Original Article

Long-term antibody responses to COVAXIN and COVISHIELD vaccines in rheumatoid arthritis patients and healthy control population – A cross-sectional study

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes inflammation and damage in the joints. It often requires treatment with disease-modifying antirheumatic drugs (DMARDs) to manage symptoms and prevent progression. The study investigates the long-term antibody responses to COVAXIN and COVISHIELD vaccines in RA patients. **Methodology:** This cross-sectional study (IEC approval no: AIIMS/BBN/IEC/AUG/2021/60-R dated Sept 05, 2022, and Ref No: 799/U/IEC/ESICMC/F490/09/2022 dated Oct 31, 2022) enrolled 103 diagnosed RA patients receiving DMARDs and 183 healthy controls. The participants who completed 1 year after the second dose of vaccination were included, and detailed information on demographic, medical, and vaccination were collected. Laboratory investigations included complete blood count, inflammatory markers, and antispike antibody levels. Statistical analyses assessed differences between COVAXIN and COVISHIELD subgroups, considering DMARDs usage and disease duration. **Results:** Among RA patients, both COVAXIN and COVISHIELD groups exhibited low disease activity. No significant ($P > 0.05$) differences were found in IL-6, CRP, or antispike antibody levels between COVAXIN and COVISHIELD subgroups in RA patients and healthy controls. Notably, 89% of female RA patients received COVISHIELD. Co-morbidities, including hypothyroidism (44%), were prevalent in COVISHIELD-received RA patients. Antibody concentration varied significantly among DMARDs usage groups in COVAXIN-vaccinated RA patients, with a notable difference between three-drug and HCQ-alone regimens. However, no such difference was observed in the COVISHIELD group. Disease duration did not significantly impact antispike antibody concentration in either of the vaccination group. **Conclusion:** RA patients had a decreased antibody response, 1 year after receiving the second dose of the COVID-19 vaccine. Nonetheless, there was no discernible difference in the antispike antibody concentration between the COVISHIELD and COVAXIN vaccination groups. Additionally, immunosuppressive medications significantly impact serological responses to these vaccines.

Keywords: Antispike antibodies, COVAXIN, COVID-19, COVISHIELD, rheumatoid arthritis

Introduction

The ongoing COVID-19 pandemic has brought into focus the critical importance of vaccination as a primary defense against the virus. Two widely administered COVID-19 vaccines in India, COVAXIN (BBV152-inactivated viral vaccine developed by Bharat Biotech) and COVISHIELD (ChAdOx1 nCoV-19

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Corona Virus Vaccine (Recombinant) manufactured by the Serum Institute of India), have played a pivotal role in mitigating the spread of the virus. COVAXIN and COVISHIELD induce immune responses through different mechanisms to provide protection against COVID-19. COVAXIN, an inactivated virus vaccine, introduces a killed version of SARS-CoV-2, prompting antigen-presenting cells (APCs) to capture and present viral antigens to helper T-cells (CD4+). This activation leads to the release of cytokines, which stimulate B-cells to mature into plasma cells and produce neutralizing antibodies, and cytotoxic T-cells (CD8+) to target and destroy infected cells. Memory B-cells and T-cells form, ensuring long-term immunity.[1] In contrast, COVISHIELD, a viral vector vaccine, uses a modified chimpanzee adenovirus to deliver the genetic code for the SARS-CoV-2 spike protein. The host cells produce and display the spike protein, which APCs process and present to helper T-cells. This triggers a similar immune cascade, leading to the production of neutralizing antibodies by plasma cells and the activation of cytotoxic T-cells. Memory cells are also generated, providing long-term immune protection. Both vaccines prepare the immune system to recognize and fight SARS-CoV-2, enhancing the body's ability to respond to future exposures and preventing COVID-19.[2,3]

However, while these vaccines have demonstrated efficacy in the general population, their performance in specific subgroups, such as individuals with underlying autoimmune conditions like rheumatoid arthritis (RA), requires further investigation.

RA is a chronic autoimmune disease characterized by inflammation, primarily in the joints, but with potential systemic effects. Patients with RA typically experience an altered immune response, and many are prescribed immunosuppressive medications to manage their condition.[4] This characteristic places them at higher risk for infections and can potentially affect their ability to generate protective immune responses following vaccination.

It has been reported in a cohort of patients with the immune-mediated disease psoriasis that methotrexate impairs functional humoral immunity to a single dose of Pfizer and BioNTech COVID-19 vaccine, whereas targeted biologics do not. It is important to note that seroconversion alone might not adequately reflect vaccine immunogenicity in patients with autoimmune diseases who are receiving therapeutic immunosuppressive drugs.[5]

Understanding the long-term antibody responses in RA patients who have received COVAXIN and COVISHIELD is crucial for several reasons. First, RA patients represent a vulnerable subset of the population, and assessing the duration and strength of their antibody responses to these vaccines is imperative to ensure that they are adequately protected against COVID-19. Second, knowing the longevity of immunity conferred by these vaccines in RA patients can inform vaccination strategies. If antibody levels wane rapidly, it may be necessary to provide booster doses or alternative approaches to enhance protection in this group. Third, to understand the influence of immunosuppressant medications on vaccine-induced antibody responses is essential for ensuring their safety and efficacy.

Recent studies have shown that autoimmune disease patients generally exhibit a reduced immune response to various vaccines compared to healthy individuals, primarily due to the disease and the immunosuppressive therapies used in treatment.[5,6] Specific studies on COVID-19 vaccines have found similar results. For instance, Mahil *et al.* (2021)[5] observed a lower seroconversion rate in immune-mediated inflammatory disease patients after mRNA COVID-19 vaccines. Moreover, real-world data indicate that while COVAXIN and COVISHIELD are effective in generating an immune response in RA patients, the antibody titers are significantly lower compared to healthy controls.[7]

This study aimed to estimate the long-term antispike antibody responses to COVAXIN and COVISHIELD in RA patients and healthy controls, investigate the impact of disease-modifying antirheumatic drugs (DMARDs) on antibody production in RA patients, and explore the association between the duration of RA and antibody responses to these vaccines. This manuscript presented here is an additional data analysis of original study where the immunological response was compared among RA patient with healthy control population.[8] The findings of this study will contribute to a better understanding of effectiveness of different types of vaccines in RA patients. This research is not only relevant to the Indian context but also provides valuable insights for managing autoimmune conditions and vaccination strategies worldwide.

Materials and Methods

This cross-sectional study was conducted at two tertiary care centers to assess the long-term antibody responses to COVAXIN and COVISHIELD vaccines in RA patients and a healthy control population. The study included diagnosed RA patients, both seropositive and seronegative, who were receiving DMARDs either as single or combination therapy. Participants were evaluated 1 year after the second dose of vaccination. Exclusion criteria encompassed individuals with cancer, autoimmune/immune suppressant disorders, pregnant or breastfeeding women, those with an active SARS-CoV-2 infection, hospitalized or critically ill patients, and RA patients who had not received vaccination.

The control group comprised participants without underlying diseases who completed the second dose of vaccination. In our study, RA patients were recruited from the outpatient rheumatology department of a tertiary care hospital, and controls were patient attendants recruited from the same outpatient department. The recruitment occurred during routine clinic visits, with eligible participants identified based on predefined inclusion and exclusion criteria. The study ran from November 2021 to March 2023.

Sample size determination utilized statistical calculations for a comparison of two proportions, with a targeted 5% absolute precision and 80% power. Assuming a serologic response rate of 86%[9] in RA patients and 95%[10] in controls after two doses, the calculated sample size was 166 participants in each group. Accounting for a 10% nonresponse rate, the final sample size increased to 184 participants in each group, resulting in a total of 368 participants.

The study was initiated after receiving approval from the Institutional Ethics Committee (IEC AIIMS/BBN/IEC/AUG/2021/60-R dated Sept 05, 2022, and Ref No: 799/U/IEC/ESICMC/F490/09/2022 dated Oct 31, 2022)). Written informed consent was acquired from participants, and data collection encompassed demographic information, comorbidities, past COVID-19 history, vaccination details, and DMARD specifics. Disease activity score (DAS-28) was recorded for RA patients. Blood samples (10 ml) were collected for complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin-6 (IL-6) neutralizing antibodies for COVID-19 (anti-S antibodies), and liver and renal function tests. The CRP and IL-6 were estimated to know the level of inflammation. The liver and renal function tests were done to assess any additional impact of vaccines on these organs.

Antispike antibody testing utilized Coviprotect from J Mitra and Co Pvt Ltd, India, employing an enzyme immunoassay to detect SARS-CoV-2 neutralizing antibodies against the receptor binding domain (RBD) in human serum/plasma. Results were considered positive if ≥30% inhibition was observed, while <30% inhibition was reported as negative. The kit demonstrated a sensitivity of 96.99% and specificity of 100%.

The data was expressed as mean ± SD if distribution following normality and median (IQR) in non-normality of the data distribution. The analysis of the data was done with STATA 16 software. The demographic details, co morbid status, previous COVID-19 infection and DAS-28 score and RA positivity were expressed as percentages. One way-ANOVA test was used to assess the effect of DMARS drug intake either single or combination on antispike antibody production in RA patients who have taken COVAXIN and COVISHIELD vaccines, separately. The antispike antibodies were expressed as median (IQR). Mann–Whitney test was used for significant difference in IL-6, CRP, and antispike antibody levels between COVAXIN and COVISHIELD subgroups of RA patients and healthy controls. One way-ANOVA test was used to assess the effect of RA disease duration on antispike antibody production in COVISHIELD and COVAXIN vaccine subgroups among RA patients. $P < 0.05$ was considered statistically significant.

Results

The study comprised 183 healthy controls (2 out of 185 received other vaccines) and 103 RA patients. The mean ages of 43.6 ± 10.2 and 44.2 ± 9.9, among RA patients who received COVAXIN ($n = 21$) and COVISHIELD ($n = 82$), respectively, and it was 35.6 ± 11.7 and 30.3 ± 8.2 in healthy controls for COVAXIN and COVISHIELD recipients, respectively. They had not received any other vaccines prior to receiving these vaccines. In the COVISHIELD-received RA group, 89% were female compared to 75% in the healthy control group and 44% had comorbidities, with hypothyroidism being the more common disease. In the same group, 89 tested positive for RA factor, and DAS-28 indicated low disease activity in both COVAXIN and COVISHIELD groups. Details are shown in Table 1.

Laboratory investigations, including Hb levels, RBC, ESR, LFT, and RFT, IL-6 among RA patients and control groups who received COVAXIN and COVISHIELD vaccines, are detailed in Table 2. The majority in both groups had negative CR*P* values. Mann–Whitney tests revealed no significant difference in IL-6 ($P = 0.2385, 0.2569$), CRP ($P = 0.5704, 0.4461$), and antispike antibody levels ($P = 0.4177, 0.0583$) between COVAXIN and COVISHIELD subgroups in RA patients and healthy controls, respectively. The antispike antibody levels between COVAXIN and COVISHIELD were not significantly different in RA patients ($P = 0.4177$) and were also not significantly different in the control group ($P = 0.0583$). [Figure 1].

Most RA patients in both COVAXIN and COVISHIELD groups were on a three-drug combination of DMARDs (71% and 62%, respectively). ANOVA results indicated a statistically significant difference in antibody concentration among various DMARDs usage groups ($P = 0.0139$) in COVAXIN-vaccinated RA patients. *Post hoc* tests revealed a significant difference in

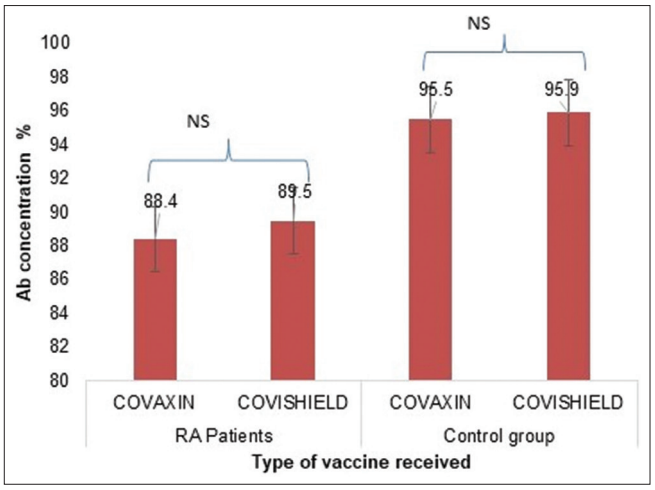

Figure 1: Antispike antibodies to COVAXIN and COVISHIELD in RA patients and healthy control group. Bar diagram illustrating the comparison of antispike antibody levels between COVAXIN and COVISHIELD vaccines in RA patients and a healthy control group. Each bar represents the mean antibody concentration (expressed in arbitrary units) measured 1 year after the second dose of vaccination, with error bars indicating standard deviation. RA patients are categorized by vaccine type (COVAXIN or COVISHIELD), while a separate category represents the healthy control group. No significant difference in antibody levels observed between COVAXIN and COVISHIELD subgroups within RA patients and healthy controls. NS = Not significant, $P < 0.05$ is considered as statistically significant

Table 1: Demographic and clinical characteristics of COVAXIN and COVISHIELD vaccine groups among RA cases and controls

Parameter	COVAXIN (RA) (*n*=21)	COVISHIELD (RA) (*n*=82)	COVAXIN (Control) (*n*=14)	COVISHIELD (control) (*n*=169)
Age (mean±SD)	43.6±10.2	44.2±9.9	35.6±11.7	30.3±8.2
Male [*n*] (%)	2 (9.52)	9 (10.98)	8 (57.14)	94 (55.62)
Female [*n*] (%)	19 (90.48)	73 (89.02)	6 (42.86)	75 (44.38)
Comorbid status – *n* (%)			NA	NA
Diabetes mellitus (DM)	0 (0)	6 (7.32)		
Hypertension (HTN)	2 (9.5)	8 (9.7)		
DM+ HTN	1 (4.8)	6 (7.3)		
Hypothyroidism	3 (14.3)	14 (17.1)		
Hyperthyroidism	0 (0)	1 (1.2)		
Polycystic ovarian disease	1 (4.76)	0 (0)		
Pulmonary tuberculosis	0 (0)	1 (1.2)		
Renal disease	0 (0)	0 (0)		
Ischemic heart disease	0 (0)	1 (1.2)		
Central nervous disorders	1 (4.7)	0 (0)		
NIL	14 (66.7)	46 (56.1)		
Covid-19 infection history, *n* (%)	2 (9.5)	12 (14.6)		
RA positive (*n*)	14 (66.7)	73 (89)	NA	NA
RA negative (*n*)	5 (23.8)	5 (6.1)	NA	NA
DAS-28 score (mean±SD)	2.85±0.96	2.94±1.10	NA	NA

DAS-28: disease activity score, NA: not applicable, RA: rheumatoid arthritis

Table 2: Levels of laboratory study variables among COVAXIN and COVISHIELD vaccine groups among RA patients and healthy controls

Investigation (units)	RA Patients (*n*=103)		Healthy controls (*n*=183)	
	COVAXIN Median (Range)	COVISHIELD Median (Range)	COVAXIN Median (Range)	COVISHIELD Median (Range)
Hb (g/dL)	11.7 (8.2–14.8)	11.7 (8–14.6)	14.3 (11.1–17.4)	14.1 (4.8–18.8)
RBC count ($\times 10^6$/microL)	3.3 (1.1–6.5)	3.4 (1.9–6.4)	4.9 (3.9–6.6)	4.8 (2.7–60.8)
WBC count	8.4 (4.8–17.4)	8 (2.5–17.4)	7 (3.9–10.4)	7.3 (3.5–90.5)
ESR (mm/hr)	20 (5–70)	23 (5–82)	18 (7–60)	16.5 (1–52)
Creatinine (mg/dL)	0.7 (0.5–1)	0.6 (0.4–1.6)	0.7 (0.4–0.9)	0.8 (0.4–14)
Urea (mg/dL)	19 (12–39)	19 (13–55)	16.5 (11–35)	18 (0.9–40)
Total bilirubin (mg/dL)	0.5 (0.3–1.4)	0.4 (0.2–1.1)	0.8 (0.3–1.7)	0.6 (0.2–3.1)
SGOT (U/L)	21 (11–161)	19 (8–58)	22.5 (10–125)	18 (7–172)
SGPT (U/L)	22 (8–110)	20 (6–44)	25 (19–132)	24 (0–500)
ALP (U/L)	89 (43–195)	82 (6.2–212)	82.5 (63–346)	79 (31–183)
IL-6 pg/mL	9.5 (1.5–27.7)	8.5 (1.5–140)	2.3 (1.1–6.8)	3.2 (1–28.7)
CRP (mg/L)	2 (1–2)	2 (1–2)	2 (1–2)	2 (1–2)

Values are presented as median (interquartile range). RA: rheumatoid arthritis, Hb: hemoglobin, RBC: red blood cell, WBC: white blood cell, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, SGOT: serum glutamic oxaloacetic transaminase, SGPT: serum glutamic pyruvic transaminase, ALP: alkaline phosphatase, IL-6: interleukin-6, CRP: C-reactive protein

mean anti-spike antibody levels between 3 drug regimes and HCQ alone users ($P = 0.049$). However, DMARDs usage groups did not differ in antispike antibody concentration among the COVISHIELD group ($P = 0.0959$) [Table 3].

There was no significant difference in the mean levels of percentage of serum antispike antibodies between the RA group who had a past COVID-19 infection or received a booster dose of the COVID-19 vaccine and those who did not.

In RA patients, antispike antibody concentration correlated with disease duration. The analysis of antispike antibody concentrations in relation to the duration of disease among RA patients revealed no statistically significant differences in antibody levels for both COVAXIN ($P = 0.1113$) and COVISHIELD ($P = 0.6329$) groups. Both vaccines show relatively stable antibody levels across different disease durations. COVAXIN shows higher antibody levels for patients with a disease duration of less than 1 year but lower levels in the 1-3 years category compared to COVISHIELD. There is no significant decline in antibody levels with increasing disease duration for either vaccine, indicating a consistent immune response over time [Table 4 and Figure 2].

Discussion

COVID-19 vaccinations have been demonstrated to prevent COVID-19 infection. Nonetheless, participants in the initial vaccination studies were in good health, did not have a known

Table 3: Effect of DMARDs drug intake either on antispike antibody production in COVISHIELD and COVAXIN received RA patients

Parameters	COVAXIN (*n*=21)			COVISHIELD (*n*=82)		
	Frequency (%)	Antispike ab concentration (mean±SD)	*P*	Frequency COVISHIELD e (%)	Antispike ab concentration (mean±SD)	*P*
Hydroxychloroquine (HCQ)	1 (4.7)	*97.32	0.0139	5 (6.1)	95.38±3.47	0.0959
Methotrexate	2 (9.5)	91.87±2.46		6 (7.3)	87.28±5.34	
Prednisolone	1 (4.8)	91.29		1 (1.2)	*98.28	
2 drug combination						
HCQ and Methotrexate OR HCQ and Sulfasalazine OR Methotrexate and Prednisolone OR Methotrexate and Leflunomide	2 (9.5)	92.035±2.96		15 (18.3)	90.45±3.78	
3 drug combination		87.14+3.06				
HCQ+ Methotrexate+ Prednisolone OR HCQ+ Methotrexate+ Leflunomide	15 (71.4)			51 (62.2)	87.85±7.44	
4 drug combination		--				
HCQ+ Methotrexate+ Prednisolone+ Leflunomide	0 (0)			4 (4.9)	87.94±3.57	

P<0.05 is considered statistically significant * Standard deviation cannot be calculated as there is only one case in this group

Table 4: Effect of duration of RA disease on anti-spike antibody levels to COVAXIN and COVISHIELD vaccine

Duration in years	COVISHIELD (*n*=81)			COVAXIN (*n*=21)		
	n	Antispike antibody level	*P*	*n*	Antispike antibody level	*P*
<1	24	87.24±9.88	0.6329	11	90.35±3.90	0.1113
1–3	17	90.38±2.91		3	83.69±0.63	
3–5	15	88.83±4.34		1	86.91	
5–10	11	90.03±5.11		4	88.29±1.19	
>10	14	89.04±6.69		2	89.19±6.24	

P<0.05 is considered statistically significant

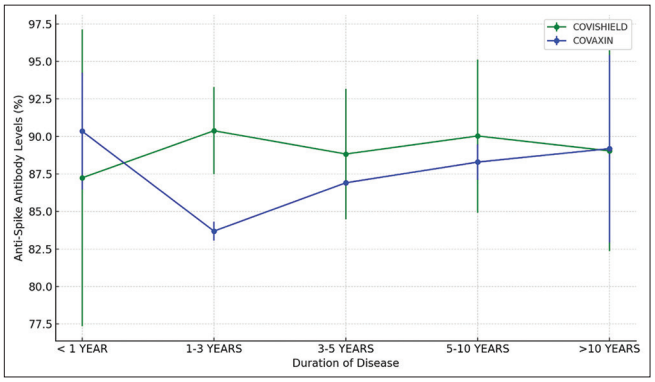

Figure 2: Antispike antibody concentration by disease duration in RA patients. This figure shows the mean concentration of antispike antibodies in RA patients vaccinated with either COVAXIN or COVISHIELD, plotted against the duration of their disease. The X-axis indicate the duration of disease in years, whereas the Y-axis indicates antispike antibody levels (%). Green markers for COVISHIELD and blue markers for COVAXIN, with error bars representing standard deviations. The figure includes error bars to indicate the variability within each group

chronic illness, and were not undergoing immunosuppressive therapies. Numerous studies have revealed inadequate immune responses to the COVID-19 vaccine in groups of patients with chronic illnesses and those undergoing immunosuppressive treatment. An in-depth knowledge of humoral immunity dynamics is necessary to develop effective immunization programs. In this context, the current cross-sectional study looked at the long-term antibody responses to the COVAXIN and COVISHIELD vaccines in patients with RA and a healthy control group 1 year after the second vaccination.

We recruited 103 RA patients (21 COVAXIN and 82 COVISHILED) and 183 control (14 COVAXIN and 169 COVISHILED). During the study period, from May 2022 to December 2022, COVAXIN availability was limited due to production constraints, leading to lower vaccination rates compared to COVISHIELD. As of March 2023, statistics indicate that COVISHIELD vaccinations in India outnumbered COVAXIN vaccinations by approximately five times. This disparity in vaccine distribution likely contributed to the lower number of participants in the COVAXIN group (21 RA patients and 14 healthy controls) compared to the COVISHIELD group (82 RA patients and 169 healthy controls) in our study.[11]

In this study, we selected antispike antibodies as the primary outcome parameter for assessing the immune response to COVID-19 vaccines, due to their central role in viral neutralization, direct targeting by vaccine design, strong correlation with protective immunity, and availability of standardized measurement methods, practical feasibility, and clinical relevance.

The studies such as by Barnes *et al.*[12] have demonstrated that immunosuppressive medication is linked to a less-than-ideal serological response to immunization. Our findings support this, showing a statistically significant difference in antibody concentrations among different DMARDs usage groups in RA patients who had received the COVAXIN vaccine, compared to the COVISHIELD group. This suggests that the type of vaccine may influence the immune response in the context of

immunosuppressive therapy. Additionally, we found that disease duration correlates with antispike antibody levels, although this correlation did not differ significantly between the two vaccine types.

A multitude of confounding variables, such as gender, age, and co morbidities, influence the humoral immune response. Age and humoral response were negatively correlated in RA patients, which was in line with earlier research findings for the general population.[13,14] However, our study did not find any significant correlation regarding age and gender[8] and disease duration. We were unable to find any difference, despite the fact that women are better at producing antibodies and that a Korean study found that female AstraZeneca vaccine recipients had higher titer.[15] In our cohort, 44% of RA patients had comorbidities, with hypothyroidism being more common in both groups and low disease activity.

Furthermore, our cohort did not show any variation in vaccination effectiveness among individuals with varying comorbidities, which is consistent with the results of the published clinical trials.

Numerous studies have reported suboptimal COVID-19 vaccine immune responses in cohorts of patients with chronic disease and in those receiving immunosuppressive therapy.[15-17] Our study demonstrated that, 1 year after receiving a second dose of the COVID-19 vaccine, antibody titers were maintained with no difference in either of the vaccine groups, despite the fact that the titers were lower than those of the control group. Additionally, we noted that antispike antibodies do not correlate with the length of the disease.

Elevated levels of inflammatory markers like CRP, IL-6 are associated with high morbidity in COVID-19 infection.[18] Vaccination against COVID-19 mitigate the elevation of cytokine and chemokine concentrations and hence have long term benefit in decreasing the inflammation. The inflammatory nature of their rheumatoid disease may account for our findings, which indicated that vaccinated RA patients had higher levels of IL-6 than healthy vaccinated controls, though the differences were not statistically significant. Further research is needed to clarify these dynamics. In another prospective study, immunologic responses to SARS-CoV-2 mRNA vaccination were assessed in 82 patients with neuroimmunologic disorders on anti-CD20 therapy in comparison with 82 age- and sex-matched healthy controls. Specific antibodies to SARS-CoV-2 were found to be lower in these patients. Seroconversion rates were lower in B cell-depleted patients compared to nondepleted patients.[19]

In an international Global Rheumatology Alliance Vaccine Survey of adults with systemic rheumatic disease who received COVID-19 vaccination showed that that patient-reported adverse events were similar to those reported in the general population. Less than 5% of participants experienced rheumatic disease flares that required medication changes. Furthermore, most patients were willing to temporarily discontinue DMARDs to enhance vaccine efficacy.[20]

Our study results align with those of Prendecki M *et al.*,[21] who investigated the effects of immunosuppressive therapies on the immunogenicity and efficacy of SARS-CoV-2 vaccination. They found that while SARS-CoV-2 vaccines do elicit an immune response in patients on immunosuppressive treatments, the response is weaker compared to that in healthy individuals.

RA patients frequently take immunosuppressive medicines and have underlying immunological dysregulation. Earlier research excluded these patients, resulting in limited information regarding the effectiveness of the COVID-19 vaccines in this vulnerable population. Consequently, the safety and success of vaccination in RA patients remained uncertain, and their antibody response patterns were more complicated. It is unclear whether these patients require a specific immunization regimen or if they need to temporarily discontinue immunosuppressive therapy (IST) before and after vaccination.

This uncertainty has been a significant concern for RA patients and healthcare providers regarding the COVID-19 vaccine's antibody response patterns in these individuals.

Assessing the antibody response in RA patients is critical, particularly in determining the necessity of stopping or continuing IST during vaccination to balance the risk of disease flare-ups against the risk of COVID-19 infection. Our study underscores the complex interplay between COVID-19 vaccination and immunosuppressive therapy in RA patients. Both COVAXIN and COVISHIELD vaccines generate an immune response, but their effectiveness is influenced by the type of immunosuppressive treatment, disease duration, and patient co morbidities. Despite lower antibody titers compared to healthy controls, vaccinated RA patients maintained their antibody levels 1 year postvaccination. This highlights the need for tailored vaccination strategies in immunocompromised populations to optimize vaccine efficacy and enhance protection against COVID-19.

Conclusion

Our study findings demonstrate that immunosuppressive medications in RA patients significantly impact serological responses to these vaccines, with variations noted between different DMARDs usage groups. Despite the reduced antibody titers in RA patients, the vaccines still provided sustained immune responses 1 year postvaccination.

The vaccine type, disease duration, and patient co morbidities influence the humoral immune response in RA patients. While both COVAXIN and COVISHIELD were effective, COVAXIN showed a statistically significant difference in antibody concentrations among DMARDs users, suggesting its potential advantage in this patient population.

Given the complex dynamics of immune responses in RA patients undergoing immunosuppressive therapy, our study underscores the importance of personalized vaccination strategies. Further

research is essential to explore the underlying mechanisms and develop more effective vaccination protocols for this group.

Limitations

This is an additional analysis from the original study examining long-term antibody responses to COVAXIN and COVISHIELD vaccines in RA patients and a healthy control population. Only 103 RA participants were recruited. The unequal sample size distribution was due to variable recruitment rates and participant availability. Another reason is the post vaccination duration where many of RA patients were already crossed 1 year by the time of our recruitment. Age- and sex-matched controls for RA patients could not be recruited because RA is more prevalent in females. The COVAXIN group was too small ($N = 21$), making statistical analysis regarding the number of drugs and disease duration likely underpowered. Correlation of antispike antibody levels with different vaccines, age, and sex was not performed.

Ethics committee approval

Approval letter no: AIIMS/BBN/IEC/AUG/2021/60-R Date: 05-09-2022 and Ref No: 799/U/IEC/ESICMC/F490/09/2022 dated 31.10.2022). Consent was obtained from participants during the study.

Key message

- Both COVAXIN and COVISHIELD vaccinations elicited comparable antispike antibody responses in RA patients, suggesting similar effectiveness in this population.
- Despite prevalent comorbidities, there were no significant differences in antibody levels between COVAXIN and COVISHIELD subgroups.
- Variability in antispike antibody concentration was observed among different DMARDs regimens in COVAXIN-vaccinated RA patients but this was not significant
- Disease duration did not significantly affect antispike antibody levels in either COVAXIN or COVISHIELD groups, suggesting that vaccination efficacy remained consistent irrespective of disease progression in RA patients

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Conflicts of interest

There are no conflicts of interest.

References

1. Ella R, Vadrevu KM, Jogdand H, Prasad S, Reddy S, Sarangi V, *et al.* Safety, and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: A double-blind, randomised, phase 1 trial. Lancet Infect Dis 2021;21:637-46.
2. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, *et al.* Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: An interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397:99-111.
3. Das S, Kar SS, Samanta S, Banerjee J, Giri B, Dash SK. Immunogenic and reactogenic efficacy of Covaxin and Covishield: A comparative review. Immunol Res 2022;70:289-315.
4. Tripathy A, Swain N, Gupta B. The COVID-19 pandemic: an increased risk of rheumatoid arthritis. Future Virol. 2021;10.2217/fvl-2020-0393. doi:10.2217/fvl-2020-0393.
5. Mahil SK, Bechman K, Raharja A, Domingo-Vila C, Baudry D, Brown MA, *et al.* The effect of methotrexate and targeted immunosuppression on humoral and cellular immune responses to the COVID-19 vaccine BNT162b2: A cohort study. Lancet Rheumatol 2021;3:e627-37.
6. 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 sub study of data from two prospective cohort studies. Lancet Rheumatol 2021;3:e778-88.
7. Deepak P, Kim W, Paley MA,Yang M, Carvidi AB, El-Qunni AA *et al.* Glucocorticoids and B Cell Depleting Agents Substantially Impair Immunogenicity of mRNA Vaccines to SARS-CoV-2. Preprint. medRxiv. 2021;2021.04.05.21254656. doi:10.1101/2021.04.05.21254656.
8. Eerike M, Parimi VP, D M, Pyati A, Sundaramurthy R, Sakthivadivel V, *et al.* Clinical and immunological responses to COVID-19 vaccination in rheumatoid arthritis patients on disease modifying antirheumatic drugs: A cross-sectional study. J Rheum Dis 2024;31:15-24.
9. 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. Erratum in: Ann Rheum Dis 2022;81:e133. doi: 10.1136/annrheumdis-2021-220647corr1.
10. Singh AK, Phatak SR, Singh R, Bhattacharjee K, Singh NK, Gupta A, *et al.* Antibody response after first and second-dose of ChAdOx1-nCOV (Covishield™®) and BBV-152 (Covaxin™®) among health care workers in India: The final results of cross-sectional coronavirus vaccine-induced antibody titre (COVAT) study. Vaccine 2021;39:6492-509.
11. Available from: https://dashboard.cowin.gov.in/.
12. Barnes E, Goodyear CS, Willicombe M, Gaskell C, Siebert S, I de Silva T, *et al.* 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.
13. Brockman MA, Mwimanzi F, Lapointe HR, Sang Y, Agafitei O, Cheung PK, *et al.* Reduced magnitude and durability of humoral immune responses to COVID-19 mRNA vaccines among older adults. J Infect Dis 2022;225:1129-40.
14. Kusunoki H, Ekawa K, Ekawa M, Kato N, Yamasaki K, Motone M, *et al.* Trends in antibody titers after SARS-CoV-2 vaccination-insights from self-paid tests at a general internal medicine clinic. Medicines (Basel) 2023;10:27.
15. Kim YK, Choi Y, Jung JI, Kim JY, Kim MH, Curtis J, *et al.* Modeling of antibody responses to COVID-19 vaccination in patients with rheumatoid arthritis. Sci Rep 2024;14:1335.
16. Martin P, Gleeson S, Clarke CL, Thomson T, Edwards H, Spensley K, *et al.* Comparison of immunogenicity

and clinical effectiveness between BNT162b2 and ChAdOx1 SARS-CoV-2 vaccines in people with end-stage kidney disease receiving haemodialysis: A prospective, observational cohort study. Lancet Reg Health Eur 2022;21:100478.

17. Furer V, Eviatar T, Freund T, Peleg H, Paran D, Levartovsky D, *et al.* Immunogenicity induced by two and three doses of the BNT162b2 mRNA vaccine in patients with autoimmune inflammatory rheumatic diseases and immunocompetent controls: A longitudinal multicentre study. Ann Rheum Dis 2022;81:1594-602.
18. Mahat RK, Panda S, Rathore V, Swain S, Yadav L, Sah SP. The dynamics of inflammatory markers in coronavirus disease-2019 (COVID-19) patients: A systematic review and meta-analysis. Clin Epidemiol Glob Health 2021;11:100727. Erratum in: Clin Epidemiol Glob Health 2022;13:100991.
19. Kornek B, Leutmezer F, Rommer PS, Koblischke M, Schneider L, Haslacher H, *et al.* B Cell Depletion and SARS-CoV-2 vaccine responses in neuroimmunologic patients. Ann Neurol 2022;91:342-52.
20. Sattui SE, Liew JW, Kennedy K, Sirotich E, Putman M, Moni TT, *et al.* Early experience of COVID-19 vaccination in adults with systemic rheumatic diseases: Results from the COVID-19 Global Rheumatology Alliance Vaccine Survey. RMD Open 2021;7:e001814.
21. Prendecki M, Clarke C, Edwards H, McIntyre S, Mortimer P, Gleeson S, *et al.* Humoral and T-cell responses to SARS-CoV-2 vaccination in patients receiving immunosuppression. Ann Rheum Dis 2021;80:1322-9.