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Humoral and Cellular Immunity to Severe Acute Respiratory Syndrome Coronavirus-2 Vaccination in Patients with Sarcoidosis

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Background: The coronavirus disease 2019 vaccine induces both antibody and T-cell immune responses and has been proven to be effective in preventing coronavirus disease 2019, including its severe disease form, in healthy individuals. However, the details of severe acute respiratory syndrome coronavirus-2 immunoglobulin-G antibody responses and severe acute respiratory syndrome coronavirus-2 specific T-cell responses in patients with sarcoidosis are unknown.

Aim: To measure and compare antibody responses and T cell responses using enzyme-linked immunosorbent assays and interferon-gamma release assay in sarcoidosis patients infected with coronavirus disease 2019 and vaccinated with CoronaVac.

Study Design: A prospective cohort study.

Methods: A total of 28 coronavirus disease 2019 polymerase chain reaction test-positive sarcoidosis patients who were infected with severe acute respiratory syndrome coronavirus-2 in the past 6 months and did not have coronavirus disease 2019 vaccination and 28 sarcoidosis patients who were administered with 2 doses of CoronaVac and never had coronavirus disease 2019 were included in this study. The immune response levels of patients were determined by measuring the severe acute respiratory syndrome coronavirus-2 immunglobulinG and interferon-gamma levels in the blood of the patients by the enzyme-linked immunosorbent assays method and interferon-gamma release assay tests, respectively.

Results: The mean age of the patients in the COVID-infected group was 48.1 ± 11.3, while the mean age of the patients in the vaccinated group was 55.6 ± 9.32. The mean time elapsed after infection was 97.32 ± 42.1 days, while 61.3 ± 28.7 days had passed since the second vaccination dose. In the COVID-infected group, immunoglobulin-G and interferon-gamma release tests were positive in 64.3% and 89.3% of the patients, respectively. In the vaccinated group, immunoglobulin-G was positive in 10.7% of the patients, and interferon-gamma release test was positive in 14.3%.

Conclusion: Innate immune responses are better than adaptive immune responses in patients with sarcoidosis. The coronaVac vaccine is insufficient to generate humoral and cellular immunities in patients with sarcoidosis.

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INTRODUCTION

Sarcoidosis is a systemic inflammatory disease that arises resulting from the abnormal accumulation of inflammatory cells into the affected organs. Although the etiopathogenesis of sarcoidosis is not fully understood, it is known to involve the development of immune effector cells that regulate cellular immunity and nonspecific inflammatory response through antigen-presenting cells and antigen-specific T-helper-1 (CD4+) lymphocytes after exposure to an unknown antigen in genetically susceptible individuals and the formation of a granuloma structure.[1] The most involved organs include the lungs and mediastinal lymph nodes, although other organs can be involved.[2] The accumulation of CD4+ lymphocytes in the involved tissues is a characteristic of this disease, while the CD4+ levels remain unaffected or decreased in other tissues and blood.

CD4+ T-lymphocytes are responsible for the regulation of B lymphocytes that generate the antibodies and natural killers and CD8+ lymphocytes to destroy the microorganisms.[3] In viral infections, CD4+ T-cells induce B-cells producing antibodies that may neutralize the viruses, and cytolytic CD8+ T-cells, which kills the virus-infected cells. In sarcoidosis, there is a deficiency in the antigen presentation-response relationships of CD4+ lymphocytes.[4] Cellular immune response and antibody formation may not occur adequately in patients with sarcoidosis infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) owing to the CD4+ lymphocyte defect. Adequate humoral immunity is induced by regular cellular immunity; therefore, insufficient humoral immunity may be present in patients with sarcoidosis. SARS-CoV-2 may provoke T-cell responses without any antibody seroconversion, and these responses may indicate more precisely SARS-CoV-2 exposure than the antibodies. The non-existence of antiviral antibodies after other viral infections has also been reported.[5-7] Vaccination has been accepted as the most effective method to control the pandemic caused by SARS-CoV-2. While effective vaccines continue to be administered, the vaccine-induced immune response remains controversial. Whether patients with sarcoidosis exhibit differential susceptibility to SARS-CoV-2 infection or innate and adaptive immunity status of patients after coronavirus disease-19 (COVID-19) infection remain unknown.

Therefore, we evaluated the level of humoral and cellular immunity status of patients by SARS-CoV-2 immunoglobulin-G (IgG) by using the ELISA method and through the interferon-gamma release assay (IGRA) in the two groups of sarcoidosis patients, which included patients with confirmed COVID-19, but not vaccinated with SARS-CoV-2 vaccine and patients who were vaccinated with two doses of CoronaVac (vaccinated group) and did not have COVID-19.

MATERIAL AND METHODS

Study Design

This study was conducted as a prospective cohort study in a university hospital between December 1, 2020, and June 1, 2021.

Ethical Considerations

Ethical approval was received from the local ethics committee of the university on July 09, 2021 (#137423).

Participants

Inclusion Criteria

All patients aged >18 years and diagnosed with sarcoidosis were included. Patients who tested positive in PCR in the past 6 months and were not yet vaccinated against SARS-CoV-2 were included in the SARS-CoV-2-infected group. Patients who did not have a COVID-19 history, but were immunized with 2 doses of CoronaVac (with the last dose of vaccine given at least 1 month ago) and with no active use of immunosuppressants in the past 6 months were included in the vaccinated group.

Exclusion Criteria

For the SARS-CoV-2-infection group: patients with severe COVID-19 (being followed in the service or intensive care unit during infection).

For all patients: additional underlying diseases that could impair the immune response (e.g., cancer, diabetes mellitus (DM), and chronic kidney failure), having been vaccinated with the Biontech vaccine, or unwilling to provide consent.

Anti-SARS-CoV-2 NCP ELISA (IgG)

In most cases, 3 samples were collected from each volunteer into tubes containing vacuumed separator gel. The serum samples obtained after centrifuging 3 ml of the blood at 5,000 rpm for 5 min were aliquoted in microcentrifuge tubes and stored at -20 °C for further testing. At the beginning of the study, the serum samples were thawed at room temperature. In addition, the ELISA kit was left at room temperature for 30 min before use. The sample sera were diluted (1:101) and the ELISA test was performed in a semi-automatic manner using the Triturus Instrument (Grifols, Barcelona, Spain). The anti-SARS-CoV-2 NCP ELISA (IgG) kit was used in accordance with the specified incubation conditions and test instructions by the manufacturer. A standard curve of different antibody concentrations in the serum samples was generated by plotting the optical density values measured for the 6 calibration serums from point-to-point according to the corresponding units (linear/linear).

For interpreting the results, <0.8 was considered negative, ≥0.8 to <1.1 as the cutoff value, and ≥1.1 as positive.

Anti-SARS-CoV-2 QuantiVac ELISA (IgG)

The serum samples were removed from -20 °C freezers on the day of the test and brought to room temperature. The test kit was then left at the room temperature for 30 min before use. Again, the semi-automated Triturus instrument was used to dilute the samples and execute the test. The Anti-SARS-CoV-2 QuantiVac ELISA (IgG) kit was run in accordance with the specified incubation conditions and test instructions by the manufacturer. The standard curves for

each antibody were generated as described earlier. A "point-to-point" plot was used to calculate the standard curve by a computer. <8 RU/ml was interpreted as a negative result, ≥8 to <11 RU/ml as the cutoff value, and ≥11 RU/ml as the positive result.

SARS-CoV-2 Interferon ɣ Release Test (IGRA)

The whole blood sample was collected in a lithium-heparin blood collection tube, and 0.5 mL of it was transferred into stimulation tubes (CoV IGRA BLANK, CoV IGRA TUBE, and CoV IGRA STIM), with the stimulation tubes left at 37 °C for 16-20 h. At the end of the incubation period, the centrifugation of the stimulation tubes was performed at 12,000 rpm for 10 min. The supernatant of the plasma was then stored in a polypropylene tube at -20 °C for further testing. The interferon-gamma (INF-ɣ) release test was performed in accordance with the manufacturer's guidelines. The photometric color intensity measurement of the ELISA plate was applied in an automatic plate reader (ELx800, BioTek, VT, USA) at the wavelength of 450 nm (reference range: 620-650 nm).

IFN-ɣ concentration was determined using a standard curve. To interpret the results, the OD values were converted to mUI/ml values by using the Magellan F50 program (version 7.2). The results were obtained by adjusting the CoV IGRA tube value with the CoV IGRA blank value. If the value was <100 ml U/ml, the interaction with SARS-CoV-2 was considered negative. If the value was 100-200 ml U/ml, it was considered as the limit value, and a value >200 ml U/ml was considered indicative of a positive interaction with SARS-CoV-2.

Data Collection

Personal and demographic information and COVID-19 and COVID-19 vaccination histories were obtained from the patients. SARS-CoV-2 IGRA and anti-SARS-CoV-2 IgG (NCP and QuantiVac) results were obtained from the laboratory records.

Study Size

Of the 240 patients with sarcoidosis in the sarcoidosis outpatient clinic, 56 met the criteria for inclusion in this study. The patients were classified as SARS-CoV-2-infected and the vaccinated groups. Using the ELISA and IGRA tests, the SARS-CoV-2 IgG and INF-ɣ levels were measured, respectively, and the immunity status of the patients against SARS-CoV-2 IgG was investigated.

While the innate immunity status of patients was evaluated for patients with a COVID-19 history without vaccination, the acquired immunity status of the patients was evaluated in patients vaccinated with 2 doses of CoronaVac and who never had COVID-19 (These patients did not have any symptom or history of contact with affected patients that could have caused any suspicion of the disease).

Statistical Analysis

The SPSS software version 20.0 (AIMS, İstanbul, Turkey) was used for statistical analyses. Categorical variables were presented as percentages and frequencies, and while the continuous variables were indicated as the medians and interquartile ranges.

RESULTS

A total of 56 patients were enrolled, of which 49 (87.5%) and 7 (12.5%) were women and men, respectively. The mean age of the patients was 53.5 ± 10.9 years. The mean follow-up time for the patients was 6.68 ± 4.03 (1-10) years with the diagnosis of sarcoidosis. Of these, 37.5% of the patients were at stage 2 and 62.5% were at stage 3 sarcoidosis. Of the total, 42.9% of the patients had no comorbidities, while 32 (57.1%) had comorbidities (Table 1).

The mean age of 28 patients (24 F/4 M) patients in the SARS-CoV-2 infected group was 48.1 ± 11.3 (30-63) years, while that of the 28 patients in the vaccinated group was 55.6 ± 9.32 (38-68) years. The mean time elapsed after infection in the SARS-CoV-2-infected group was 97.32 ± 42.1 (45-180) days, while 61.3 ± 28.7 (37-120) days had passed since the second vaccination dose was administered in the vaccinated group. The follow-up period of patients in the SARS-CoV-2-infected group diagnosed with sarcoidosis and the vaccinated group was 7.41 ± 4.89 years and 5.96 ± 3.15 years, respectively. The mean body mass indexs distributions according to the sarcoidosis stage and comorbidity are depicted in Table 1.

A total of 15 (53.6%) of the 28 patients in the SARS-CoV-2-infected group were included in the study within the first 3 months of the disease diagnosis, while 13 (46.4%) patients were included at 3-6 months (Table 1). In the SARS-CoV-2-infected group, within 3 months of infection, the antibody test with QuantiVac ELISA was positive in 13 (86.6%) of the 15 patients, and the antibody test was positive in 5 of 13 patients (38.4%) who had passed >3 months after infection (Table 2).While the patients with positive anti-SARS-CoV-2 NCP ELISA (IgG) results were 64.3% (n = 18) in the SARS-CoV-2-infected group, it was 3.5% (n = 1) in the vaccinated group. Anti-SARS-CoV-2 QuantiVac ELISA (IgG) result was positive in 64.3% (n = 18) of the SARS-CoV-2-infected patients and 10.7% (n = 3) of the vaccinated patients (Table 2).

While 89.3% of the patients in the SARS-CoV-2-infected group were positive with the IGRA test, positivity was 14.3% in the vaccinated group (Table 2).

DISCUSSION

Anti-SARS-CoV-2 NCP IgG and anti-SARS-CoV-2 QuantiVac IgG were detected in 64.3% of the SARS-CoV-2-infected group, while the SARS-CoV-2 IGRA test was positive in 89.3% of the same patients in 3-6 months of infection. T-cells can provide long-term immune memory, while specific antibody responses decrease over time after an infection. Dan et al. reported that each of the following immune cells of adaptive immunity, including CD4+ T-cells, memory B-cells, and CD8+ T-cells against SARS-CoV-2 demonstrated different kinetics at ≥6 months of infection.[8] Kruse et al.[9] reported that the T-cell response measured by the T-spot test at 8 weeks after COVID-19 infection was 83.6%. These results from infected patients may facilitate the understanding of the establishment of T-cell surrogate endpoints in the future, although supplementary studies are needed presently.

TABLE 1. Demographic Characteristics of the Study Patients by Groups

	All patients	COVID infected group	Vaccinated group
	N (%)/med. ± Std	N (%)/med. ± Std	N (%)/med. ± Std
Patients	56	28	28
Gender			
Female	49 (87.5%)	24 (85.7%)	25 (89.3%)
Male	7 (12.5%)	4 (14.3%)	3 (10.7%)
Age (years)	53.5 ± 10.9	48.1 ± 11.3	55.6 ± 9.32
Time after immunization (days)	79.31 ± 36.8 (37-180)	97.32 ± 42.1 (45-180)	61.3 ± 28.7 (37-120)
BMI (kg/m^2)	27.77 ± 3.94	27.13 ± 3.21	28.41 ± 4.13
Follow-up period with the diagnosis of sarcoidosis (years)	6.68 ± 4.03	7.41 ± 4.89	5.96 ± 3.15
Sarcoidosis stage			
1	0 (0%)	0 (0%)	0 (0%)
2	21 (37.5%)	11 (39.3%)	10 (53.8%)
3	35 (62.5%)	17 (60.7%)	18 (46.2%)
4	0 (0%)	0 (0%)	0 (0%)
Comorbidity			
Absence	24 (42.9%)	11 (39.3%)	13 (46.4%)
Presence	32 (57.1%)	17 (60.7%)	15 (53.6%)
Hypertension	24 (42.8%)	10 (35.7%)	14 (50%)
Diabetes mellitus	13 (23.2%)	5 (17.8%)	8 (28.6%)
Other	19 (33.9%)	8 (28.5%)	11 (39.3%)
Time after COVID-19			
<3rd month	29 (51.8%)	15 (53.6%)	14 (50%)
Between 3-6 month	27 (48.2%)	13 (46.4%)	14 (50%)

Std., standard deviation; COVID-19, coronavirus disease-19; BMI, body mass index

Anti-SARS-CoV-2 NCP IgG, anti-SARS-CoV-2 QuantiVac IgG, and SARS-CoV-2 IGRA were detected negative in 96.5%, 89.3%, and 85.7% of the vaccinated group, respectively. After vaccination, 10.7% of patients with sarcoidosis were found positive for IgG and 14.3% for IGRA. There are conflicting results reported for the efficacy of vaccination in sarcoidosis patients in the literature. For example, Tavana et al.[10] vaccinated 23 sarcoidosis patients to 26 controls and concluded that the immunological response to multiple influenza antigens was not different between the sarcoidosis patients and the healthy controls. Currently, the effectiveness of vaccination in patients with sarcoidosis is unknown.

Antibody titers can decrease rapidly after SARS-CoV-2 immunization,[11] and high antibody titers were detected in post-infection controls.[12-14] It is unknown as to at what level and for how long does antibody titers persistent. In a study, the persistence of cellular and humoral responses continued for 8 months after the Ad26.COV2.S vaccination.[15] We measured the anti-SARS-CoV-2 QuantiVac-IgG titers in 56 sarcoidosis patients between 37 and 180 days after infection, and found them to be positive (≥11 RU/ml) in 10.7% of patients after vaccination and in 64.3% of patients after natural immunization.

A study compared sarcoidosis patients with healthy controls and noted a slight antibody response in the sarcoidosis patients after tetanus vaccination.[5] In the present study, we detected the low antibody levels after SARS-CoV-2 CoronaVac vaccination in sarcoidosis patients. In another case study, the humoral response did not occur after vaccination with two mRNA vaccine doses in patients using immunosuppressive agents due to rheumatological diseases.[7] A study investigated the CD4+ T-lymphocyte cell response against SARS-CoV-2 and found SARS-CoV-2 IGRA to be a useful indicator of the immune response for screening individuals infected with SARS-CoV-2.[16] In a study conducted on a large population in Chile, antibodies were detected in 95.7% of the study population. After 9 weeks of vaccination with the second dose of CoronaVac, a faster decrease in the proportion was noted in patients with diseases such as DM, and hypertension in the follow-ups.[17] Similarly, we recorded a low antibody value of 10.7% in patients with sarcoidosis after vaccination with CoronaVac for 37-120 days. In chronic renal failure patients undergoing dialysis and renal transplantation, lower anti-SARS-CoV-2 IgG levels were detected due to the impaired humoral immunity.[18] To the best of our knowledge, this is the first study to evaluate immune response against SARS-CoV-2 in sarcoidosis patients. These data reveal that the humoral and cellular immunity of sarcoidosis patients were insufficient against the CoronaVac vaccine.

TABLE 2. IgG and IGRA Results by Groups

	All patients	COVID infected group	Vaccinated group
	N (%)/med. ± std	N (%)/med. ± std	N (%)/med. ± std
Time after infected or vaccinated COVID-19			
<3rd month	-	15 (100%)	14 (100%)
Anti-SARS-CoV-2 QuantiVac ELISA			
Positive		13 (86.6 %)	2 (14.3%)
Negative		2 (13.4 %)	12 (85.7%)
SARS-CoV-2 IGRA			
Positive		13 (86.6 %)	2 (14.3%)
Negative		2 (13.4 %)	12 (85.7%)
Between 3-6 months		13 (100%)	14 (100%)
Anti-SARS-CoV-2 QuantiVac ELISA	-		
Positive		5 (38.4%)	1 (7.1%)
Negative		8 (61.6.%)	13 (92.9%)
SARS-CoV-2 IGRA			
Positive		12 (92.3%)	2 (14.3%)
Negative		1 (7.6%)	12 (85.7%)
Anti-SARS-CoV-2 NCP ELISA (IgG)			
Positive	19 (34.00%)	18(64.3%)	1 (3.5%)
Negative	37 (66.0%)	10 (35.7%)	27 (96.5%)
Anti-SARS-CoV-2 QuantiVac ELISA (IgG)			
Positive	21 (37.5%)	18 (64.3%)	3 (10.7%)
Negative	35 (62.5%)	10 (35.7%)	25 (89.3%)
SARS-CoV-2 IGRA			
Positive	29 (51.8%)	25 (89.3%)	4 (14.3%)
Negative	27 (48.2%)	3 (10.7%)	24 (85.7%)

Std., standard deviation; COVID-19, coronavirus disease-19; BMI, body mass index; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IgG, immunglobulinG; IGRA, interferon-gamma release assay

In this study, only the antibodies levels and IGRA values were examined after natural immunization and acquired immunization with CoronaVac. No data were collected to provide mRNA vaccination information. Another limitation of this study is that blood samples of the patients were collected at different times after immunization, which does not reflect simultaneous results.

In patients with sarcoidosis, the innate immunity to SARS-CoV-2 was found to decrease over time. Innate immune responses are better than adaptive immune responses in patients with sarcoidosis. The coronaVac vaccine is insufficient to induce humoral and cellular immunities in patients with sarcoidosis. The IGRA method generated innate and adaptive immune responses against SARS-CoV-2 with a higher sensitivity relative to that against IgG detection in patients with sarcoidosis.

Ethics Committee Approval: Ethical approval was obtained from İstanbul University-Cerrahpaşa, Cerrahpaşsa Faculty of Medicine Ethics Committee on 09.07.2021 (#137423).

Data Sharing Statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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