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Immunogenicity and Adverse Events after Coronavirus Disease 2019 (COVID-19) Vaccination in Patients with Systemic Inflammatory Autoimmune Diseases

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ABSTRACT

Background: Individuals with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) face a heightened risk of severe coronavirus disease 2019 (COVID-19). However, the effectiveness and safety of vaccines relative to the broader population has been a subject of debate.

Objective: To assess immunogenicity and to compare adverse effects following COVID-19 vaccinations in patients with SLE and RA vs matched healthy controls.

Patients and methods: This work included 30 SLE, 30 RA and 30 age and sex-matched healthy controls. Assessment was done 2-6 weeks after BBIBP-CorV (Sinopharm BIBP COVID-19) vaccine including measuring serum IgG neutralizing anti-spike antibodies, a questionnaire for adverse events and assessing disease activity for patients.

Results: There wasn't significant difference in the titer of neutralizing antibodies between patients and controls (p= 0.51). Fatigue, local redness, and swelling were more in control group (p< 0.0001, p=0.008 and p=0.008 respectively). Tingling sensation was higher in patients (0.006). Disease activity was significantly higher in RA and SLE patients after vaccination (p=0.001 and p=0.002 respectively). Flares occurred in 12 (40%) of SLE patients and 13 (43%) of RA patients, mainly in a mild form (58% of flares in SLE and 62% in RA).

Conclusion: The BBIBP-CorV (Sinopharm BIBP) COVID-19 vaccine is immunogenic in patients and control groups. Adverse events were mainly minor with less frequent fatigue, local swelling and redness and more tingling sensation among SLE and RA than controls. In RA and SLE patients, disease flare may occur after COVID-19 vaccine mainly in a mild form.

Keywords: COVID-19; Autoimmune Diseases; Sinopharm BIBP; RA; SLE.

INTRODUCTION

COVID-19 has been a global epidemic, and immunization is critical to limiting its spread [1].

Many efforts were made to develop a vaccination against the causal agent: SARS-CoV-2 is a coronavirus that causes acute respiratory syndrome. One approach is the classical inactivated vaccines, which employ a viral strain that has been weakened or rendered inactive thus, mounting an immune response without causing the disease (BBIBP-CorV, Chinese Academy of Medical Sciences) [2]. Spike glycoprotein is a highly immunogenic protein, and people who have recovered from coronavirus-related illnesses such as SARS and COVID-19 have antibodies against spike glycoprotein. Therefore, evaluating the serum IgG neutralizing antibody level against this glycoprotein is a good way to assess the immunogenicity and, consequently, the efficacy of the vaccination [3].

COVID-19 vaccinations might have negative effects, just like any other vaccine. The majority of COVID-19 vaccine adverse effects that have been reported are mild to severe and transient, and include fever, exhaustion, headaches, chills, muscular aches, diarrhea, and injection site soreness [4]. However, there were serious side effects reported after launching COVID-19 vaccine. There have been several reports of thrombosis including severe cases of pulmonary embolism that led to death [5].

People with RA and SLE, among other systemic inflammatory autoimmune diseases, are considered to have an elevated risk of SARS-CoV-2 infection because of reduced immunological defenses caused by the disease or medication [6]. This highlights how crucial immunization is for this patient population. Nonetheless, throughout the last 20 years, vaccination hesitation has generally grown. This reticence may have been strengthened with regard to the COVID-19 vaccine due to the quick development of several COVID-19 vaccines and concerns about the potential side effects of several COVID-19 vaccines, particularly thrombosis [7]. This raises concern about vaccination in individuals with systemic inflammatory autoimmune disease mainly SLE and RA in whom thrombosis is already a common encounter [8]. Therefore, it is important to know whether the adverse effects of COVID-19 vaccine are more common in this specific group of patients over healthy controls or not.

The aim of this study was to assess immunogenicity and to compare adverse effect following COVID-19 vaccinations in patients with SLE and RA vs matched healthy controls.

PATIENTS AND METHODS

This study included 30 SLE patients fulfilling the European League Against Rheumatism (EULAR) classification criteria 2019 [9], 30 RA patients fulfilling the EULAR criteria [10], and 30 age-matched healthy controls.

All patients were >18 years old and only patients in remission state, before taking the vaccine as documented in their files, were included. Patients with other autoimmune diseases and those receiving

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immunomodulatory drugs for other causes were excluded.

The Outpatient Clinic of the Department of Internal Medicine - Rheumatology Division at Ain Shams University Hospital was where all patients were recruited. Control participants were chosen among medical and non-medical staff members of Ain Shams University Hospital. The study was carried out 2-6 weeks after vaccination. All participants got 2 doses of BBIBP-CorV vaccination, four weeks apart [11].

All patients had a complete history-taking and clinical assessment. SLE disease activity index (SLEDAI) [12], and disease activity score (DAS28 CRP)[13] for the SLE and RA patients were assessed respectively.

A survey questionnaire in Arabic adapted from **Djanas *et al.*** [14] was handed out to be filled by the participants on day of clinical assessment. It included medical and social background as well as questions about symptoms noticed after taking the vaccine including fever, headache, cough, diarrhea, vomiting, dyspnea, arthritis, arthralgia, fatigue, myalgia, tingling, lymphadenopathy, skin rash, anaphylaxis, local swelling, local redness and occurrence of any clinically diagnosed thrombosis. Serum IgG neutralizing antibody level against SARS-CoV-2 spike glycoprotein was measured quantitatively using Elecsys® Anti-SARS-CoV-2 S immunoassay [15]. It is an electro-chemiluminescence immunoassay; one step double antigen sandwich assay performed on Cobas e411 analyzer (test time 18 min.). Test is interpreted positive if ≥ 0.8 U/mL.

Ethical approval:

The Ethics Committee of the Faculty of Medicine at Ain Shams University has authorized this study (FMASU MS223/2022).

Following receipt of all information, signed consent was provided by each participant. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis

After gathering, editing, coding, and entering the data, IBM SPSS version 23.0 was used. When the quantitative data were parametric, they were shown as mean±SD and range; when they weren't, they were shown as median and interquartile range (IQR). Numbers and percentages were used to represent the qualitative characteristics.

The qualitative data were compared using the X^2-test. The one-way ANOVA test was used to compare more than two groups given quantitative data and a parametric distribution. When the p-value was less than 0.05, it was deemed significant.

RESULTS

There were 30 subjects in each group with similar age and sex distribution. Median disease duration was 4 (2 – 12) years in SLE group and 7 (3 – 14) years in RA group. There was no difference in smoking status or DM but HTN was significantly higher in RD patients (Table 1).

Table (1): Descriptive and Comparative data between control, rheumatoid arthritis and systemic lupus erythematosus groups regarding Demographic data

		Control group	**RA group**	**SLE group**	**P-value**
		No. =30	**No. = 30**	**No. = 30**	
Age	Mean±SD	36.07 ± 13.22	38.57 ± 8.65	35.97 ± 10.99	0.588
	Range	22 – 60	24 – 60	17 – 57	
Sex	Female	20 (40.0%)	26 (86.7%)	26 (86.7%)	0.821
	Male	10 (60.0%)	4 (13.3%)	4 (13.3%)	
DM	No	28 (93.3%)	29 (96.7%)	26 (86.7%)	0.338
	Yes	2 (6.7%)	1 (3.3%)	4 (13.3%)	
HTN	No	26 (86.7%)	18 (60.0%)	12 (40.0%)	**0.001***
	Yes	4 (13.3%)	12 (40.0%)	18 (60.0%)	
Smoking	No	24 (80.0%)	27 (90.0%)	26 (86.7%)	0.533
	Yes	6 (20.0%)	3 (10.0%)	4 (13.3%)	
Disease duration (years)	Median (IQR)	-	7 (3 – 14)	4.0 (2 – 12)	0.414
	Range	-	0.3 – 20	0.1 – 20.0	

*: Significant; DM: Diabetes mellitus; HTN: Hypertension; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus.

The most frequent adverse effects after the vaccine in SLE group were fever (70%) and arthralgia (66.7%), and in RA group were arthralgia (73.3%) and local muscle pain (66.7%), while in the control group there were local muscle pain (73%) and local redness and swelling (70%).

There was higher reporting of local redness and swelling as well as sense of fatigue after the vaccine in the control group in comparison to SLE and RA groups. The subjective sense of tingling sensation was higher in RA then SLE groups than in controls. One SLE patient developed thrombosis in the form of cerebrovascular stroke that caused left sided weakness and dysarthria at the time of the event and improved afterwards.

SLEDAI score of this patient was 17 indicating severe activity. The titer of anti-spike antibodies didn't differ significantly between the groups (Table 2). The titer didn't differ regarding demographic data.

Table (2): Comparison between control, rheumatoid arthritis and systemic lupus erythematosus groups regarding side effects after BBIBP-CorV vaccine and titer of anti-spike antibodies after BBIBP-CorV vaccine

Symptoms	Control group		RA group		SLE group		P-value
	No.	%	No.	%	No.	%	
Fever	19	63.3%	14	46.7%	21	70.0%	0.164
Headache	17	56.7%	10	33.3%	14	46.7%	0.191
Cough	4	13.3%	4	13.3%	5	16.7%	0.914
Diarrhea	2	6.7%	0	0.0%	2	6.7%	0.351
Vomiting	0	0.0%	1	3.3%	2	6.7%	0.355
Dyspnea	1	3.3%	6	20.0%	7	23.3%	0.073
Arthralgia	15	50.0%	22	73.3%	20	66.7%	0.155
Arthritis	0	0.0%	4	13.3%	1	3.3%	0.064
Fatigue	27	90.0%	13	43.3%	15	50.0%	**<0.001***
Muscle pain	22	73.3%	20	66.7%	21	70.0%	0.853
Tingling	0	0.0%	9	30.0%	7	23.3%	**0.006***
LN swelling	0	0.0%	1	3.3%	0	0.0%	0.364
Rash	0	0.0%	0	0.0%	1	3.3%	0.364
Anaphylaxis	0	0.0%	0	0.0%	0	0.0%	NA
Redness	21	70.0%	16	53.3%	9	30.0%	**0.008***
Swelling	21	70.0%	16	53.3%	9	30.0%	**0.008***
Thrombosis	0	0.0%	0	0.0%	1	3.3%	0.364
Titer<250	3	10.0%	4	13.3%	5	16.7%	0.749
Titer>250	27	90.0%	26	86.7%	25	83.3%	

*: Significant; NA: Not applicable; No: Number.

All SLE patients involved in the study were receiving oral steroids and hydroxychloroquine. There was no difference in titer of antibodies with the use of different immunosuppressive medications (Table 3).

Table (3): Comparison between titer of anti-spikes antibodies with the use of different immuno- suppressive drugs.

Treatment	Total		Titer<250		Titer>250		P-value
	No.	%	No.	%	No.	%	
Azathioprine	18	60.0%	4	80.0%	14	56.0%	0.317
Mycophenolate mofetil	6	20.0%	1	20.0%	5	20.0%	1.000
Cyclophosphamide	2	6.7%	0	0.0%	2	8.0%	0.513
Methotrexate	22	73.3%	3	75.0%	19	73.1%	0.935
Leflunomide	8	26.7%	2	50.0%	6	23.1%	0.257

Disease activity as measured by SLEDAI and DAS 28 CRP significantly increased after vaccination and they were mainly mild flares (Table 4).

Table (4): Comparative data in systemic lupus erythematosus and rheumatoid arthritis patients regarding disease activity before and after BBIBP-CorV vaccine

	Before		After			P-value
	No.	%	No.	% of total	% of flares	
SLE group (n = 30)						
Remission	30	100%	18	60.0%		**0.002***
Mild	0	0%	7	23.3%	58%	
Moderate	0	0%	2	6.7%	17%	
Severe	0	0%	3	10.0%	25%	
Total flare	0	0%	12	40%		
SLEDAI (mean ±SD)			18.7 ± 13.9			
RA group (n=30)						
Remission	30	100%	17	56.70%		**<0.001***
Mild	0	0%	8	26.70%	62%	
Moderate	0	0%	4	13.30%	31%	
Severe	0	0%	1	3.30%	7%	
Total flare	0	0%	13	43.3%		
DAS28 CRP (mean ±SD)			4.46 ±0.7			

*: Significant.

DISCUSSION

Vaccination is very important in patients with rheumatic diseases [16], but the safety and effectiveness of vaccinations in these patients have yet to be determined [17].

All subjects in the current study received BBIBP-CorV vaccine as it was the most prevalent vaccine in Egypt at the time of the study.

In this investigation, there wasn't significant difference among patients and controls regarding fever, headache, cough, diarrhea, vomiting, arthralgia, arthritis, muscle pain, LN swelling, rash, anaphylaxis and thrombosis. **Wack *et al.*** [18] studied the safety and effectiveness of the COVID-19 vaccination in patients with immune-mediated inflammatory diseases, and it was found that the frequency and severity of adverse effects were comparable to those in healthy individuals. Similar findings were reported by **Furer *et al.*** [19] in their study on safety and immunogenicity of the BNT162b2 mRNA (Pfizer) COVID-19 vaccine and **Hasseli *et al.*** [20] on mRNA vaccines using an online survey. However, in their study, compared to healthy controls, patients with immunological disorders had more frequently minor systemic side effects as tiredness and myalgia (53.8% vs. 43.2% and 42.3% vs. 31.6%). Regarding headaches, a same trend was seen (38.5% vs. 35.1%). Fever was reported by 13.5% of the healthy sample, whereas it was totally absent in the sick. Pain was similar in the two groups. Both groups also reported experiencing chest discomfort, nausea, and vomiting, as well as an aggravation of pre-existing asthma. On the other hand, in the current study, fatigue, local redness and swelling were reported more in control group. This could be explained by the intake of steroids in patients' groups[21]. Tingling sensation were more in patients' group than in controls. This could be a part of disease flare or a specific side effect awaiting further studies.

In contrast to these results, another work [22] on 128 individuals with SLE and 154 with RA in comparison with a control group stated that local and systemic reactogenicity were reported more in patients. Nevertheless, as both studies were carried out on a small sample size and following distinct different vaccination, it is difficult to draw firm conclusions from them.

Thrombosis is a major concern of COVID-19 vaccines. Events of vaccine-induced thrombosis with thrombocytopenia syndrome are not restricted to the time following vectored vaccinations; they can also sporadically arise following immunization with other vaccines, such as BBIBP-CorV [23,24]. In the current study, one SLE patient experienced stroke after vaccination in the context of disease activity but no significant association with the vaccine could be proved. This is in support of the safety of inactivated COVID-19 vaccines [25]. Meanwhile, many other studies didn't find thrombosis a concern after vaccination [26,27].

In this study, there wasn't statistically significant difference between the studied groups regarding titer of anti-spike antibodies after 2 doses of BBIBP-CorV vaccine, with a percentage having an antibody titer >250 of 90%, 86.7%, 83.3% in control, RA and SLE groups respectively.

This is similar to the reported seroconversion percentage of 79% after BBIBP-CorV in a review by **Ghiasi *et al.*** [26] and in agreement with **Medeiros-Ribeiro *et al.*** [28] who carried out a phase IV study of the CoronaVac (Sinovac COVID-19) on 1,193 individuals with autoimmune rheumatic illnesses and 492 controls and found that with the second vaccination dose, there was a noteworthy humoral response of neutralizing IgG Ab against SARS-CoV-2 virus. Also, with the study done by **Gianfrancesco *et al.*** [29] on 1147 healthy controls, 546 individuals with

multiple sclerosis, and 3682 individuals with rheumatic illnesses, following the second dosage, seroconversion surpassed 80% in every patient treatment cohort with the exception of those receiving anti-CD20 therapy. A rate of 86% was reported by **Braun-Moscovici *et al.*** [27].This point raises concern about the importance of receiving more than one dose of the vaccine in rheumatological patients. The CDC suggests (with FDA authorization) that a third primary series dose, given at least 28 days after the second dose of COVID-19 vaccine for certain immunocompromising conditions [30].

In the current study, the use of conventional immune suppressive drugs did not affect the titer of antibodies significantly; namely methotrexate (MTX) and leflunomide in RA group, and azathioprine, mycophenolate mofetil (MMF) and cyclophosphamide in SLE group. All patients were on corticosteroids and hydroxychloroquine. **Gianfrancesco *et al.*** [29] showed that seroconversion rates were comparable across all of their designated treatment groups (treatment with prednisone monotherapy, TNF inhibitor monotherapy, MTX, anti-TNF therapy and MTX and anti-CD20 therapy) except from patients on anti-CD20 medications, of whom just 3 (43%) out of 7 were seropositive. They also reported that therapy with MTX resulted in lower antibody titer after the first dose, but patients mounted a sufficient immune response after the second.

Wack *et al.*'s study [18] revealed that patients on B-cell-depleting treatments, such as rituximab, belimumab, and ocrelizumab, had the greatest decrease in immunological response to the COVID-19 vaccinations that were then available. Additionally, when 133 adults with chronic inflammatory diseases were compared to 53 immunocompetent controls, **Deepak *et al.*** [31] discovered that, when compared to other biologics and disease-modifying anti-rheumatic drugs (DMARDs), patients receiving B-cell depleting agents had the greatest reduction in antibody response. **Furer *et al.*** [19] **and Braun-Moscovici *et al.*** [27] also published findings that were similar. Due to their relative scarcity at our facility, biologics were not used to treat any of the present patients, and those who did get them were unwilling to be vaccinated because they believed there might be adverse consequences.

In concordance, **Braun-Moscovici *et al.*** [27]**,** showed that 86% of participants had a noteworthy humoral response against the SARS-CoV-2 virus following the second vaccination, while 14% did not: Twenty-four out of forty-seven rituximab-treated patients, three out of eight abatacept-treated patients, four out of twenty-one patients treated with MMF only, two out of eleven belimumab-treated patients, and one out of five anti-IL17-treated patients mounted Ab titres approximately one log higher than the patients treated with biologics and MMF alone. **Furer *et al.*** [19] **and Braun-Moscovici *et al.*** [27] found that MMF-treated individuals had reduced vaccination immunogenicity.

In this study MMF did not seem to affect the humoral response but it is hard to draw a conclusion since only 6 out of 30 SLE patients were treated with MMF. **Haberman *et al.*** [32] found a reduced humoral response in MTX-treated patients, in their study, which was conducted on 51 patients versus 26 healthy controls. While in this work, MTX was neutral. Worth to mention that some of their MTX-treated patients were on concomitant treatment with rituximab. All these differences could be explained by the different type of vaccine, different number of participants and different study population.

In the present investigation, no statistically significant difference was found in the titer of ant-spike antibodies regarding age in the studied groups. This is in concordance with **Braun-Moscovici *et al.*** [27] who found that the capacity to establish a strong humoral response was not significantly correlated with the patient's age or the kind of inflammatory rheumatological condition. In contrast, **Müller *et al.*** [33] observed that older age results in lower IgG neutralizing antibodies, but this is because they compared patients younger and older than 60 y while all patients in our study were younger than 60.

In the present investigation, there was a substantial change in terms of disease activity following COVID vaccination, usually in a mild form. This agrees with **Watad *et al.*** [34] who reported that the majority of cases had disease flare that quickly settled with corticosteroid therapy. **Izmirly *et al.*'s study** [35] found that 11.4% of SLE patients had flares, with 1.3% of those cases being severe, however, the change wasn't statistically significant. In contrast, **Furer *et al.*** [19] **and Braun-Moscovici *et al.*** [27] found that post vaccination indices of disease activity remained stable. This could be the result of the difference in population, sample size and the type of the vaccine.

Among the study limitations is that this is a single center experience with a small number of participants that could not allow us to withdraw solid conclusions about the effects of immunosuppressives or other comorbidities. The available kits of the antibodies did not measure titers above 250 U/mL making comparison less accurate. The level of antibodies before vaccination was not measured, and there was no solid data about previous COVID-19 infection. In addition, conclusions cannot be generalized to other COVID 19 vaccines.

CONCLUSION

Adverse events were mainly minor with less frequent fatigue, local swelling and redness and more tingling sensation among SLE and RA than controls. This COVID-19 vaccination is immunogenic in both rheumatic patients and control groups.

The use of multiple immune suppressive medications examined (MTX, azathioprine, MMF, and

cyclophosphamide) did not impact the humoral response following two doses of the vaccine. In RA and SLE patients, disease flare may occur after COVID-19 vaccine mainly in a mild form.

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