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Changes in SARS-CoV-2 antibody titers 6 months after the booster dose of BNT162b2 COVID-19 vaccine among health care workers

Takeshi Mochizuki[1], Takaki Hori[2], Koichiro Yano[3], Katsunori Ikari[3], Ken Okazaki[3]

Departments of [1]Rheumatology and Orthopedic Surgery and [2]Cardiovascular Surgery, Kamagaya General Hospital, Kamagaya; [3]Department of Orthopedic Surgery, Tokyo Women's Medical University, Tokyo, Japan

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Corresponding author:
Takeshi Mochizuki, MD, PhD
Department of Orthopaedic Surgery, Kamagaya General Hospital, 929-6 Hatsutomi, Kamagaya, Chiba 273-0121, Japan
Tel: +81-47-498-8111, Fax: +81-47-498-5050
E-mail: twmutamo@gmail.com

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Purpose: In Japan, the data on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody titers after the booster dose of the coronavirus disease 2019 (COVID-19) vaccine are insufficient. The aim of this study is to evaluate changes in SARS-CoV-2 antibody titers before, 1, 3, and 6 months after the booster dose of the BNT162b2 COVID-19 vaccine among health care workers.

Materials and Methods: A total of 268 participants who received the booster dose of the BNT162b2 vaccine were analyzed. SARS-CoV-2 antibody titers were measured before (baseline) and at 1, 3, and 6 months after the booster dose. Factors associated with changes in SARS-CoV-2 antibody titers at 1, 3, and 6 months were analyzed. Cutoff values at baseline were calculated to prevent infection of the omicron variant of COVID-19.

Results: The SARS-CoV-2 antibody titers at baseline, and 1, 3, and 6 months were 1,018.3 AU/mL, 21,396.5 AU/mL, 13,704.6 AU/mL, and 8,155.6 AU/mL, respectively. Factors associated with changes in SARS-CoV-2 antibody titers at 1 month were age and SARS-CoV-2 antibody titers at baseline, whereas changes in SARS-CoV-2 antibody titers at 3 and 6 months were associated with the SARS-CoV-2 antibody titers at 1 month. The cutoff values of the SARS-CoV-2 antibody titers at baseline were 515.4 AU/mL and 13,602.7 AU/mL at baseline and 1 month after the booster dose, respectively.

Conclusion: This study showed that SARS-CoV-2 antibody titers increase rapidly at 1 month after the booster dose of the BNT162b2 vaccine and begin to decrease from 1 to 6 months. Hence, another booster may be needed as soon as possible to prevent infection.

Keywords: COVID-19 vaccine booster, Japan, Health care workers, SARS-CoV-2 antibody titer

Introduction

The coronavirus disease 2019 (COVID-19) infection is continuously fluctuating worldwide. After receipt of the COVID-19 vaccine, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody titers progressively decrease, and the decline in antibody titers increases the risk of breakthrough infection. Recently, the third-dose vaccination (booster) using BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines has been administered in Japan. Booster vaccines prevent infection, hospitalization, and death due to COVID-19 [1-5]. In people who received the booster dose of the BNT162b2 vaccine the incidence of omicron infection after 35 days was 2.4% as com-

pared with 4.5% in those who did not receive a booster dose. Moreover, the effectiveness of the booster dose against hospitalization and death due to omicron infection was 76.5% higher than those in the previous case series [1]. Similarly, as compared with the non-booster dose, the relative effectiveness of the booster dose of the BNT162b2 vaccine was reported to be 75% and 70% against infection and hospitalization, respectively [2]. Moreover, in older people who received the booster dose, the risks of COVID-19 infection were 75% lower and the risk of hospitalization and death was 82%–83% lower than those who did not receive a booster [5].

The reduction in SARS-CoV-2 antibody titers over time is well-known [6-8]. At 6 months after the initial two-dose vaccination, the median neutralizing antibody titers were <20 for omicron BA.1 and BA.2 variants [9]. The neutralizing antibody titers of participants with COVID-19 breakthrough infections were lower than those in matched participants without COVID-19 breakthrough infections [10].

The Ministry of Health, Labor, and Welfare in Japan recommends the booster dose of the COVID-19 vaccine. However, data on SARS-CoV-2 antibody titers after receipt of the COVID-19 vaccine booster dose are insufficient. Therefore, in this study, we aim to evaluate the changes in SARS-CoV-2 antibody titers before, and 1 month and 3 months after the booster dose of BNT162b2 vaccine among health care workers.

Materials and Methods

We enrolled 323 health care workers in our hospital who received the booster dose of the BNT162b2 vaccine 6 months after two doses of the BNT162b2 vaccine. SARS-CoV-2 antibody titers were measured before (baseline) and 1 month (±1 week), 3 months (±1 week), and 6 months (±1 week) after the booster dose of the BNT162b2 vaccine using the SARS-CoV-2 immunoglobulin G (IgG) II Quant Reagent Kit (Abbott Japan, Tokyo, Japan); results ≥50 AU/mL in this test are considered positive. The limit of the maximum value in the SARS-CoV-2 IgG II Quant Reagent Kit was 40,000 AU/mL; therefore, if SARS-CoV-2 antibody titers are ≥40,000 AU/mL, the SARS-CoV-2 antibody titers were 40,000 AU/mL based on the analysis. We investigated factors associated with changes in SARS-CoV-2 antibody titers at 1 month and 3 months after the booster dose of the BNT162b2 vaccine.

This study was approved by the independent ethics committee of Kamagaya General Hospital (approval no., TGE0 1852-064) and was undertaken following the principles of the Declaration of Helsinki. Informed consent was obtained from the participants after explaining the study protocol.

Statistical analysis

We included 268 participants at 3 months and 233 participants at 6 months in the study analysis (Fig. 1). Using simple and multiple regression analyses, we evaluated the factors associated with changes in SARS-CoV-2 antibody titers at 1 month and 3 months after the booster dose of the BNT162b2 vaccine. Multiple regression analyses were performed using variables with a p-value of <0.1 based on the simple regression analyses. These variables included age, sex, body weight, allergic comorbidities, and/or collagen disease, current smoking, alcohol intake, regular exercise, and SARS-CoV-2 antibody titers at baseline. When analyzing factors associated with changes in SARS-CoV-2 antibody titers at 3 months, we

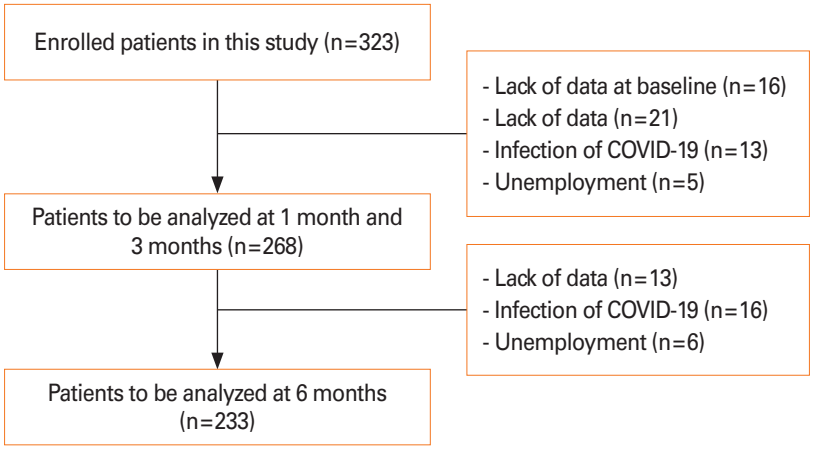

Fig. 1. Flow diagram of participant selection in this study. Reasons for exclusion from analysis: lack of data, infection of coronavirus disease 2019 (COVID-19), and unemployment.

also added SARS-CoV-2 antibody titers at 1 month. The cutoff values of SARS-CoV-2 antibody titers at baseline and 1 month for COVID-19 infection using SARS-CoV-2 antibody titers at baseline and 1 month with or without COVID-19 infection was measured by the receiver operating characteristic (ROC) method with corresponding sensitivity and specificity and the area under the curve (AUC). A p-value of <0.05 was considered significant. All analyses were performed using the R Statistical Package ver. 3.3.2 (http://www.r-project.org/).

Results

The characteristics of the study participants included in the analyses of the changes in the SARS-CoV-2 antibody titers at baseline were as follows: mean age, 38.7±11.7 years; 66.8% female; mean body weight, 60.4±12.1 kg; presence of allergic or autoimmune diseases, 8.6%; current smokers, 7.5%, daily alcohol intake, 15.3%; and exercised regularly, 14.9%.

The SARS-CoV-2 antibody titers at baseline, and 1, 3, and 6 months were 1,018.3±2,851.1 AU/mL, 21,396.5±11,357.9 AU/mL, 13,704.6±10,655.9 AU/mL, and 8,155.6±8,632.7 AU/mL in all participants, respectively (Fig. 2). SARS-CoV-2 antibody titers at 1, 3, and 6 months were 35.9, 21.4, and 8.0 times from those at baseline. The change in the SARS-CoV-2 antibody titers at 1 to 6 months was –62.9%±38.1%.

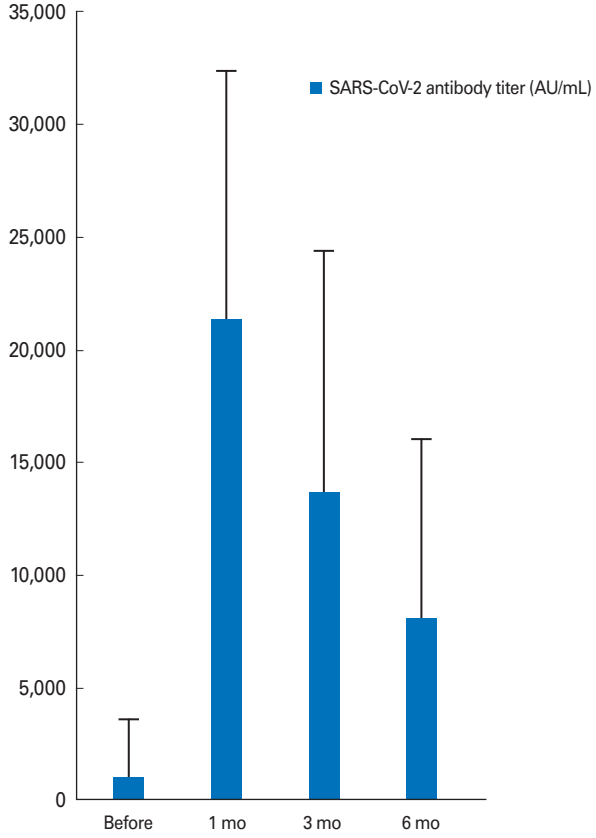

Fig. 2. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody titers at baseline, 1, 3, and 6 months after the booster dose of the BNT162b2 vaccine. SARS-CoV-2 antibody titers at 1 month and 3 months were 35.9, 21.4, and 8.0 times from those at baseline.

Factors associated with changes in the SARS-CoV-2 antibody titers 1 month after the booster dose of the BNT162b2 vaccine were age and the values of the SARS-CoV-2 antibody titers at baseline (Table 1). The factor associated with changes in SARS-CoV-2 antibody titers at 3 and 6 months after the booster dose of the BNT162b2 vaccine were their values at 1 month.

In this study, 29 participants experienced COVID-19 infection within 1–6 months after receiving the BNT162b2 booster dose (Fig. 1). The SARS-CoV-2 antibody titer at baseline was 561.6±381.8 AU/mL in participants with COVID-19 infection and 1,018.3±2,851.1 AU/mL in those without COVID-19 infection (p=0.047). The SARS-CoV-2 antibody titer at 1 month was 14,481.3±8,907.2 AU/mL in participants with COVID-19 infection and 21,396.5±11,357.9 AU/mL in participants without COVID-19 infection, respectively (p=0.005). As calculated by the ROC method, the cutoff values of SARS-CoV-2 antibody titers at baseline and 1 month for COVID-19 infection were 515.4 AU/mL (sensitivity: 66.8%, specificity: 62.1%, and AUC: 0.630) and 13,602.7 AU/mL (sensitivity: 67.9%, specificity: 59.0%, and AUC: 0.687), respectively.

Discussion

This study shows that SARS-CoV-2 antibody titers increase rapidly 1 month after receipt of the booster dose of the BNT162b2

Table 1. Factors associated with change in SARS-CoV-2 antibody titers at 1 months after the booster dose of the BNT162b2 vaccine

Variable	p-value	
	Univariate analysis	Multivariate analysis
Age	0.004	0.004
Sex	0.114	NA
Body mass index	0.158	NA
Comorbidities of allergic and/or collagen disease	0.150	NA
Current smoker	0.450	NA
Alcohol intake	0.378	NA
Regular exercise	0.460	NA
SARS-CoV-2 antibody titers at baseline	0.002	0.002

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; NA, not applicable.

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vaccine, but decrease rapidly after 6 months.

Changes in SARS-CoV-2 antibody titers and neutralizing antibodies were similar over 6 months [7]. Anti-spike IgG was highly correlated with an anti-receptor binding domain (RBD) IgG (Pearson's correlation coefficient r=0.926), and increased levels of anti-spike IgG and anti-RBD IgG significantly decreased the rate of symptomatic COVID-19 infection [11]. In this study, SARS-CoV-2 antibody titers at 1, 3, and 6 months were 35.9, 21.4, and 8.0 times from those at baseline, respectively. Previous studies reported that at 2 weeks after receipt of the booster dose of the BNT162b2 vaccine, the median neutralizing antibody titers were 6.1 and 8.4 times for omicron BA.1 and BA.2 variants, respectively [9]. The booster dose of the BNT162b2 vaccine increased significantly by 50% neutralizing dilution titers against delta and omicron variants. However, 50% neutralizing dilution titers against omicron were lower than those against delta [12]. To prevent omicron infection, SARS-CoV-2 antibody titers should be maintained at high levels. Age and SARS-CoV-2 antibody titers at baseline were associated with changes in SARS-CoV-2 antibody titers 1 month after the booster dose of the BNT162b2 vaccine. Older participants and those with lower SARS-CoV-2 antibody titers at baseline tend to have higher changes in SARS-CoV-2 antibody titers at 1 month after the booster dose of the BNT162b2 vaccine. We suggest that several participants had the opportunity to have high SARS-CoV-2 antibody titers as a result of receiving the booster dose of the BNT162b2 vaccine. However, the SARS-CoV-2 antibody titer gradually decreased. Similarly in this study, SARS-CoV-2 antibody titers rapidly decreased by 38.1% and 61.9% from 1 month to 3 and 6 months, respectively, after the booster dose of the BNT162b2 vaccine. SARS-CoV-2 antibody titers at 1 month were associated with changes in SARS-CoV-2 antibody titers at 6 months.

Protection against COVID-19 infection decreased over time with decrease in the SARS-CoV-2 antibody titers following the second dose of the BNT162b2 vaccine. The effectiveness rates of the BNT162b2 vaccine against COVID-19 infection at 2 weeks–2 months, >4 months, and >5 months were 96.2%, 83.7%, and 69.7%, respectively [13]. In Israel, the Ministry of Health recommended the booster dose of the BNT162b2 vaccine for persons aged ≥60 years who had received a second vaccine dose at least 5 months earlier [14]. The results of the present study suggest the time of booster dose administration of the BNT162b2 vaccine and the need for additional booster doses to protect against future COVID-19 infection. This study demonstrated the cutoff values of SARS-CoV-2 antibody titers at baseline and 1 month for COVID-19 infection. Hence, the results of this study may provide insights into COVID-19 vaccine booster strategies.

This study has some limitations. First, the relationship with COVID-19 occurrence was not investigated. However, as of April 2022, omicron infection continues in Japan. We believe that our results provide necessary information to recommend the booster dose of the COVID-19 vaccine. Second, the age of the oldest participants was 75 years; therefore, this study contains insufficient data on elderly participants. Future studies should include data on the booster dose of the BNT162b2 vaccine in elderly people.

In conclusion, in this study, we found the booster dose of the BNT162b2 vaccine rapidly increased SARS-CoV-2 antibody titers at 1 month among health care workers in Japan, but that these titers decreased rapidly from 1 month to 6 months after receipt of the booster dose of the BNT162b2 vaccine. Our findings suggest that another booster vaccination might be needed in the future. We believe that the information in this study plays a critical role in determining the need for a booster dose of the COVID-19 vaccine and the next booster vaccination.

ORICD

Takeshi Mochizuki *https://orcid.org/0000-0002-8316-8671*
Takaki Hori *https://orcid.org/0000-0003-3911-4518*
Koichiro Yano *https://orcid.org/0000-0002-9514-2719*
Katsunori Ikari *https://orcid.org/0000-0001-9066-2005*
Ken Okazaki *https://orcid.org/0000-0003-1274-8406*

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