Original Article

Immunogenicity of Covishield vaccine in patients with autoimmune rheumatic diseases

Vikas Gupta[1], Vikram Kumar Gupta[2], Navjot Kaur Bajwa[3], Ashi Sachdeva[4], Rupali Garg[5], Abhra Ghosh[3]

[1]Department of Clinical Immunology and Rheumatology, DMC and H, Ludhiana, Punjab, India, [2]Department of Social and Preventive Medicine, DMC and H, Ludhiana, Punjab, India, [3]Department of Biochemistry, DMC and H, Ludhiana, Punjab, India, [4]Medical Officer, Umeed Multispeciality Hospital, Sangrur, Punjab, India, [5]General Medicine, DMC and H, Ludhiana, Punjab, India

Abstract

Introduction: The Coronavirus disease 2019 (COVID-19) pandemic has been the biggest threat to humankind during the last 3 years. It has caused the loss of more than 6.9 million precious lives across the world. The only method by which the massacre could be stopped was by mass vaccination or mass immunization. The patients suffering from autoimmune rheumatic disorders (AIRDs) and treated with immunosuppressants were the high-priority candidates for vaccination. However, the data regarding the efficacy of COVID-19 vaccines in this group of patients are very less. Hence, this study was planned to study the immunogenicity of Covishield in patients with AIRDs attending the rheumatology OPD at DMCH, Ludhiana. **Materials and Methods:** It was a prospective cohort study and was planned by the Department of Biochemistry and Department of Clinical Immunology and Rheumatology at Dayanand Medical College and Hospital, Ludhiana. Fifty patients with AIRDs attending the DMCH rheumatology OPD and 52 age and sex-matched healthy controls who had received two doses of Covishield vaccine were included in this study. Patients having any other immunosuppressive conditions like uncontrolled diabetes, hepatitis, malignancy or HIV were excluded. Patients who had suffered from previous laboratory-confirmed COVID-19 infection (by RT-PCR) were also excluded. Blood samples were collected following all aseptic precautions from patients and controls on the 28th day after administration of a second dose of Covishield vaccine and total antibodies to the severe acute respiratory syndrome coronavirus 2 spike (S) protein receptor binding domain was measured using Elecsys Anti-SARS-CoV-2 S kit from Roche. **Results:** It was observed that no significant difference was there in antibody titre between cases and controls (6213 ± 4418 vs. 8331 ± 7979, $P = 0.1022$). It was also observed that no statistically significant difference in antibody titre in cases without prednisolone and those taking treatment with prednisolone was found ($P = 0.7058$). A similar observation was found in terms of methotrexate also ($P = 0.457$). No significant difference in antibody titres was there when compared with controls (for prednisolone, $P = 0.169$, for methotrexate, $P = 0.078$). We found that only the patients receiving mycophenolate mofetil showed a statistically significant decrease in antibody titre in comparison to healthy controls ($P = 0.03$). Our study showed no statistically significant difference in antibody titres between patients suffering from different AIRDs. **Conclusion:** Our study supplements the fact that patients with AIRDs in India can receive Covishield as the primary vaccine against COVID-19 without concerns regarding decreased immunogenicity or increased adverse effects.

Keywords: Autoimmune rheumatic diseases, COVID-19, Covishield

Introduction

Immunization successfully uses immunotherapy to treat infectious diseases by stimulating the immune system to produce specific antibodies or specific lymphocytes to fight off pathogens. Immunotherapy creates an immunological memory

Address for correspondence: Dr. Abhra Ghosh, Department of Biochemistry, Dayanand Medical College and Hospital, Ludhiana, Punjab – 141 001, India.
E-mail: abhraghoshcmc@gmail.com

Received: 20-06-2023 **Revised:** 04-12-2023
Accepted: 05-12-2023 **Published:** 24-05-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_1021_23

How to cite this article: Gupta V, Gupta VK, Bajwa NK, Sachdeva A, Garg R, Ghosh A. Immunogenicity of Covishield vaccine in patients with autoimmune rheumatic diseases. J Family Med Prim Care 2024;13:1904-10.

that can be long-lasting.[1] However, since immunization boosts immunological memory, there is a possibility that the induction of protective immunity by appropriate vaccines in patients suffering from autoimmune diseases might not be enough for sufficient protection due to therapy with immunosuppressive medications.[2]

The immunogenicity of a vaccine given to a patient suffering from autoimmune disease depends on multiple factors – type of disease, duration of disease, type of immunotherapy (immunomodulator or immunosuppressant), type of vaccine, etc., Data from different studies have mixed inference regarding immunogenicity of vaccines in patients suffering from autoimmune diseases.[3]

The Coronavirus disease 2019 (COVID + 19) pandemic has been the biggest threat to humankind during the last 3 years. It has caused the loss of more than 6.9 million precious lives across the world.[4] The World Health Organization and apex health bodies of all countries were on war footing to find measures to contain and eradicate the disease. It was observed that appropriate COVID-19 behaviors could only contain the disease to some extent. The only method by which the massacre could be stopped was by mass vaccination or mass immunization.

During trials of all potential COVID-19 vaccine candidates' development, patients suffering from autoimmune rheumatic diseases (AIRDs) were excluded as volunteers to keep them safe from any unwanted adverse reactions. This led to a collection of very scarce data regarding the immunogenicity of COVID-19 vaccines in this group of patients.[5]

The patients suffering from AIRDs and treated with immunosuppressants were the high-priority candidates for vaccination. Though the approved vaccines which are available in the market are considered safe and efficacious enough in patients of autoimmune diseases, there is some evidence that a delayed and suppressed immune response to SARS-CoV-2 vaccines, predominantly mRNA vaccines, is seen in patients with AIRDs who are on immunosuppressives.[6-8]

The two vaccines predominantly used in India are adenoviral vector-borne AZD1222 (ChAdOx1 nCoV-19, AstraZeneca COVID-19 vaccine "Covishield") and the indigenous whole-virion β-propiolactone-inactivated BBV152 (Bharat Biotech COVID-19 Vaccine ""Covaxin").[9]

In the realm of healthcare, the significance of comprehensive knowledge among primary care doctors regarding COVID-19 vaccination in patients with various underlying diseases cannot be overstated. As frontline healthcare providers, primary care doctors play a pivotal role in guiding patients, especially those grappling with pre-existing conditions like AIRDs, through the vaccination decision-making process. A nuanced understanding of the interplay between chronic illnesses like AIRDs and COVID-19 is imperative for these practitioners. With such knowledge, they can tailor vaccination recommendations, address concerns, and ensure optimal outcomes. This informed approach not only safeguards vulnerable populations but also contributes to broader public health objectives by fostering widespread immunity. The knowledge base of primary care doctors serves as a linchpin in the collective effort to navigate the complexities of COVID-19 vaccination, fostering a healthier and more resilient society.

However, similar to other COVID-19 vaccines, there is insufficient safety data regarding the efficacy and seroconversion rate of Covishield in patients with AIRDs. This lack of information has led to confusion among primary care physicians regarding the potential and safety of Covishield.

Hence, this study was planned to study the immunogenicity of Covishield in patients with AIRDs attending the Rheumatology OPD at DMCH, Ludhiana. We assessed the humoral immune response after Covishield vaccination in patients of AIRDs and compared the results to healthy controls reporting for vaccination at our institute.

Methods

Study design

The study was a prospective cohort study and was planned by the Department of Biochemistry and Department of Clinical Immunology and Rheumatology of our institute. Institutional ethics clearance was taken for the study vide letter no. DMCH/R and D/2021/92.

Inclusion and exclusion criteria

Fifty patients with AIRDs attending the rheumatology OPD of our hospital, who had received two doses of Covishield vaccine, were included in this study. Patients having any other immunosuppressive conditions like uncontrolled diabetes, hepatitis, malignancy or HIV were excluded. Patients who had suffered from previous laboratory-confirmed COVID-19 infection (by RT-PCR) were also excluded. Fifty-two age-matched healthy controls were selected from the vaccine recipients who had taken their vaccines at the DMCH vaccination centre. Patients and healthy controls were screened for total antibodies to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein receptor binding domain (RBD) before administration of the vaccine and enrolment into the study. This helped us to identify subjects who had possible covid infection but was not diagnosed by RT-PCR. Only the patients and healthy controls who had no antibodies present in their blood were selected for the study. Assuming good antibody response (>212 U/mL) in 99% of healthy controls and 54% of AIRDs cases,[10] at 0.05 confidence interval and power 95%, total 40 (20 cases and 20 controls) subjects were needed for the study. To further increase the significance of the study, we included 50 cases and 52 age-matched controls in the study.[11,12]

Clinical details

Demographic details, types and duration of AIRDs, types and duration of immunosuppressive drugs taken, any other

comorbidities, details of vaccination and any adverse reactions after vaccination were recorded.

Antibody assays

Blood samples were collected following all aseptic precautions from patients and controls on the 28th day after administration of the second dose of Covishield vaccine in a yellow top gel tube. Serum was separated and total antibodies to the SARS-CoV-2 spike (S) protein RBD was measured using Elecsys Anti-SARS-CoV-2 S kit from Roche, Switzerland on Roche Cobas 8000. Immune responses in all study participants were classified based on anti-SARS CoV2-S antibody titres as good responders (GR) (>212 U/mL), inadequate responders (0.8–212 U/mL) and nonresponders (<0.8 IU/mL).[12]

Statistical analysis

Statistical analysis was done using Microsoft Excel and Jamovi[13] Software. Unpaired *t*-test, one way ANOVA and linear regression were used to find out the statistical significance.

Results

We studied 50 patients with AIRDs and compared them with 52 age-matched controls. The mean ± SD age for the patient group was 45.4 ± 13.0 years, whereas in the control group, it was 45.4 ± 12.4 years. In the patient group, 22% (n = 11) were males, whereas in the control group, 50% (n = 26) were males. Sex matching was not possible between the two groups due to a lack of motivation for testing in controls to get their antibody titre checked.

Seropositive rheumatoid arthritis (RA) was the most common diagnosis (n = 22) followed by seronegative RA (n = 11), systemic sclerosis (n = 5) and systemic lupus erythematosus (SLE) (n = 4).

Table 1 contains the details of participants in both cohorts based on the type of AIRD, drugs, types of treatment received, etc.

No significant difference was seen in antibody titre between cases and controls. All the study participants were identified as GR based on their antibody titre (GR >212 U/mL, Table 2, Figure 1).[11]

The study participants enrolled as patients were divided into different groups based on types of AIRDs, and the drugs used. Depending on the type of AIRD, the patients were divided into five groups – sero-positive RA (n = 22), sero-negative RA (n = 11), systemic sclerosis (n = 5), SLE (n = 4) and others (n = 8). Patients were also divided into groups based on immunomodulators (hydroxychloroquine and sulfasalazine) and immunosuppressives (methotrexate, leflunomide, azathioprine and tacrolimus). They were also grouped on the basis of whether they received (prednisolone, n = 37) or not (n = 13), and whether they received methotrexate (MTX) (n = 26) or not (n = 24) since steroids, and MTX are generally considered to reduce immunogenicity to vaccines.

Table 1: Demographic characteristics of patients with AIRDs and healthy controls

Demographic characteristics	*n*=50 Patients (%)	*n*=52 Healthy controls (%)
Median age (Years)	43	43.5
Mean age±SD (Years)	45.4±13.0	45.4±12.4
Male	11 (22)	26 (50)
Female	39 (78)	26 (50)
AIRDs types		
Seronegative RA	11 (22)	.
Seropositive RA	22 (44)	.
Systemic sclerosis	5 (10)	.
SLE	4 (8)	.
Others*	8 (16)	.
Treatment for AIRDs		
Without prednisolone	13 (26)	.
With prednisolone	37 (74)	.
With methotrexate	26 (52)	.
Without methotrexate	24 (48)	.
Specific drugs		
Prednisolone	37 (74)	.
Hydroxychloroquine (HCQ)	28 (56)	.
Methotrexate (MTX)	26 (52)	.
Azathioprine	6 (12)	.
Leflunomide	5 (10)	.
Mycophenolate mofetil	4 (8)	.
Sulfasalazine	1 (2)	.
Tacrolimus	1 (2)	.

*Others include patients with secondary amyloidosis, mixed connective tissue disease and vasculitis

Table 2: Comparison of antibody titres in patients of AIRDs and healthy controls

	n	Antibody titre (U/mL, Mean±SD)	SEM	df, *t*	*P* (two-tailed)
Cases	50	6213±4418	625	100,	0.1022
Control	52	8331±7979	1106	1.69494	(Nonsignificant)

It was also observed that no statistically significant difference in antibody titre was seen between the patients who received prednisolone and those who did not. Similarly, no statistically significant difference in antibody titre was seen between the patients who received MTX and who did not [Table 3].

One-way ANOVA analysis on antibody titres in various subsets of disease groups resulted in nonsignificant differences in antibody titres [Table 4, Figure 2].

Linear regression was also applied. But for antibody, titres in patients for age, sex and adverse event following immunization (AEFI) yielded statistically nonsignificant results.

Discussion

AIRDs are a subgroup of autoimmune diseases, which have clinical, laboratory and immunological implications in common amongst them. Factors like previous infections, genetic alteration, hormonal imbalances or environmental toxins, etc., lead to

Table 3: Comparison of antibody titres in different subgroups of patients

	n	Antibody titre (U/mL, Mean±SD)	SEM	df, *t*	*P* (two-tailed)
Cases without prednisolone	13	5368±4784	1488	48, 0.798	0.7058 (Nonsignificant)
Cases with prednisolone	37	6509±4311	708		
Cases with methotrexate	26	5799.31±4512	885	48, 0.759	0.457 (Nonsignificant)
Cases without methotrexate	24	6661.29±4364	890		

Table 4: Comparison of antibody titres across multiple subgroups of patients

	n	Mean±SD	SEM	*f*	*P* (two-tailed)
Sero −ve RA	11	8360±6081	1834	0.471	0.756
Sero +ve RA	22	5723±4041	862		(Nonsignificant)
Primary sclerosis	5	5364±2744	1227		
SLE	4	5307±3588	1794		
Others	8	5592±3947	1395		

dysregulation and exaggeration of immunological response which explains the pathophysiology of this subgroup of diseases.[14]

Our study was planned and designed to investigate the immunogenicity of the most used COVID-19 vaccine in India – Covishield in patients with AIRDs attending the rheumatology DMCH OPD. The patients of AIRDs were subgrouped into different types of AIRDs based on their primary diagnosis.

The total anti-SARS-CoV2 S antibody against spike (S) protein RBD was measured in both cases and the control group, and it was found that no statistically significant difference of titre was there between these two groups ($P = 0.1022$, Table 2).

There is a scarcity of data, both globally and in India, on antibody response against Covishield in patients suffering from AIRDs. A study by Ahmed *et al.*[11] reported that more than 82% of patients with AIRDs responded well to two doses of Covishield and the sufficient antibody titre was found 4–6 weeks post vaccination, though no comparison with a normal population was done and patients with other immunosuppressive conditions like diabetes and malignancy were not excluded in this study. There are few studies from Europe that shed some insights on seroconversion rates after COVID-19 vaccination in patients of AIRDs. A study on the effects of BNT162b2 mRNA vaccine by Furer *et al.*[15] found that the seropositivity rate in patients with AIRDs was significantly lower than in the controls. Another study by Braun-Moscovici[16] found out that 86% of patients suffering from AIRDs had significant humoral response to BNT162b2 mRNA vaccination. They also reported that there were no major adverse effects in these patients, nor there were any flare-ups of the diseases. Another study by Widhani *et al.*[17] also stated that patients with AIRDs showed significantly more breakthrough COVID-19 infections and lower IgG seroconversion, and neutralizing antibodies after inactivated COVID-19 vaccination compared with healthy controls after COVID-19 mRNA vaccination compared with healthy controls. A study by Frommert *et al.*[10] showed that patients of AIRDs received two doses of AZD1222 (Covishield, as available in the Indian market), which produced significantly fewer antibody

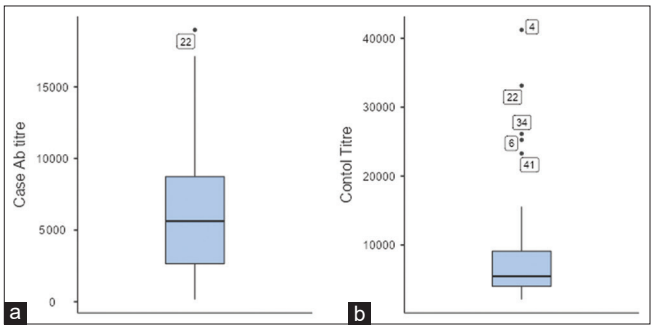

Figure 1: (a and b) BOX WHISKER plots for cases and control in relation to antibody titre

titres than in the patients receiving mRNA vaccines and the control population. On the contrary, a study from Germany by M Geisen *et al.*[6] found that the administration of anti-SARS-CoV-2 mRNA vaccine led to the development of sufficient antibodies in immunosuppressed patients without considerable adverse effects or induction of disease flares. Though the vaccine type used in our study is different, the findings of our study are in association with the study by M Geisen *et al.*[6]

A study by Jeewandara *et al.*[18] on Sri Lankan population showed that the total antibodies to the RBD were highest for the recipients of Sputnik V and AZD1222 vaccine (Covishield). It has also been established that the neutralization of SARS-CoV-2 requires antibodies against conformational receptor binding epitope. This condition can explain better immunogenic response and less severe breakthrough infections in people of Indian subcontinent origin who have received Covishield as the primary vaccine.[19]

Our patient group was subgrouped based on the type of drugs used for treatment. Patients were subgrouped based on whether they were receiving prednisolone or not as a combination therapy. The total anti-SARS-CoV2 S antibody against spike (S) protein RBD was measured in both groups and no statistically significant difference was found between the patient subgroups ($P = 0.7058$, Table 3). When compared with the control group, none of the subgroups of the patients showed a significant difference in antibody titres (with and without prednisolone, $P = 0.169$ and $P = 0.096$, Table 5). In a study by Boekel *et al.*,[3] it was found that patients receiving prednisolone therapy did not show a reduced seroconversion rate when compared to healthy controls. A similar finding was stated by another study by Frommert *et al.*,[10] and both of these studies are in line with our study findings. It has also been established by various studies that at a dose of <20 mg/day of prednisolone, sufficient immune response is generated against other nonlive influenza vaccines. As Covishield is a nonlive

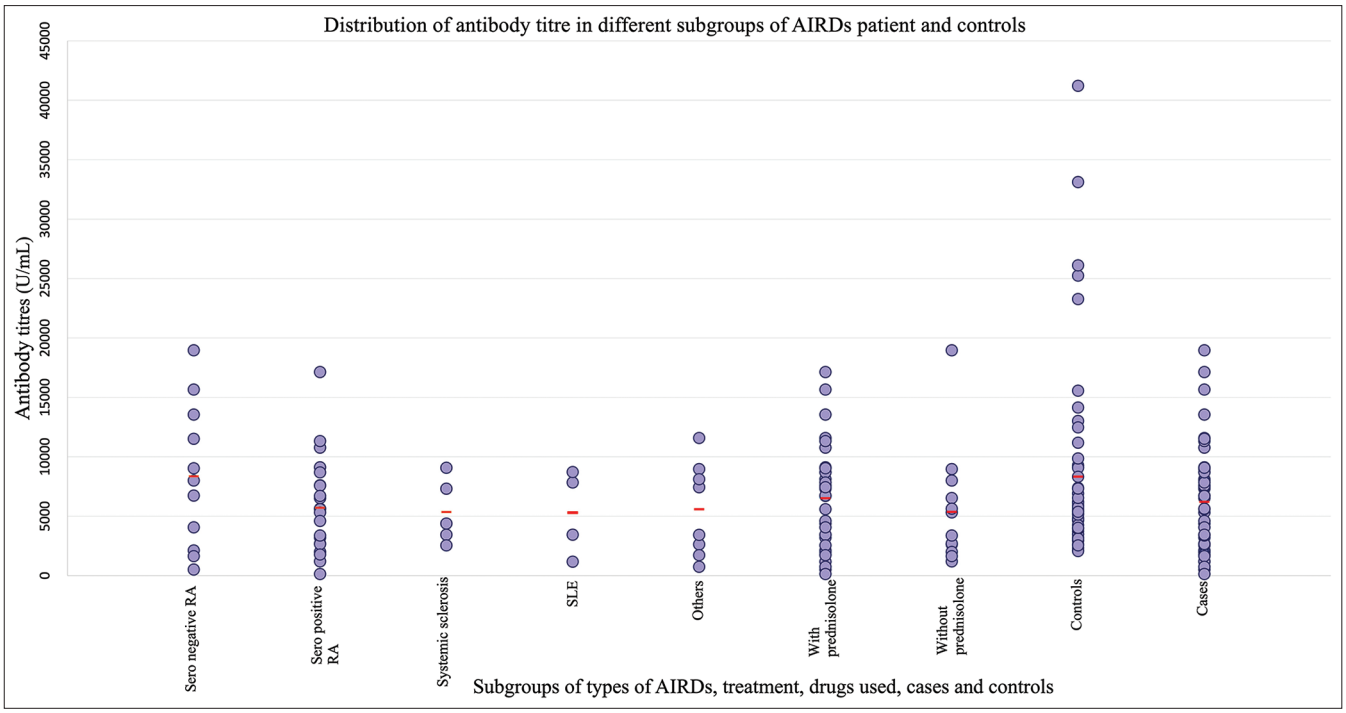

Figure 2: Distribution of antibody titre in different subgroups of AIRD patients and controls

vaccine, it can be postulated that prednisolone will not alter the immune response against it.[20,21]

Another subgroup criterion was the use of MTX as mono or combination therapy and no significant difference in antibody titre was found when compared with the control group and also a subgroup of patients not receiving MTX (with and without methotrexate, $P = 0.078$ and $P = 0.244$, Table 5). This finding was the opposite of the findings obtained by other available studies with Covishield or mRNA vaccines in the literature.[3,10,11,22] There are also studies that suggest that pausing MTX therapy in patients of AIRDs increases the anti-SARS CoV-2 antibody response.[23,24] It has been hypothesised that MTX decreases humoral responses to conventional influenza vaccines.[25] However, our study showed that continuation of the therapy can also generate sufficient antibodies in patients of AIRDs and our findings are similar to that found by a study by Tran AP *et al.*[26] In our study, we found that only the patients receiving mycophenolate mofetil as combination therapy showed a statistically significant decrease in antibody titre in comparison to healthy controls ($P = 0.03$, Table 5).

We also looked into the fact whether type of AIRD affects the antibody response. Our study population had patients suffering from sero-positive RA, sero-negative RA, systemic Sclerosis, SLE and others. Studies in the literature show mixed results, where rheumatoid arthritis and SLE showed inadequate antibody response against COVID-19 vaccine, whereas systemic sclerosis showed adequate response in comparison to healthy controls.[10] Our study showed no statistically significant difference in antibody titres between patients suffering from different AIRDs ($P = 0.756$, Table 4). The impact of the type of disease on antibody titre in comparison to controls was also analysed and found to be nonsignificant [Table 5]. We also analysed the relation between antibody titres with disease duration and no statistically significant difference was found [Figure 3].

Table 5: Impact of disease type and immunosuppressive therapy on antibody titres in comparison to controls

	Controls	*P* (two tailed)
Primary diagnosis (Cases)		
Sero positive RA (*n*=22)	52	0.067
Sero negative RA (*n*=11)		0.989
Systemic sclerosis (*n*=5)		0.097
SLE (*n*=4)		0.201
Others (*n*=8)		0.141
Drugs		
With Prednisolone (*n*=37)		0.169
Without prednisolone (*n*=13)		0.096
With methotrexate (*n*=26)		0.078
Without methotrexate (*n*=24)		0.244
With azathioprine (*n*=6)		0.885
With mycophenolate mofetil (*n*=4)		0.03

Table 6: Comparison of AEFI in patients and control group

Type of AEFI (first reported)	Patients	Controls
No AEFI	26 (52)	33 (63)
Fever	14 (28)	13 (25)
Headache	3 (6)	1 (2)
Arthralgia	6 (12)	4 (8)
Others	1 (2)	1 (2)

Analysis of the rate of occurrence of adverse effects following immunisation showed no significant differences between patients

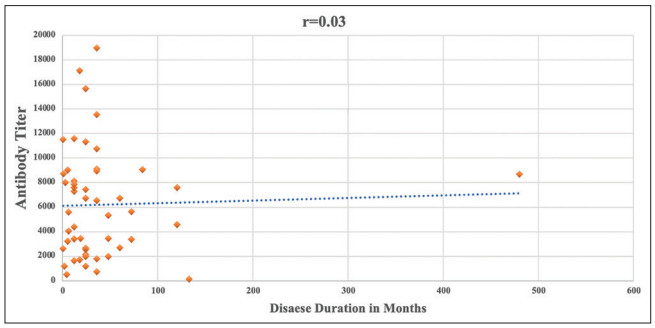

Figure 3: Correlation of antibody titre with AIRD duration

and control groups and supports the findings of Park *et al.*[27] and Mohanasundaram K *et al*,[28] [Table 6].

Limitations

Our study has a few limitations. First, the sample cohort is smaller in comparison to similar studies from developed countries where mRNA vaccines were used primarily. The treatment regime used in our patients was restricted to conventional low-cost drugs. We used a total antibody to measure the immunogenicity and antibody response against the vaccine, whereas the inclusion of IgG titre would have given us the option to explore more horizons.

Conclusions

Our study has some important and relevant findings. Firstly, our study found that the immunogenicity of Covishield is not hampered due to AIRDs. It supports the fact that nonlive COVID-19 vaccines can be given to patients with AIRDs and adequate immune response will be generated without developing significant AEFI. Secondly, our study also concludes that, apart from mycophenolate mofetil, no other immunosuppressive drug (including methotrexate, leflunomide, azathioprine and tacrolimus), or immunomodulatory drug (including sulfasalazine and hydroxychloroquine) hamper the immune response to Covishield.

In summary, it has been concluded that individuals in India with AIRDs can confidently opt for Covishield as their primary COVID-19 vaccine. The evidence indicates no significant worries about reduced immunogenicity or heightened adverse effects. Armed with this conclusive information, primary care physicians will not only be able to provide accurate information regarding COVID-19 vaccination to their patients but also play a crucial role in formulating public health strategy, fortifying resilience against COVID-19 within a diverse and medically intricate population.

Acknowledgement

Dr Ekta Bansal, Prof and HOD, Department of Biochemistry and Dr Nandita Maini Jindal, Assistant Professor, Department of Biochemistry for their continuous support in conducting this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Justiz Vaillant AA, Grella MJ. Vaccine (Vaccination). 2023 Aug 8. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023.
2. Furer V, Rondaan C, Agmon-Levin N, van Assen S, Bijl M, Kapetanovic MC, *et al.* Point of view on the vaccination against COVID-19 in patients with autoimmune inflammatory rheumatic diseases. RMD Open 2021;7:e001594. doi: 10.1136/rmdopen-2021-001594.
3. Boekel L, Steenhuis M, Hooijberg F, Besten YR, van Kempen ZLE, Kummer LY, *et al.* Antibody development after COVID-19 vaccination in patients with autoimmune diseases in the Netherlands: A substudy of data from two prospective cohort studies. Lancet Rheumatol 2021;3:e778-88. doi: 10.1016/S2665-9913(21)00222-8.
4. World Health Organization. WHO Coronavirus (COVID-19) dashboard. Available from: https://covid19.who.int/. [Last accessed on 2023 Jun 15].
5. Arnold J, Winthrop K, Emery P. COVID-19 vaccination and antirheumatic therapy. Rheumatology (Oxford) 2021;60:3496-502.
6. Geisen UM, Berner DK, Tran F, Sümbül M, Vullriede L, Ciripoi M, *et al.* Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort. Ann Rheum Dis 2021;80:1306–11.
7. Haberman RH, Herati R, Simon D, Samanovic M, Blank RB, Tuen M, *et al.* Methotrexate hampers immunogenicity to BNT162b2 mRNA COVID-19 vaccine in immune-mediated inflammatory disease. Ann Rheum Dis 2021;80:1339-44.
8. Bugatti S, De Stefano L, Balduzzi S, Greco MI, Luvaro T, Cassaniti I, *et al.* Methotrexate and glucocorticoids, but not anticytokine therapy, impair the immunogenicity of a single dose of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic inflammatory arthritis. Ann Rheum Dis 2021;80:1635-8.
9. Vaccine information, ICMR New Delhi-COVID-19 Vaccine. vaccine.icmr.org.in. Available from: https://vaccine.icmr.org.in.
10. Frommert LM, de Silva AN, Zernicke J, Scholz V, Braun T, Jeworowski LM, *et al.* Type of vaccine and immunosuppressive therapy but not diagnosis critically influence antibody response after COVID-19 vaccination in patients with rheumatic disease. RMD Open 2022;8:e002650. doi: 10.1136/rmdopen-2022-002650.
11. Ahmed S, Mehta P, Paul A, Anu S, Cherian S, Shenoy V, *et al.* Postvaccination antibody titres predict protection against COVID-19 in patients with autoimmune diseases: Survival analysis in a prospective cohort. Ann Rheum Dis 2022;81:868-74.
12. ClinCalc Sample Size Calculator for Two Independent Study Group. Available from: https://clincalc.com/stats/samplesize.aspx. [Last accessed on 2023 Jun 09].
13. The Jamovi project (2022). jamovi (Version 2.3) [Computer Software] Sydney, Australia. Available from: https://www.jamovi.org.
14. Moutsopoulos HM. Autoimmune rheumatic diseases: One

or many diseases? J Transl Autoimmun 2021;4:100129. doi: 10.1016/j.jtauto.2021.100129.

15. Furer V, Eviatar T, Zisman D, Peleg H, Paran D, Levartovsky 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.
16. Braun-Moscovici Y, Kaplan M, Braun M, Markovits D, Giryes S, Toledano K, *et al.* Disease activity and humoral response in patients with inflammatory rheumatic diseases after two doses of the Pfizer mRNA vaccine against SARS-CoV-2. Ann Rheum Dis 2021;80:1317-21.
17. Widhani A, Hasibuan AS, Rismawati R, Maria S, Koesnoe S, Hermanadi MI, *et al.* Efficacy, immunogenicity, and safety of COVID-19 vaccines in patients with autoimmune diseases: A systematic review and meta-analysis. Vaccines (Basel) 2023;11:1456.
18. Jeewandara C, Aberathna IS, Danasekara S, Gomes L, Fernando S, Guruge D, *et al*. Comparison of the immunogenicity of five COVID-19 vaccines in Sri Lanka. Immunology 2022;167:263-74.
19. Gattinger P, Niespodziana K, Stiasny K, Sahanic S, Tulaeva I, Borochova K, *et al.* Neutralization of SARS-CoV-2 requires antibodies against conformational receptor-binding domain epitopes. Allergy 2022;77:230-42.
20. Inoue S, Shibata Y, Takabatake N, Igarashi A, Abe S, Kubota I. Influence of corticosteroid therapy on the serum antibody response to influenza vaccine in elderly patients with chronic pulmonary diseases. EXCLI J 2013;12:760-5.
21. Fischer L, Gerstel PF, Poncet A, Siegrist CA, Laffitte E, Gabay C, *et al.* Pneumococcal polysaccharide vaccination in adults undergoing immunosuppressive treatment for inflammatory diseases–a longitudinal study. Arthritis Res Ther 2015;17:151.
22. Feuchtenberger M, Kovacs MS, Eder A, Nigg A, Schäfer A. Methotrexate significantly reduces the humoral vaccination response against SARS-CoV-2 in older but not younger patients with rheumatoid arthritis. Rheumatol Int. 2022;42:959-66.
23. Araujo CSR, Medeiros-Ribeiro AC, Saad CG, Bonfiglioli KR, Domiciano DS, Shimabuco AY, *et al.* Two-week methotrexate discontinuation in patients with rheumatoid arthritis vaccinated with inactivated SARS-CoV-2 vaccine: A randomised clinical trial. Ann Rheum Dis 2022;81:889-97.
24. Habermann E, Gieselmann L, Tober-Lau P, Klotsche J, Albach FN, Ten Hagen A, *et al.* Pausing methotrexate prevents impairment of omicron BA. 1 and BA. 2 neutralisation after COVID-19 booster vaccination. RMD Open 2022;8:e002639. doi: 10.1136/rmdopen-2022-002639.
25. Park JK, Lee YJ, Shin K, Ha YJ, Lee EY, Song YW, *et al.* Impact of temporary methotrexate discontinuation for 2 weeks on immunogenicity of seasonal influenza vaccination in patients with rheumatoid arthritis: A randomised clinical trial. Ann Rheum Dis 2018;77:898-904.
26. Tran AP, Tassone D, Nossent J, Ding NS. Antibody response to the COVID-19 ChAdOx1nCov-19 and BNT162b vaccines after temporary suspension of DMARD therapy in immune-mediated inflammatory disease (RESCUE). RMD Open 2022;8:e002301. doi: 10.1136/rmdopen-2022-002301.
27. Park JK, Lee EB, Shin K, Sung YK, Kim TH, Kwon SR, *et al.* COVID-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: Clinical guidance of the Korean College of Rheumatology. J Korean Med Sci 2021;36:e95. doi: 10.3346/jkms. 2021.36.e95.
28. Mohanasundaram K, Santhanam S, Natarajan R, Murugesan H, Nambi T, Chilikuri B, *et al.* Covid-19 vaccination in autoimmune rheumatic diseases: A multi-center survey from southern India. Int J Rheum Dis 2022;25:1046-52.