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Effect of time interval and immunosuppressive treatment on durability of humoral immune response in rheumatoid arthritis patients following COVID-19 vaccination

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Abstract

Background and objective: The durability of humoral immune response for medium term period of COVID-19 vaccines in Rheumatoid arthritis patients and the role of immunosuppressive treatment have not been yet well investigated. Therefore, we aimed to evaluate the influence of time and immunosuppressive medications on the vaccine efficiency in rheumatoid arthritis patients compare to controls.

Methods: This case control study was conducted from November 2021 to January 2023 included one hundred thirty-one subjects, divided into four groups; where the first group consist of (n=49) unvaccinated rheumatoid arthritis patients, while the second group consist of (n=34), vaccinated rheumatoid arthritis patients, compared with other two group of healthy subjects (n=25 unvaccinated and 23 vaccinated). Blood samples were collected (12 to 16) weeks after the second vaccine dose receipt for measuring serum IgG.

Results: The difference in mean of IgG between the four study groups was non-significant (*P* = 0.079), the vaccinated rheumatic patients mean IgG 1.43 and 1.65 in vaccinated healthy control. The mean IgG among vaccinated RA patients on biological treatment was 1.70, and higher than non-biological treatment group (1.03). The prevalence of IgG positivity was significantly (*P* = 0.005) higher among the controls (56.3%) than the Rheumatoid arthritis patients (31.3%), and significantly higher among the vaccinated (50.9%) than the unvaccinated (32.4%) with (*P* = 0.033). The same pattern observed when the four groups are compared (*P* = 0.007).

Conclusion: IgG positivity rate obviously decreased mainly in Rheumatoid arthritis groups after medium time interval, with no significant effect for immunosuppressant drugs on vaccination response.

Keywords: Humoral immune response; COVID-19 vaccine; Durability; Immunogenicity; Rheumatic disease.

Introduction

Rheumatoid arthritis (RA), one of immune-mediated inflammatory disorders (IMIDs), is a severe and degenerative autoimmune disease of the joints. Inflammation of the affected joints advances symmetrically, leading to cartilage degeneration, bone erosion, and disability.[1]

Rheumatoid arthritis has a prevalence that is relatively stable across the globe, hovering between 0.5 and 1.0% of the population. However, the disease is more prevalent in particular cultures, such as Indigenous North Americans. Rheumatoid arthritis can strike at any age, although the condition is most prevalent in people's third through fifth decades of life.

Furthermore, the disease affects females at a rate that is two to three times higher than that of males. It is likely that the effects of estrogen on immunological function are a contributing factor in the fact that women are more likely to be affected by this disease.[2] Immune-mediated inflammatory disorders (IMIDs) are

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frequently treated with immunosuppressant or immunomodulator, such as steroids, methotrexate (MTX), thiopurines, small-molecule inhibitors, and a variety of biologic treatments that target critical molecules or cells implicated in the inflammatory response. Patients with IMIDs frequently have an elevated risk of infection due to the disease, immunosuppressive or immunomodulatory medications used to treat the disease, comorbidities, and/or hospitalizations induced by disease flares or consequences.[3-5]

Infections can be averted with chemoprophylaxis and/or vaccination; in fact, recommendations for the management of IMID patients urge vaccination in accordance with local immunization schedules and patient-specific risks, unless there exists contraindications.[6-10] the contemporary severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and the emergence of population-wide vaccination campaigns raise doubts concerning the safety and efficacy of SARS -CoV-2 immunization in IMID patients, especially those under immunomodulatory or immunosuppressive medication. A range of SARS-CoV-2 vaccinations are available, most utilize non-replicating viral vectors or mRNA for the spike protein of the virus, though others use more validated technology, such as inactivated virus or live attenuated virus.[11.12]

It is possible that the medications patients are taking will impact the vaccine's capacity to develop an effective immune response against SARS-CoV-2. To evaluate the effect of immunosuppressant medication on immune response and validate the impact of time interval on the progression of vaccine immune responses in immunosuppressed cohorts over time. Medium to longer-term studies with more diverse study populations are required, thus we aimed to evaluate the effect of immunosuppressive treatments on vaccine's immune response with relative long-time interval (12-16 weeks) after second dose receipt and how far the vaccine is efficient in patients with RA compared with controls.

Methods

Patients and Study Design

The case control study conducted in Hawler medical university/College of Pharmacy/Clinical Analysis Department. One hundred thirty-one subjects were enrolled, adult rheumatoid arthritis patients (aged ≥18 years) recruited into the study according to the following rheumatoid arthritis (RA) (RA)/ACR/European League Against Rheumatism (EULAR) 2010 classification criteria[13] or American College of Rheumatology 2012 (ACR 2012) criteria for RA patients.[14]

Study population divided in to four groups, first group were RA patients of non-vaccinated (n=49), who admitted in rheumatology and medical rehabilitation department in Rizgary Teaching Hospital, second group (n=34) were patients who vaccinated with coronavirus-2 vaccine and they had rheumatoid arthritis compared to healthy controls, in which subdivided into, first subgroup (n=25) was unvaccinated subjects and second subgroup (n=23) was for healthy people who have been vaccinated withcov-2 vaccine. Blood samples were collected at time interval (12-16) weeks after second dose receipt, from the vein of each participant in Rizgary teaching hospital in Erbil city, from November 2021 to January 2023.

The study protocol specified for detecting immunogenicity by measuring the serum IgG neutralizing antibody levels against SARS-CoV-trimeric spike S1/S2 glycoproteins for all groups. Other diseases and medication used have been documented. All Patients were persisted all medications throughout the vaccination period, treatments categorized with its IgG positivity rate and compare to each other's to assess effect of immunosuppressive treatments on vaccine's immunogenicity. Venous blood samples were obtained from enrolled patients by venipuncture.

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Five milliliters were withdrawn from all groups into sterile plain tubes and left for 20 min at room temperature to clot. Then it was centrifuged for 10 min. Serum was separated and stored at -20 ◦C for the later determination of Specific IgG antibody against the virus 2-CoV-SARS by Enzyme Linked-Immuno-Sorbent Assay (ELISA).

The cut off value was used to determine the positive and negative answers, and the index value was applied by dividing the optical absorption of the sample by the cut off value: Cut-off Index (COI) = OD of sample/Cut-off value

The study was approved by the Ethical Committee of collage of pharmacy, in accordance with the Declaration of Helsinki for Good Clinical Practice. All patients and controls provided informed consent before entering the study.

The exclusion criteria included pregnancy, history of past vaccination allergy, and recent COVID-19 infection, cancer, recent MI, liver disease, and renal disease.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 26). Normality of data was checked using the Shapiro-Wilk test, accordingly non-parametric tests were used when indicated. Chi square test of association was used to compare proportions of two or more groups. Fisher's exact test was used when the expected frequency (value) was less than 5 of more than 20% of the cells of the table. Mann-Whitney test was used to compare the mean ranks of two groups. Kruskal-Wallis test and its post hoc test (Dunn-Bonferroni) was used to compare the mean ranks of four groups. A *P* value of ≤ 0.05 was considered as statistically significant.[15]

Results

It is evident in Table 1 that the majority of the control group individuals (whether vaccinated or not) were aged less than 40 years range (from 18 up to 40 years), while the majority of the rheumatoid arthritis (RA) patients were aged ≥ 40 years with range (from 40 up to 70 years), there were significant differences in the age distribution of the patients and controls (*P* <0.001).The largest proportion (91.8%) of the unvaccinated RA patients were females, compared with 68% of the unvaccinated controls (*P* = 0.047).

The majority (87%) of the whole sample were living in urban area, but there was no significant difference between the groups (*P* = 0.548). Less than half (44.3%) of the whole sample had history of COVID-19 attack, but the difference was not significant between the groups (*P* = 0.446) (Table 1).

The duration of the disease of more than half (55.9%) of the vaccinated RA patients was ≥ 15 years, compared with 16.3% of the unvaccinated RA patients (*P* = 0.001). Around half (41.2%) of the vaccinated RA patients were not taking biological treatment, compared with 14.3% of the unvaccinated RA patients (*P* = 0.026) (Table 2).

https://doi.org/10.15218/zjms.2025.007

Table 1 Basic characteristics

	Control		Rheumatoid arthritis patients		Total	
	Unvaccinated	Vaccinated	Un-vaccinated	Vaccinated		
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	*P*
Age						
< 40	22 (88.0)	22 (95.7)	10 (20.4)	5 (14.7)	59 (45.0)	
40-49	0 (0.0)	1 (4.3)	16 (32.7)	10 (29.4)	27 (20.6)	
50-59	2 (8.0)	0 (0.0)	21 (42.9)	9 (26.5)	32 (24.4)	
≥ 60	1 (4.0)	0 (0.0)	2 (4.1)	10 (29.4)	13 (9.9)	<0.001**
Gender						
Male	8 (32.0)	6 (26.1)	4 (8.2)	7 (20.6)	25 (19.1)	
Female	17 (68.0)	17 (73.9)	45 (91.8)	27 (79.4)	106 (80.9)	0.047**
Residency						
Urban	21 (84.0)	22 (95.7)	41 (83.7)	30 (88.2)	114 (87.0)	
Rural	4 (16.0)	1 (4.3)	8 (16.3)	4 (11.8)	17 (13.0)	0.548**
Previous COVID attack						
Yes	12 (48.0)	13 (56.5)	18 (36.7)	15 (44.1)	58 (44.3)	
No	13 (52.0)	10 (43.5)	31 (63.3)	19 (55.9)	73 (55.7)	0.446*
Total	25 (100.0)	23 (100.0)	49 (100.0)	34 (100.0)	131 (100.0)	

*By Chi square test. **By Fisher's exact test.

Table 2 Duration and biological treatment intake of patients with rheumatoid arthritis by vaccination status

	Rheumatoid arthritis patients		Total	
	Unvaccinated	Vaccinated		
	No. (%)	No. (%)	No. (%)	*P*
Duration of the disease (years)				
< 5	11 (22.4)	2 (5.9)	13 (15.7)	
5-9	20 (40.8)	7 (20.6)	27 (32.5)	
10-14	10 (20.4)	6 (17.6)	16 (19.3)	
≥ 15	8 (16.3)	19 (55.9)	27 (32.5)	0.001*
Biological treatment				
None	7 (14.3)	14 (41.2)	21 (25.3)	
Infliximab	35 (71.4)	16 (47.1)	51 (61.4)	
Adalimumab	1 (2.0)	0 (0.0)	1 (1.2)	
Rituximab	6 (12.2)	4 (11.8)	10 (12.0)	0.026**
Total	49 (100.0)	34 (100.0)	83 (100.0)	

*By Chi square test. **By Fisher's exact test.

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The majority of the vaccinated individuals, whether patients or controls received the Pfizer vaccine, either alone (93%) or in combination with Sinopharm (1.8%) or in combination with AstraZenica (1.8%). No significant difference was detected between the vaccinated controls and the vaccinated RA patients regarding the type of vaccine (*P* = 0.099) (Table 3).

It is evident in table 4 that there were no significant differences between the vaccinated and unvaccinated RA patients regarding the medical history (*P* >0.05) except for the vitamin intake, where 77.6% of the unvaccinated patients used to take vitamins, compared with 50% of the vaccinated patients (*P* = 0.010) (Table 4).

Table 3 Type of the vaccines taken

	COVID vaccinated control	Vaccinated RA patients	Total	
	No. (%)	No. (%)	No. (%)	*P*
Pfizer	20 (87.0)	33 (97.1)	53 (93.0)	
Sinopharm	2 (8.7)	0 (0.0)	2 (3.5)	
Sinopharm and Pfizer	1 (4.3)	0 (0.0)	1 (1.8)	
AstraZenica and Pfizer	0 (0.0)	1 (2.9)	1 (1.8)	0.099*
Total	23 (100.0)	34 (100.0)	57 (100.0)	

*By Fisher's exact test.

Table 4 Medical history of rheumatoid arthritis patients by the vaccination status

	Rheumatoid arthritis patients		Total	
	Unvaccinated N = 49	Vaccinated N = 34		
	No. (%)	No. (%)	No. (%)	*P*
Treatments	49 (100.0)	34 (100.0)	83 (100.0)	0.165**
Corticosteroids	26 (53.1)	20 (62.5)	46 (56.8)	0.576*
Non-corticoid	10 (20.4)	12 (37.5)	22 (27.1)	0.161*
DMARDs	46 (93.9)	32(94.1)	78 (94.0)	1.000**
Vitamins	38 (77.6)	17(50.)	55 (66.2)	0.010*
Diseases and risk factors				
Diabetes	4 (8.7)	7 (20.6)	11 (13.2)	0.160**
Hypertension	11 (23.9)	12 (35.3)	23 (27.7)	0.167*
CVD and MI	4 (8.7)	7 (20.6)	11 (13.2)	0.164**
Obesity	13 (28.2)	5 (14.7)	18 (21.7)	0.109*
FH of atherosclerosis	1 (2.2)	0 (0.0)	1 (1.2)	1.000**
Smoking	1 (2.2)	1 (2.9)	2 (2.4)	1.000**
Family history	10 (21.7)	6 (17.7)	16 (19.3)	0.634*

DMARDS: Disease-modifying antirheumatic drugs
CVD: Cardiovascular disease
MI: Myocardial infarction
FH: Family history

https://doi.org/10.15218/zjms.2025.007

No significant difference was detected between the four groups in the mean and mean rank of IgG level (*P* = 0.079), as presented in Table 5.

No significant differences were detected between the unvaccinated RA patients and the vaccinated RA patients whether they were not on biological treatment (*P* = 0.913) or they were on biological treatment (*P* = 0.668). The mean IgG among vaccinated RA patients who were on biological treatment was 1.70, which was higher than that of the unvaccinated RA patients (1.37), and the difference was not significance (*P* = 0.668) (Table 6).

Table 5 Immune response (IgG) of the four study groups

	N	Mean IgG	(SD)	Mean rank	*P**
A) Unvaccinated control	25	1.46	1.15	66.44	
B) Vaccinated control	23	1.65	1.05	83.87	
C) Unvaccinated RA patients	49	1.32	1.64	59.38	0.079
D) Vaccinated RA patients	34	1.43	1.56	63.13	
Total	133	1.43	1.43		

*By Kruskal Wallis test. Post-hoc test was not done because the *P* value was not significant.

Table 6 IgG level of unvaccinated and vaccinated rheumatoid arthritis patients whether they are taking biological treatment or not

	Unvaccinated RA patients			Vaccinated RA patients			*P**
	Mean IgG	SD	Mean rank	Mean IgG	SD	Mean rank	
No biological treatment	1.00	0.84	10.71	1.03	0.84	11.14	0.913
Biological treatment	1.37	1.74	30.82	1.70	1.88	32.93	0.668

*By Mann Whitney test.

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In present study no significant association was detected between IgG positivity with the following factors: age (*P* = 0.632), gender (*P* = 0.191), residency (*P* = 0.552), biological treatment intake (*P* = 0.439), biological treatment types (*P* = 0.372), smoking (*P* = 0.530), and duration of the disease (*P* = 0.201). On the other hand, the prevalence of IgG positivity was significantly (*P* = 0.005) higher among the controls (56.3%) than the RA patients (31.3%), and it was significantly (*P* = 0.033) higher among the vaccinated (50.9%) than the unvaccinated (32.4%). The same pattern can be observed when the four groups are compared (*P* = 0.007) as presented in Table 7.

Table 7 IgG positivity by the studied factors

	IgG positivity			
	Negative	**Positive**	**Total**	***P* value**
Group				
Unvaccinated control	12 (48.0)	13 (52.0)	25 (100.0)	
Vaccinated control	9 (39.1)	14 (60.9)	23 (100.0)	
Unvaccinated RA Patients	38 (77.6)	11 (22.4)	49 (100.0)	
Vaccinated RA Patients	19 (55.9)	15 (44.1)	34 (100.0)	0.007*
Age (years)				
< 40	34 (57.6)	25 (42.4)	59 (100.0)	
40-49	19 (70.4)	8 (29.6)	27 (100.0)	
50-59	18 (56.3)	14 (43.8)	32 (100.0)	
≥ 60	7 (53.8)	6 (46.2)	13 (100.0)	0.632*
Gender				
Male	12 (48.0)	13 (52.0)	25 (100.0)	
Female	66 (62.3)	40 (37.7)	106 (100.0)	0.191*
Residency				
Urban	69 (60.5)	45 (39.5)	114 (100.0)	
Rural	9 (52.9)	8 (47.1)	17 (100.0)	0.552*
Biological treatment intake				
Yes	44 (71.0)	18 (29.0)	62 (100.0)	
No	13 (61.9)	8 (38.1)	21 (100.0)	0.439*
Biological treatment types				
None	13 (61.9)	8 (38.1)	21 (100.0)	
Infliximab	34 (66.7)	17 (33.3)	51 (100.0)	
Adalimumab	1 (100.0)	0 (0.0)	1 (100.0)	
Rituximab	9 (90.0)	1 (10.0)	10 (100.0)	0.372**
Smoking				
Yes	1 (50.0)	1 (50.0)	2 (100.0)	
No	30 (69.8)	13 (30.2)	43 (100.0)	0.530**
Duration of disease (years)				
< 5	12 (92.3)	1 (7.7)	13 (100.0)	
5-9	18 (66.7)	9 (33.3)	27 (100.0)	
10-14	9 (56.3)	7 (43.8)	16 (100.0)	
≥15	18 (66.7)	9 (33.3)	27 (100.0)	0.201*
Group (RA / Control)				
Control	21 (43.8)	27 (56.3)	48 (100.0)	
RA	57 (68.7)	26 (31.3)	83 (100.0)	0.005*
Vaccination status				
Unvaccinated	50 (67.6)	24 (32.4)	74 (100.0)	
Vaccinated	28 (49.1)	29 (50.9)	57 (100.0)	0.033*

*By Chi square test. **By Fisher's exact test.

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Discussion

The main goal of the present study was to investigate the medium-term immunogenicity of COVID-19 vaccines, which evaluated by measurement of serum anti-SARS-CoV-2 IgG antibody, in a RA patient and the effect of immunosuppressive treatment compare to healthy control group. According to our study results the relatively low percent of IGg positivity in vaccinated RA group (44.1%) and was statistically significantly lower than vaccinated healthy control group (60.9%), however, this obvious low percent IgG alerts to need for determination over the medium-to-long term and have to be evaluated to monitor the need for earlier revaccination and/or an elevate the vaccine dose to confirm maximizing long-lasting immunity and protection. However, there was no sufficient data on the immunogenicity, efficiency of the COVID-19 vaccine in patients who receives immunosuppressive treatment in medium and long term and further studies are required.

The aforementioned outcome was found in a prospective longitudinal study that observed a significant decline in humoral responses within six months of receiving the second dose of the BNT162b2 vaccine in a large cohort of 4868 healthy individuals.[16] Others, however, reported a steady decline in anti-S IgG titers over the course of 6 months.[16] While there was a rapid decline in neutralizing antibody titers for the first 70–80 days, and the rate of decline slowed after that. However, researchers should proceed with caution when applying these findings because almost all studies used healthy subjects while research on our study time interval for RA patients was limited.

About (96.9%) of vaccinated rheumatoid arthritis patients used of DMARDs (MTX as alone or in combination with other treatments) with no significant difference between vaccinated and unvaccinated RA patients in term of treatment pattern, whereas associated with a significant higher seropositivity rate in vaccinated versus unvaccinated (44.1 vs 22.4 %, P = 0.007), the data of our study implicate for the management of anti-COVID-19 vaccination in patients of RA, with a wide spectrum immunosuppressive treatments, including csDMARDs (Conventional synthetic disease modifying antirheumatic drugs) like methotrexate, sulfasalazine, hydrochloroquine those three agent were taken by our patients, anticytokine biologics and JAKi (Janus kinase inhibitors), can be safely continued without significant attenuating vaccine-induced immunogenicity, this measured outcome also supported by absence of significant difference in the mean and mean rank of IgG level (P = 0.079) between the four study groups (vaccinated, unvaccinated, healthy control and RA patients). This finding is consistent with research showing that patients treated with TNFi (Tumor necrosis factor inhibitors),[17-21] IL-6i (Interleukin 6 inhibitors),[22-24] and IL-17i (interleukin 17 inhibitors) experience significant immunogenicity in response to influenza and pneumococcal vaccinations.[25-28] While JAKi only made up a small percentage of treatments in our analysis, we did find that it had a mild, non-significant negative impact on the production of vaccine-induced antibodies.

Even though it was commonly recommended to postpone the taken of these immunosuppressants before vaccination according ACR,[29] we did not find adequate evidence to support the beneficial effect of such measures, but this is may be due to the lack of relevant trial results, thus there is a need for more research to clarify which prescriptions should withheld and for how long.

Numerous research has demonstrated that the humoral response can persist for weeks or months in healthy people. Without the presence of cancer, autoimmune illness, immunosuppressive medication, or end-stage renal failure, antibody titers were correlated with age and gender.[30] Our data was in contrast

https://doi.org/10.15218/zjms.2025.007

with the above findings in which we showed no significant difference in rate of IgG positivity between study groups from direction of gender, age, type of RA treatment, residency, duration of RA disease, we thought the remarkable causes of such variation were; first, due to a significant difference on period of the time after the second dose receipt as a time point for sample collection, and second the age of a studied groups, However, our time point for sample collection (3-4) months after second dose of vaccine which the IgG may be at a decline phase while the mentioned study time point 50 days after second dose whilst the IgG peaks at the highest level, this is from one hand, the age range from another hand, the study group (median age: 49 years, range: 25–70 years and median age: 85 years, range: 80–95 years)[30] that highly significant differed from age of our study group (healthy control group age range from 18 up to 40 years with mean 26.7 years and RA group from 40 up to 70 with mean 49 years),time interval was 3-4 month after second dose receipt.

However, the time interval between vaccination and time points of sampling, differed essentially among studies, and such interval poorly studied in RA.

Finally, this study has some limitation, the effective one was vaccine hesitancy in both patients and healthy groups that considerably affect sample size, age matching between groups, and the duration of sample collection relatively long, the common causes for refusing vaccination was that, they worried from serious adverse events and disease flare after vaccination.

Second limitation was, several medications mostly received in combination by RA patients, so the impact of single drug in immune response couldn't clearly demonstrate.

Conclusion

It is evident that the IgG positivity rate decreased primarily in RA groups during the time interval of the present study. The immunosuppressant drugs have no significant effect on vaccination response. Immunogenicity of COVID-19 vaccines in rheumatic patients is reasonable, albeit, less than healthy subjects, and it was recommended for full vaccination.

Competing interests

The authors declare that they have no competing interests.

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