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Note

Antibody titers and neutralizing activity in cases of COVID-19 after a single dose of vaccination

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ABSTRACT

Vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have shown high efficacy in preventing the onset of disease. However, the immune response to infection immediately after the first vaccination remains unknown. We examined the anti-SARS-CoV-2-binding-antibody titers and neutralizing activity in patients who developed coronavirus disease 2019 after the first vaccination. The amount of anti-SARS-CoV-2-binding antibodies and neutralizing activity drastically increased from the first to the second collection. Our results may provide important data on the course of immune response following vaccination.

Vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have shown 94%–95% efficacy in preventing the onset of disease after two or three doses of vaccination. However, the efficacy immediately after the first dose of vaccination is reported to be not significantly different from that in the placebo group [1,2]. Moreover, the immune response to infection immediately after the first vaccination remains largely unknown. In this study, we retrospectively examined the serum anti-SARS-CoV-2-binding-antibody titers and neutralizing activity against the viruses in patients who developed the disease after the first vaccination.

A retrospective observational study of nine patients who developed coronavirus disease 2019 (COVID-19) after the first dose of vaccination was conducted between May 2021 and August 2021 at the National Center for Global Health and Medicine (NCGM), Tokyo, Japan. This center has approximately 780 hospital beds. The data for the following parameters were collected from patient medical records: demographics (age and sex), background and comorbid conditions, vaccine type and timing, time of specimen collection, strains, and outcomes. The neutralizing activity of sera against the clinically isolated SARS-CoV-2 strains SARS-CoV-2$^{05\text{-}2N}$ (PANGO lineage B), SARS-CoV-2^{QHN002} (PANGO lineage B.1.1.7, GISAID Accession ID; EPI_ISL_804008), and SARS-CoV-2^{TKY01734} (PANGO lineage B.1.617.2, GISAID Accession ID; EPI_ISL_2080609) was determined as previously described by employing TMPRSS2-overexpressing VeroE6 (VeroE6^{TMPRSS2}) cells (RRID: CVCL_YQ49) as the target cells [3]. The amounts of anti-SARS-CoV-2-Spike-binding IgG (S-IgG), anti-SARS-CoV-2-Spike-binding IgM (S-IgM), and anti-SARS-CoV-2-Nucleocapsid-binding IgG (N-IgG) antibodies were determined by using the HISCL anti-SARS-CoV-2 immunoassay (Sysmex, Kobe, Japan) as described previously [4]. Viral RNA was extracted from nine patients' nasopharyngeal swab samples. The Illumina COVIDseq test (Illumina, Inc. USA) was used for cDNA synthesis, target amplification, and library preparation according to the manufacturer's instructions. Libraries were pooled, normalized, and sequenced on the Illumina iSeq 100 System. Raw reads were analyzed through the Illumina BaseSpace DRAGEN COVID Lineage v3.5.9, and the SARS-CoV-2 genome sequences were determined. This study was approved by the ethics committee of the NCGM (approval no. NCGM-S-004302-00).

Two (22.2%) patients received the BNT162b2 (Pfizer/BioNTech) vaccine, 6 (66.7%) received the mRNA-1273 (Moderna) vaccine, while the vaccine was uncertain in one (11.1%). The median (interquartile range; IQR) time from the first vaccine dose to onset was 8 (6.75–9.75) days (Table 1). Among the nine patients, 7 (77.8%) were infected with the delta (AY.29) variant and 1 (11.1%) with the alpha (B.1.1.7) variant. Except for one HIV-infected patient, none of the other patients were immunosuppressed. Eight (88.9%) patients required supplemental oxygen while no patient required mechanical ventilation or died. All patients developed COVID-19 within 13 days after the first dose of vaccination. On admission, the geometric mean (range) values of S-IgG,

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Abbreviations

BIPAP Biphasic positive airway pressure
COVID-19 Coronavirus disease 2019
CPAP Continuous positive airway pressure
NCGM National Center for Global Health and Medicine
N-IgG Anti-SARS-CoV-2-Nucleocapsid-binding IgG
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
S-IgG Anti-SARS-CoV-2-Spike-binding IgG
S-IgM Anti-SARS-CoV-2-Spike-binding IgM

N-IgG, and S-IgM were 32.8 (2.4, 486), 0.9 (0.1, 357.4), and 64.2 (4.7, 741.2) SU/mL, respectively, which drastically increased to 168.4 (20.9, 1463), 30.7 (0.1, 509.9), and 231.7 (23.8, 2074.9) SU/mL, respectively at the second collection. For S-IgG, 32.8 SU/mL and 168.4 SU/mL correspond to 195.7 BAU/mL and 999.2 BAU/mL, respectively, when converted to WHO units. The 50% neutralizing titer (NT_{50}) against the wild-type, alpha, and delta strains on administration was 125.5 (<40, 625.3), 239.1 (<40, 656.7), and 140.0 (<40, 1034.1)-fold, respectively, which drastically increased to 474.1 (63.7, 2348.8), 1148.6 (264.3, 4080.6), and 908.3 (85.9, 4249.5) (geometric mean, range)-fold, respectively, at the second collection (Fig. 1). In one case, N-IgG was not elevated at the first and second sampling, presumably because the patient had a mild disease [5].

The first specimen was collected at a median of 13.5 days after the first dose of vaccination, which was 7 days after COVID-19 onset in our study. Since the incubation period of COVID-19 was approximately 5 days [6] before the spread of the omicron variant, we estimate that our patients became infected approximately 2 days after vaccination. Several studies have shown that the amount of S-IgG or neutralizing titer of serum against SARS-CoV-2 are under the detection limit for the first week and gradually elevate in the second week after administration of the first dose of an mRNA vaccine [7–10]. Therefore, the patients were likely to have been infected before the mRNA vaccine-induced immunity was established.

Notably, the geometric mean of S-IgG and NT_{50} against the wild-type strain on admission (approximately 14 days after the initial vaccination) in the current study was 32.8 SU/mL (195.7 BAU/mL) and 125.5-fold, respectively, which was significantly higher than that in our previous report on the COVID-19 mRNA vaccine [10]. Other studies that evaluated S-IgG at various collection times from the first vaccination reported values of 100 BAU/mL at 14 days [11], 91.36 BAU/mL at 14 days [12], 18.9 BAU/mL at 20 days [13], and 172 BAU/mL at 22 days [14]. These data suggest that the natural SARS-CoV-2 infection further induced S-IgG and neutralizing antibodies after the initial dose of COVID-19 mRNA vaccine in the participants.

In patients with SARS-CoV-2 infection alone, the amount of S-IgG and the neutralizing titer do not increase until the second to third week after infection [15]. In fact, N-IgG, an indicator of infection, was not elevated in our patients at the time of the first sample collection. Thus, the increase in S-IgG level and neutralizing titer at the time of initial sampling may primarily reflect an immune response due to vaccination rather than infection. However, since both values were higher than those reported previously, humoral immunity was considered to have been already established at this point, and S-IgG and neutralizing titer increased more quickly due to infection with SARS-CoV-2. Although it is difficult to evaluate the effectiveness of a single vaccination in preventing infection in this study, our results may provide important data on the course of immune response following vaccination.

Table 1
Patient characteristics, vaccination details, strains, and outcomes of COVID-19 infections after the first vaccination (n = 9).

Demographics	No. (%)
Male	8 (88.9)
Age [median, IQR]	49 [46, 60]
Smokers	4 (44.4)
Vaccine type	
Pfizer-BioNtech	2 (22.2)
Moderna	6 (66.7)
Unknown	1 (11.1)
Strains	
Alpha variant	1 (11.1)
Delta variant	7 (77.8)
Unknown	1 (11.1)
Comorbidity	
Any comorbidity	8 (88.9)
Liver disease	3 (33.3)
Diabetes	3 (33.3)
Obesity	3 (33.3)
Dyslipidemia	3 (33.3)
Hyperuricemia	3 (33.3)
Hypertension	1 (11.1)
HIV	1 (11.1)
Pituitary adenoma	1 (11.1)
Cerebral infarction	1 (11.1)
Outcome	
No oxygen	1 (11.1)
Oxygen support	5 (55.6)
High-flow oxygen device use	2 (22.2)
Noninvasive mechanical ventilation[a]	1 (11.1)
Death	0 (0)
Length of hospital stay [median, IQR]	8 [6,10]
Days [median, IQR]	
From vaccination to onset[b]	8 [6.75, 9.75]
From onset to admission	6 [5,7]
From vaccination to first sampling[b]	13.5 [13, 15.5]
From vaccination to second sampling[b]	20 [19.75, 41.5]
From onset to first sampling	7 [5,8]
From onset to second sampling	13 [11, 28]

IQR; interquartile range.
[a] Noninvasive mechanical ventilation includes biphasic positive airway pressure (BIPAP) or continuous positive airway pressure (CPAP).
[b] One patient who could not remember the vaccination date and only recalled the month was excluded from the analysis.

Authors' contributions

NOkumura, SS, HM, and NOhmagari designed the study. NOkumura, SS, YA, and MS implemented the study and collected data. YT, NI and KM determined the antibody titers and neutralizing activity. JT were responsible for the mutational analysis. NOkumura, SS, and YA wrote the first draft of the manuscript. HM and NOhmagari supervised this study. All authors revised the manuscript and approved the final version.

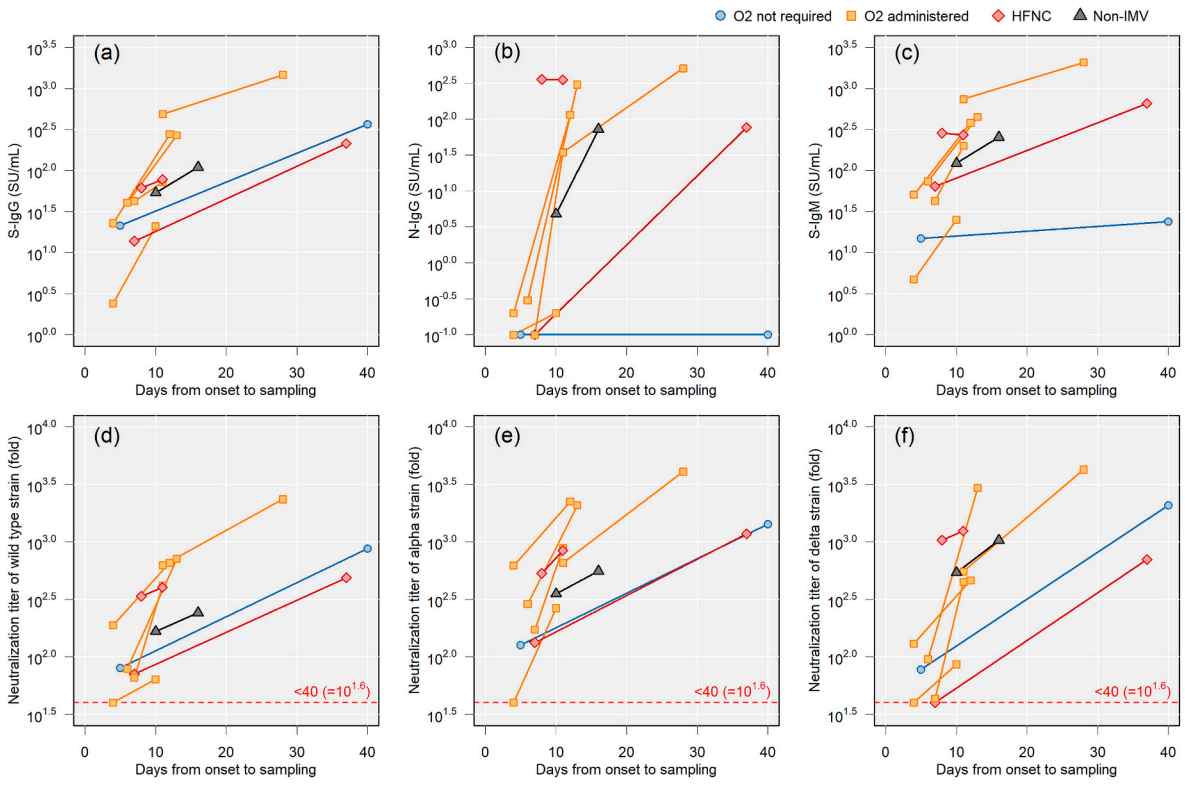

Fig. 1. Antibody titer and neutralizing titer in patients with COVID-19 infection after the first vaccination
NT50 values determined to be less than 20-fold were treated as 20-fold. The lowest detection limit for S1-binding-IgG and S1-binding-IgM quantification was 0.1 SU/mL, and values lower than 0.1 SU/mL were calculated as 0.1 SU/mL.

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Declaration of competing interest

All the authors have nothing to declare.

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