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Note

Anti-spike protein antibody titer at the time of breakthrough infection of SARS-CoV-2 omicron

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ABSTRACT

By December 2021, about 80% of people over the age of 12 had been vaccinated in Japan, and almost all people were vaccinated with the mRNA vaccine. We investigated here the anti-spike protein antibody titer at the time of breakthrough infection of SARS-CoV-2 omicron. A total of 32 SARS-CoV2 omicron breakthrough infection was included in the study. The median antibody titer at breakthrough infection was 776 AU/mL overall, of which the median antibody titer of BNT162b2 vaccinated was 633 AU/mL and that of mRNA-1273 vaccinated was 9416 AU/mL. This result suggests that low levels of antibody titers 6 months after vaccination do not provide sufficient antibodies to prevent the omicron variant breakthrough infection, which may occur with a higher anti-spike antibody titer after vaccination with mRNA-1273. However, antibody titers in some patients were comparable to those immediately after the second vaccination with either mRNA vaccine.

The most prevalent variant of concern in Japan in early 2022 is named omicron. Its immune escape potential was predicted by mutations in the part of the spike and has been confirmed by observations of an increased incidence of reinfections and breakthrough infections [1]. By December 2021, about 80% of people over the age of 12 had been vaccinated in Japan, and mRNA vaccines were used for almost all of them. In such a situation, some questions had been of great concern; can commercially available assays be used to predict people at high risk of developing breakthrough infections, who is more prioritized to receive a third dose, or who has the greatest benefit of neutralizing antibody therapy at the time of infection? To answer these questions, we investigated the anti-spike protein antibody titer at the time of breakthrough infection of SARS-CoV-2 omicron.

We conducted a retrospective analysis of all patients who were diagnosed with COVID-19 by reverse transcription polymerase chain reaction using nasopharyngeal swabs or saliva sample in January 2022. We included only individuals infected with SARS-CoV-2 omicron after two doses of the mRNA vaccine who had the results of anti-spike protein antibody titer measured by Alinity SARS-CoV-2 IgG II Quant assay (Abbott, USA), which is designed to detect IgG antibodies, including neutralizing antibodies, to the receptor binding domain of the S1 subunit of the spike protein of SARS-CoV-2 in serum and plasma by chemiluminescent immunoassay. SARS-CoV-2 omicron was identified by VirSNiP SARS-CoV-2 Spike L452R and VirSNiP SARS-CoV-2 Spike S371L/S373P (TIB MLBIOL, Germany), in which about 100 bp long fragment is amplified and analyzed running a melting curve, using specific detection probe for each mutation above and we regarded L452R– S371L+ S373P+ as SARS-CoV-2 omicron. Patients with immunodeficiency diseases were not included in this study, because antibody response may be attenuated in the patients with cellular immunodeficiency. Asymptomatic patients were excluded because the time since infection was unknown. Mann–Whitney *U* test were used to evaluate the difference in antibody titer between the BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna). Statistical significance was defined as 2-sided P values < 0.05.

A total of 32 SARS-CoV2 omicron breakthrough infections were included in the study as described in Supplementary Table 1. Among 32 eligible patients, twenty-eight were vaccinated with BNT162b2 and four

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were vaccinated with mRNA-1273. All of them were Japanese and had mild to moderate COVID-19. The median age was 54 years (range: 16–94 years), and 77% (14/32) were male. The median number of months from the second vaccination to the breakthrough infection was 5 months (range: 2–7 months), and the antibody titer was measured 5 days (range 2–8) after the onset. Anti-spike protein antibody titers at the time of breakthrough infection of SARS-CoV-2 omicron are summarized in Table 1. The median antibody titer at breakthrough infection was 776 AU/mL (IQR: 411–1805) overall, of which the median antibody titer of BNT162b2 vaccinated was 633 AU/mL (IQR: 400–994) and that of mRNA-1273 vaccinated was 9416 AU/mL (IQR: 7470–16671). The number of months from the second vaccination to the breakthrough infection in the mRNA-1273 group are significantly shorter than those in the BNT162b2, whereas there was no significant difference between the mRNA-1273 group and the BNT162b2 group in the number of days from the onset date to the test.

As of January 2022, millions of people have been infected or vaccinated worldwide and SARS-CoV-2 neutralizing antibodies have been shown to predict disease severity and survival [2]. Clinicians should now treat patients as having basic immunity to SARS-CoV-2. Commercial SARS-CoV-2 IgG assays would become increasingly important to quickly obtain the patient's immune status, predict their disease severity, and decide treatment options [3]. Israel et al. reported that the median SARS-CoV-2 IgG antibody titer (Abbott Architect®) after BNT162b2 vaccination decreased by 95.5% at 6 months (i.e., 447 AU/mL) compared to the highest median antibody response (i.e., 9913 AU/mL) at one month after the second vaccination [4]. Our data showed that neutralizing antibody titers were considered to be attenuated in those who had breakthrough infection after BNT162b2 vaccination, and most of them were consistent with the attenuated antibody titer 6 months after vaccination. On the other hand, those vaccinated with the mRNA-1273 had a shorter time from the second vaccination to breakthrough infection and higher antibody titers at the time of infection than those vaccinated with the BNT162b2. This result suggests that breakthrough infection may occur with a higher anti-spike antibody titer after vaccination with mRNA-1273, but it is difficult to draw any conclusions due to the limitations of this study such as small sample size, the influence of Japanese vaccination strategy and the fact that the vaccination of BNT162b2 and mRNA-1273 started at different times. In Japan, BNT162b2 was available earlier than mRNA-1273. If the omicron variant outbreak occurred earlier in Japan, it is possible that more BNT162b2 vaccinated individuals could be infected when the time since the second vaccination was shorter and the antibody titer was higher. In this study, breakthrough infection occurred in 75% of patients with antibody titers below 2000 AU/mL, but antibody titers in some patients were comparable to those immediately after the second vaccination, as shown in Supplementary Table 1. Moreover, a previous report has shown that binding and functional antibodies measured using both a lentivirus-based pseudovirus assay and a live-virus focus reduction neutralization test against variants other than omicron variant persisted in most subjects, albeit at low levels, for 6 months after the primary series of the mRNA-1273 [5], however, our data suggest that low levels of antibody titers 6 months after vaccination do not provide sufficient antibodies to maintain functional binding to the omicron variant. Several studies have shown that neutralizing antibody titer is a potential biomarker for the protection against SARS-CoV-2 infection [2,6]. However, commercially available assays have not been calibrated using common reference standards, making it difficult to define the exact level of neutralizing antibodies required for preventing symptomatic COVID-19 and to compare with current and future studies [7]. Moreover, clinical data regarding SARS-CoV-2 omicron breakthrough infection was scarce. In our study, most patients had low antibody titers at the time of breakthrough infection, but some patients were infected even with high antibody titers, therefore, no threshold titer could be determined. Nevertheless, some report described the effectiveness of boosters on the omicron variant [8–10]. Third vaccinations are recommended regardless of their antibody titer to prevent the COVID-19 caused by omicron variant.

Table 1
Comparison of Anti-spike protein IgG at the time of infection of Omicron variant.

	Total (N = 32)	mRNA-1273 (N = 4)	BNT162b2 (N = 28)	*P* value
Age (IQR)	54 (37–78)	37 (34.5–48)	57.5 (42.8–72.3)	0.16[a]
Male/Female	20/12	3/1	17/11	0.99[b]
Number of months from the second vaccination (IQR)	5 (4–6)	4 (4–5)	5.5 (5–6)	0.03[a]
Number of days from onset (IQR)	4 (3–6)	4 (4–6)	4 (3–5.3)	0.43[a]
Anti-spike protein igG (IQR)	776 (411–1805)	9416 (7470–16671)	633 (400–994)	0.0015[a]

[a] Mann–Whitney *U* test.
[b] Fisher's exact test.

Contributions

EA carried out the project and drafted the manuscript. EA, MS, MK, TT and HY were responsible for the clinical management of patients. EN, MI, TK and YN contributed to measurement of antibody titer. MS revised the manuscript. All authors approved the final manuscript.

Ethics approval

Ethics approval was granted by the ethics board of the Institute of Medical Science, University of Tokyo (2020-5-0420).

ICMJE statement

All authors meet the ICMJE authorship criteria.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2022.03.021.

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