ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20221074

Evaluation and follow-up of antibody formation after CoronaVac vaccine

Büşra Çalişir[1]*, Nilay Çöplü[2], Melike Yasar-Duman[1], Cetin Kilinc[1], Ridvan Ozbek[3], Celal Demir[4], Zafer Ergül[5]

SUMMARY

OBJECTIVE: The aim of this study was to monitor the time-dependent change by evaluating the antibody levels at the 4th, 7th, 10th, 13th, and 16th weeks after the second dose of the CoronaVac vaccine.

METHODS: The study group (n=65) were between 21 and 60 years old and received two doses of the CoronaVac vaccine. Blood samples were collected after 4th, 7th, 10th, 13th, and 16th weeks of the second dose of the vaccine administration. There was a coronavirus disease 2019 recovered group (n=29) who were SARS-CoV-2 real-time PCR test result positive before the vaccination period, and no coronavirus disease 2019 history group (n=36). Age, BMI, gender, smoking, comorbidity, coronavirus disease 2019 contact history, and working in the coronavirus disease 2019 service history of the individuals were recorded.

RESULTS: No statistically significant difference was found in the descriptive findings of the individuals according to coronavirus disease 2019 recovered group and no coronavirus disease 2019 history group. It was observed that antibody levels in the coronavirus disease 2019 recovered group were found to be higher for each period of serum collection compared to the no coronavirus disease 2019 history group, which were statistically significant. The distribution curves of the antibody levels according to the timing of blood collection in coronavirus disease 2019 recovered group, no coronavirus disease 2019 history group, and total subjects were extrapolated, and it was observed that the estimated time for the antibodies to reach the threshold value of the test was 214, 145, and 166 days after vaccination.

CONCLUSION: It is important to make booster doses, as the CoronaVac vaccine will lose its effect after the fifth month due to the decrease in Ab levels. In addition, since the antibody levels decrease later in those who have a history of coronavirus disease 2019 infection and are vaccinated, individuals who have no previous history of coronavirus disease 2019 should be given priority for vaccination.

KEYWORDS: COVID-19. Vaccines, inactivated. Immunity, humoral .

INTRODUCTION

The coronavirus disease 2019 (COVID-19) has become a serious public health problem, causing a pandemic. It has led to high morbidity and mortality worldwide[1]. Vaccines have been seen as the most important solution to end the COVID-19 pandemic. CoronaVac is a type of inactivated vaccine used against COVID-19. It is prepared by injecting pathogen strains that are killed by chemical (formaldehyde) or physical (UV and heat) methods that do not cause disease, and the body is made to produce antibodies against them[2]. After demonstrating the safety and effectiveness of the vaccine in Phase 1/2 studies conducted in various countries, Phase 3 studies were initiated[3]. In the Phase 3 study conducted in Turkey, the effectiveness of the CoronaVac vaccine was found to be 83.5%[4]. Considering the rapidly increasing number of cases and deaths, the CoronaVac (Sinovac Life Sciences, Beijing, China) vaccine was given an emergency use approval on January 13, 2021, by the Medical Medicines and Devices Agency of Turkey, and vaccination started with healthcare professionals in Turkey. The vaccine was administered as two doses, 28 days apart[3].

The vaccine has been shown to provide strong protection against COVID-19; however, it is thought that there may be a loss of protection due to decreased immunity over time and viral variation due to various mutations[5]. Studies of the immune response in people with a prior history of COVID-19 infection have shown that antibody levels drop 4 months after infection[6].

[1]Kastamonu Training and Research Hospital, Division of Medical Microbiology – Kastamonu, Turkey.
[2]Kastamonu University, Faculty of Medicine, Department of Medical Microbiology – Kastamonu, Turkey.
[3]Kastamonu Training and Research Hospital, Division of Urology – Kastamonu, Turkey.
[4]Kastamonu University, Faculty of Medicine, Department of Internal Medicine – Kastamonu, Turkey.
[5]Kastamonu University, Faculty of Medicine, Department of General Surgery – Kastamonu, Turkey.
*Corresponding author: busraozeycalisir@gmail.com
Conflicts of interest: the authors declare there is no conflict of interest. Funding: none.
Received on August 11, 2022. Accepted on August 28, 2022.

In this study, the aim was to monitor the time-dependent change by evaluating the antibody levels at the 4th, 7th, 10th, 13th, and 16th weeks after the second dose of the CoronaVac vaccine in healthcare workers. It was also aimed to evaluate whether there is a difference between antibody levels by dividing healthcare workers who received the CoronaVac vaccine into two groups: those with a previous history of COVID-19 and those without evidence of previous infection. Thus, it is aimed to provide a prediction about how long the expected benefit from the vaccine will last by monitoring the antibody levels and to provide data for the booster dose requirement of the vaccine.

METHODS

Study design and participants

This prospective study was conducted in our hospital between March and June 2021. The study group included 65 healthcare workers who were 21–60 years old and received two doses of the CoronaVac (Sinovac Life Sciences) vaccine. Besides, the study group was selected from subjects whose antibody level was above the threshold at the fourth week after the vaccination in a previous study. Blood samples were collected after the 4th, 7th, 10th, 13th, and 16th weeks of the second dose of the vaccine administration. After the serum samples were centrifuged, the samples were stored at -20°C until testing. Among the individuals, there were COVID-19 recovered group (CRG) (n=29), who were SARS-CoV-2 real-time PCR test result positive before the vaccination period, and no COVID-19 history group (NCHG) (n=36). The descriptive properties of the individuals were collected through a questionnaire. The queries were about age, BMI, gender, smoking, comorbidity (hypertension, diabetes, asthma/chronic obstructive lung disease, malignancy, autoimmune disease, thyroid patient, hyperlipidemia, and coronary artery disease), COVID-19 contact history, and working in COVID-19 service history (Table 1).

SARS-CoV-2 immunoglobulin G II quant test (anti-spike immunoglobulin G)

Serum samples were studied using the SARS-CoV-2 immunoglobulin G (IgG) II Quant (Abbott; IL, USA) Chemiluminescent Microparticle Immunoassay, which was developed to detect IgG antibodies against the spike protein S1 subunit of the COVID-19. The assays were carried out on the analyzers Architect I2000sr (Abbott) according to the manufacturer's instructions. Test results of ≥50 AU/mL were evaluated as positive.

Statistical analysis

All statistical analyses were performed using the SPSS 22.0 (IBM SPSS Statistics, IBM Corp., Chicago, IL, USA) software for Windows. The accordance of the numeric variables with the normal distribution was assessed with the Kolmogorov-Smirnov test. Demographic and clinical characteristics of CRG and NCHG were compared using Kruskal-Wallis tests for continuous variables, chi-square tests, and Mann-Whitney U tests for categorical variables. The median (interquartile range, IQR) was used to define the nonparametric variables, while frequency and percentage were used for categorical variables. In all of the analyses, the statistical significance level was accepted as a $p<0.05$.

Table 1. Descriptive findings of subjects according to coronavirus disease 2019 recovered group and no coronavirus disease 2019 history group.

Variables		CRG (N=29)	NCHG (N=36)	Total (N=65)	p
Age		42 (31–46)	37 (32–44,75)	38 (32–45.5)	0.387[m]
BMI (kg/m^2)		27.54 (26.14–30.18)	26.20 (23.34–29.55)	27.35(24.32–29.99)	0.359[t]
Gender	Male	14 (42.4)	19 (57.6)	33 (50.8)	0.718[k]
	Female	15 (46.9)	17 (53.1)	32 (49.2)	
Smoking	Yes, n (%)	9 (40.9)	13 (59.1)	22 (33.8)	0.667[k]
	No, n (%)	20 (46.5)	23 (53.5)	43 (66.2)	
Alcohol consumption	Yes, n (%)	4 (44.4)	5 (55.6)	9 (13.8)	0.991[k]
	No, n (%)	25 (44.6)	31 (55.4)	56 (86.2)	
Comorbidity	Positive, n (%)	11 (57.9)	8 (42.1)	19 (29.2)	0.166[k]
	Negative, n (%)	18 (39.1)	28 (60.9)	46 (70.8)	
COVID-19 contact history	Yes, n (%)	20 (44.4)	25 (55.6	45 (69.2)	0.967[k]
	No, n (%)	9 (45)	11(55)	20 (30.8)	
Working in COVID-19 service history	Yes, n (%)	17 (54.8)	14 (45.2)	31 (47.7)	0.113[k]
	No, n (%)	12 (35.3)	22 (64.7)	34 (52.3)	

[m]Mann-Whitney U test; [t]independent sample t test; [k]chi-square test.

Ethics committee approval

Ethical approval was obtained for the study from the Medical Research Ethical Committee of the Kastamonu University Faculty of Medicine (approval no: 2020-KAEK-143-70).

RESULTS

No statistically significant difference was found for the descriptive findings of the individuals according to CRG and NCHG (Table 1). In the study group, median age was 38 years, median BMI was 27.35, there were no obese subject, nearly half of the individuals had worked in COVID-19 service history, smoking was prevalent in 33.8%, comorbid conditions were present in 29.2%, and COVID-19 contact history made up 70.8% of the sample.

There were five individuals whose antibody levels sharply increased at the 13th week and decreased at the 16th week but were still higher than at the 4th week, which may indicate acute COVID-19 infection. Three of them were in CRG, and two were from NCHG. These subjects were excluded from the further analysis.

The distribution of antibody levels according to the time of blood collection after CoronaVac vaccination and the comparison of CRG and NCHG are presented in Table 2. It was observed that antibody levels in the CRG were found to be higher for each period of serum collection compared to the NCHG, and they were statistically significant. Likewise, the change of the antibody levels from the fourth week to the other weeks of serum collection were analyzed according to CRG and NCHG, and it was observed that the difference was statistically significant in the 4th–10th weeks and the 4th–13th weeks. In the 10th week, there was an increase in antibody levels in 12 and 17 subjects from CRG and NCHG, respectively, and 10 and 13 of the subjects, respectively, had either COVID-19 contact history or were working in COVID-19 service in the last 3 months history.

The distribution curves of the antibody levels according to the timing of blood collection in CRG, NCHG, and total subjects are presented in Figure 1. These curves were extrapolated, and it was observed that the estimated time for the antibodies to reach the threshold value of the test were 214, 145, and 166 days after vaccination for CRG, NCHG, and total subjects, respectively.

DISCUSSION

The reduction in efficacy of the COVID-19 pandemic is dependent on the success of widespread vaccination; however, the efficacy and resilience of immune responses vary depending on the type of vaccine and the characteristics of the vaccinated population. Data on the duration of the protective effect of

Table 2. The distribution of antibody levels according to the time of blood collection after CoronaVac vaccination and the comparison of coronavirus disease 2019 recovered group and no coronavirus disease 2019 history group.

	Time after CoronaVac vaccination	CRG (n=25)		NCHG (n=34)		p
		Average±s.d.	Median (min–max)	Average±s.d.	Median (min–max)	
COV-2IgG (AU/Ml)	4th week	1734.0±1406.5	1458.9 (265.3–6637.9)	1104.7±727.6	836.1 (214.2–3835.0)	**0.044**[m]
	7th week	1399.9±1671.7	866.9 (176.0–7921.8)	607.0±499.8	448.2 (153.8–2815.9)	**0.004**[m]
	10th week	1443.2±1584.3	1051.8 (156.8–7684.4)	607.6±403.0	536.0 (115.4–1997.2)	**0.002**[m]
	13th week	1476.1±2008.1	977.1 (122.9–10095.8)	508.9±399.2	429.9 (82.8–2071.6)	**0.001**[m]
	16th week	872.4±1235.7	473.9 (51.3–6145.6)	283.0±206.8	204.7 (47.8–1005.9)	**0.001**[m]
Change p	4th week / 7th week	-334.1±677.4	-268.5 (-2069–1283.9) 0.009[w]	-497.7±395.4	-414.8 (-1526.7 to -20.4) <0.001[w]	0.276[m]
	4th week / 10th week	-290.7±481.6	-195.8 (-1198.8–1046.5) 0.001[w]	-497.1±395.5	-400.8 (-1837.8 to -4.9) <0.001[w]	**0.049**[m]
	4th week / 13th week	-257.9±867.3	-302.9 (-1375.2–3457.9) <0.001[w]	-595.8±415.5	-458.2 (-1763.4 to -32.5) <0.001[w]	**0.033**[m]
	4th week / 16th week	-861.6±621.0	-705.5 (-2297.5 to -90.2) <0.001[w]	-821.7±570.5	-640.0 (-2829.1 to -166.4) <0.001[w]	0.890[m]

[m]Mann-Whitney U test; [w]Wilcoxon test; s.d.: standard deviation. Bold indicates significant value.

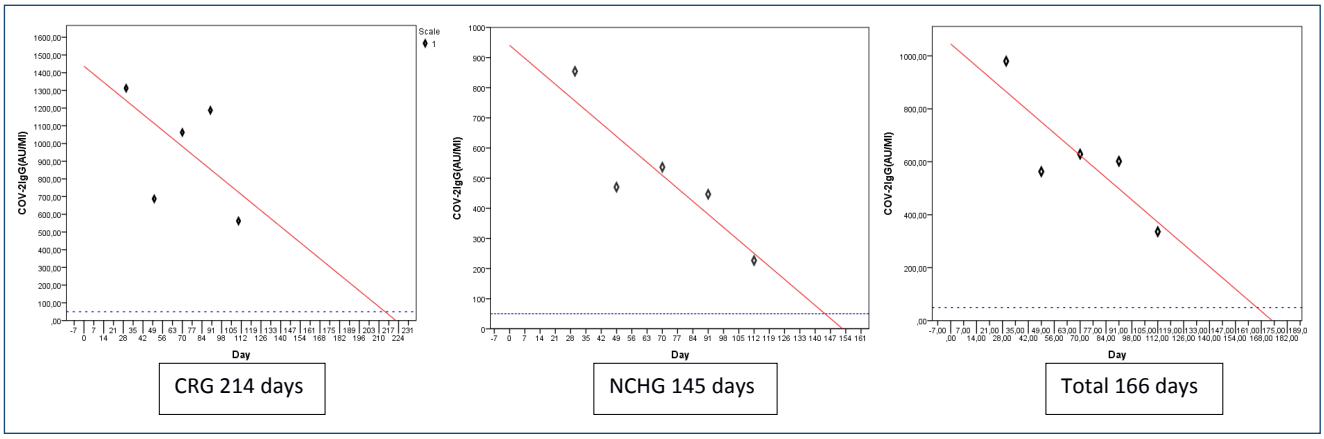

Figure 1. The distribution curves of the antibody levels according to the timing of blood collection from coronavirus disease 2019 recovered group, no coronavirus disease 2019 history group, and total subjects.

the vaccine and the timing of the booster dose are still needed. In this study, time-dependent changes in antibody titers were monitored in a total of 65 healthcare workers vaccinated with two doses of the CoronaVac (Sinovac), 29 of whom had a history of pre-vaccination COVID-19 infection. Follow-up after two doses of the CoronaVac vaccine showed dramatic decreases in median antibody levels over time. During the entire study period, antibody levels in the group with a previous COVID-19 infection were found to be significantly higher than in the group without a COVID-19 infection. When the descriptive findings of the two groups were examined, it was seen that there was no significant difference between the two groups in terms of age, gender, BMI, smoking status, comorbidity, history of contact with COVID-19, and history of working in COVID-19-related services.

Although Ab levels were observed to be over the threshold value of the test for at least 4.8 months by extrapolation, COVID-19 infection developed in 5/65 (7.7%) cases at the 13th week after vaccination. It seems that Ab alone is not sufficient to prevent infection. It is well known that not only spike antibodies but also T-cell- and B-cell-mediated immune factors play a role in the response against SARS-CoV-2[7]. The fact that three of these people have CRG indicates that the protection is limited after a natural infection. In a study conducted on 20,000 healthcare workers in the United Kingdom, the rate of protection from reinfection for the first 5 months after COVID-19 infection was reported as 83%[8]. In a study conducted in China, 25 (4.5%) people were found to be infected with COVID-19 in a 6-month follow-up after two doses of CoronaVac vaccine. Of these cases, 20 were within the first 4 months[9].

In Table 2, the antibody levels in the serum taken from the fourth week after the second dose of vaccination and their differences between CRG and NCHG were shown, excluding those who had acute infections. According to the table, antibodies from CRG were found to be significantly higher than those from NCHG at all serum collection times. A sudden increase in the 10th week suggested an acute infection. When we extrapolate Ab levels, at 241, 145, and 166 days the Ab levels remain above the threshold for CRG, NCHG, and total. The decrease in Ab levels to the test threshold means the end of the immune response obtained from the vaccine. Ab persists for an average of 5.5 months, which can vary between 4.8 and 8 months. A study conducted in Thailand showed a significant decrease in antibody levels 3 months after the second dose of CoronaVac vaccine[10]. In another CoronaVac study, a 56.7% decrease was observed between antibody levels measured at the first and third months after the second dose[11]. Several other studies have reported that the antibody response after two doses of CoronaVac greatly protects against re-infection for 6 months[12,13]. In another study, antibody responses at the fourth month decreased by 61% compared to responses at the first month and even became seronegative by 10%[9]. In another study, a decrease in antibody titers was observed 3 months after the CoronaVac vaccine. Similar to our study, this decrease was more rapid and significant in those with no previous history of COVID-19 infection[14,15]. In a study of 850 vaccinated participants in Hong Kong, it was reported that the median antibody titers in the BNT162b2 mRNA vaccine group remained above the threshold for 6 months, while the median antibody titers in the CoronaVac vaccine group dropped significantly after 2 months[16]. Ab presence durations are similar between vaccine and natural infection. Several studies of the immune response in people with a history of COVID-19 infection have shown that antibody levels drop 4 months after being infected[17,18].

The limitations of the study are that the RT-PCR test, which is the gold standard in the acute diagnosis of COVID-19,

cannot be routinely performed for screening during follow-up periods and therefore asymptomatic infected individuals may have been overlooked. In addition, longer term follow-up of cases with a larger sample size will increase the reliability of the study.

CONCLUSION

It is important to apply booster doses, as the CoronaVac vaccine will lose its effect after the fifth month due to the decrease in Ab levels. In addition, since the antibody levels decrease later in those who have a history of COVID-19 infection and are vaccinated, individuals who have no previous history of COVID-19 should be given priority in vaccination, and it was thought that the period between booster doses may be longer in those with a history of COVID-19.

AUTHORS' CONTRIBUTIONS

BC: Investigation, Methodology, Software, Supervision. **NC:** Methodology, Supervision, Validation, Writing – review & editing. **MYD:** Investigation, Software, Supervision. C**K:** Investigation, Software, Supervision. **RO:** Methodology, Validation. **CD:** Methodology, Investigation. **ZE:** Investigation, Supervision.

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