4	0.09
Diabetes Mellitus	663.12 ± 897.1	1168.9 ± 964.2	<b>0.001</b>
Hypertension	1154.2 ± 1010	1000.2 ± 1000.2	0.36
Diagnosis			
Rheumatoid Arthritis	1057.4 ± 960.4	935.5 ± 970.9	0.18
Spondyloarthritis	1005.6 ± 995.3	1019.7 ± 959.2	0.9
Systemic Lupus Erythematosus	958.9 ± 944.9	1022.3 ± 967.1	0.69
Vasculitis	810.86 ± 973.7	1027.8 ± 963.9	0.28
Systemic Sclerosis	436.1 ± 730.2	1030.5 ± 965.7	<b>0.04</b>
Connective Tissue Disease	1450.5 ± 1238.4	1014.6 ± 963.7	0.43
Drugs			
Hydroxychloroquine (357 ± 68 mg)	1059.7 ± 961.1	928.35 ± 964.1	0.15
Methotrexate (13.67 ± 7.8mg)	936.7 ± 919.1	1116.5 ± 1011.6	<b>0.04</b>
Sulfasalazine (1238 ± 435mg)	1187.7 ± 976.2	955.5 ± 952.9	<b>0.02</b>
Leflunomide (14.8 ± 5.6mg)	946.9 ± 934.9	1020.9 ± 966.7	0.6
Steroids (3.5 ± 3.1 mg in prednisolone equivalents)	907.3 ± 989.5	1035.6 ± 957.7	0.2
Rituximab	909.1 ± 1064.2	1025.1 ± 952.9	0.43
Mycophenolate Mofetil (2113 ± 818 mg)	542.9 ± 895.9	1042.6 ± 960.7	<b>0.008</b>
Tofacitinib (9 ± 2.1 mg)	871.8 ± 1033.9	1025.8 ± 957.6	0.35
AZD1222, delayed 2 <sup>nd</sup> dose	1310.6 ± 977.8	736.7 ± 864.75	<b>0.04</b>

Female, Comorbidity, Diagnosis, Drugs, AZD1222, delayed second dose  
*p* values are fine

disease and drugs. There is some difference in the baseline characteristics since Group 1 were vaccinated earlier (as per initial government policy) while Group 2 were vaccinated later (after the policy had been changed).

The analysis has its limitations. Firstly, the proportion of comorbidities was higher in Group 1, inherent to the government policy prioritizing vaccination in persons with multimorbidity that could itself have led to poor immunogenicity [22]. Secondly, we have not assessed neutralizing antibodies or T cell responses to the vaccine. However, we have previously shown that antibody titres are the most important predictors of breakthrough infection [7]. And lastly, data on whether immunosuppressants were withheld at the time of vaccination was not available.

In conclusion, increasing the gap between doses of the AZD1222 vaccine from 4 weeks to 10–14 weeks was found to be more beneficial in terms of antibody response in patients with AIRD. There was a trend towards higher

breakthrough infections in the short interval group, supporting the antibody data.

**Data availability** Data will be available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate** The study was approved by the Institutional Ethics Committee of Sree Sudheendra Medical mission (IEC/2021/35)]. Written informed consent was taken from the participants of the study.

**Conflicts of interest** SA has received honorarium as speaker from Pfizer, Dr Reddy's, Cipla and Novartis (outside of the current work). The other authors declare no conflicts of interest.

**Patient and public involvement statement** Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

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