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Case Report

Antibody responses after two doses of SARS-CoV-2 mRNA-1273 vaccine in an individual with history of COVID-19 re-infection

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ABSTRACT

We present a case of a 58-year-old Japanese man with a history of 2 previous COVID-19 infections, who received 2 doses of mRNA-1273 vaccine. We are not aware of any previous study regarding antibody tendency after 2 infections and 2 vaccinations. We evaluated his IgG titer of antispike protein and neutralizing activity from the first infection before and after 2 doses of vaccine. Both antispike IgG titer and neutralizing activity showed a tendency to decline almost 1 year after initial infection; they rapidly increased after the first vaccination, and they remained high after the second vaccination. Although this is a single case report, it seems to have generalizability because the findings are consistent with previous reports regarding single infections or 3 doses of vaccination. Our findings suggest that a single booster shot may provide sufficient protection and aid the understanding of immunologic responses of vaccination in patients with COVID-19 with history of re-infection.

Introduction

Since December 2019, COVID-19 caused by SARS-CoV-2 has spread worldwide (Hayakawa et al., 2020). As of January 25th, 2022, 544 re-infected COVID-19 cases have been reported worldwide (BNO news. 2022; Inada et al., 2021).

Medical history of COVID-19 appears to have a protective effect against re-infection but especially among older people, protection against repeat infection is merely 47% (Hansen et al., 2021). Since the end of 2020, 2 messenger RNA vaccines—mRNA-1273 (Moderna) and BNT162b2 (Pfizer)—which induce the antispike protein of SARS-CoV-2, have shown high efficacy in preventing COVID-19 onset and severe disease (Golob et al., 2021). Many countries, including Japan and the United States, recommend that everyone should be vaccinated regardless of history of COVID-19 (Centers for Disease Control and Prevention, United States. 2022; Ministry of Health, Labour and Welfare, Japan. 2022). Only a single dose of mRNA vaccine can elicit rapid immune responses in seropositive participants (Krammer et al., 2021). However, to the best of our knowledge, there are no reports of antibody responses and implications of vaccination among individuals with a history of COVID-19 re-infection.

Here, we evaluated the trend in antispike protein antibody titers, including neutralizing antibodies, in a patient with COVID-19 re-infection after 2 doses of mRNA vaccine and discussed the implications of vaccination in patients who experienced re-infection.

Case presentation

A 58-year-old Japanese man with a medical history of hyperlipidemia was diagnosed with COVID-19 re-infection 4 months after

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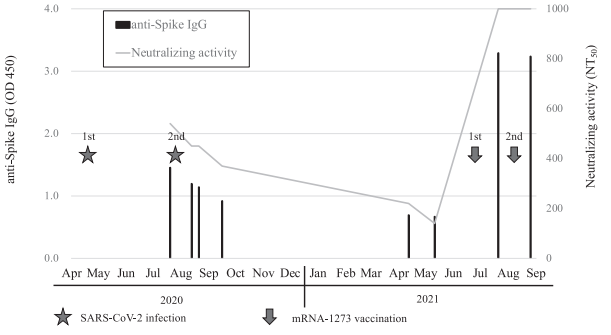

Figure 1. Timeline of antispike protein IgG and neutralizing activity. The patient was diagnosed with COVID-19 infection twice, on April 17th and July 31st, 2020, and was vaccinated with mRNA-1273 on July 5th and on August 2nd, 2021. Two NT_{50} values after vaccination were above the upper limit (NT_{50}:>1,000).

his initial COVID-19 infection (Inada et al., 2021). Although phylogenic investigations were not done for both episodes, according to the epidemiology of SARS-CoV-2 in Japan, the causative variants were assumed to be PANGO lineage B.1.1.162 and B.1.1.284, which were domestic minor variants of SARS-CoV-2 in Japan (Sekizuka et al., 2021). Fifteen months after the initial infection, he received 2 doses of mRNA-1273 vaccinations 4 weeks apart. After each vaccination, he developed a fever of 40°C for 1 and 2 days, respectively, which improved with antifebrile medication. We evaluated the antispike protein antibody titer, including neutralizing antibody, approximately 1 year after the initial infection and after each vaccination.

The measurement of antiSARS-CoV-2 spike IgGs was performed as per standard protocol. Briefly, recombinant spike-protein-coated plates were incubated with 1/800-diluted patient sera at 37°C for 1 hour. After washing, the plate was incubated with horseradish peroxidase-conjugated antihuman IgG (GeneTex, Irvine, CA, USA) at 37°C for 30 minutes and developed with 3,3,5,5-tetramethylbenzidine substrate (Nacalai Tesque, Kyoto, Japan). Samples from healthy volunteers without SARS-CoV-2 infection were used as negative controls, whereas those from infected patients with high levels of antispike IgGs were used as positive controls. Each sample was assayed in triplicate. The cut-off value was the negative control mean +3 standard deviation.

The neutralizing activity of the sera of the patients was determined as previously described (Maeda et al., 2021a). In brief, each serum was serially diluted 4-fold in the culture medium. The diluted sera were incubated with 50% tissue culture infectious dose ($TCID_{50}$) of viruses at 37°C for 20 minutes, after which the sera-virus mixtures were inoculated into $VeroE6_{TMPRSS2}$ cells (1.0×10^4/well) in 96-well plates. The SARS-CoV-2 strain, SARS-CoV-205-2N (PANGO lineage B) (Maeda et al., 2021b), was used in this assay. After culturing the cells for 3 days, the levels of cytopathic effect (CPE) observed in SARS-CoV-2-exposed cells were determined using the WST-8 assay using the Cell Counting Kit-8 (Dojindo, Kumamoto, Japan). The serum dilution that resulted in 50% inhibition of CPE was defined as a 50% neutralization titer (NT_{50}).

The anti-SARS-CoV-2 spike protein IgG antibody level and NT_{50}, which remained high after re-infection with SARS-CoV-2, declined about 1 year after the initial infection (anti-SARS-CoV-2 spike protein IgG antibody level was 0.67, and NT_{50} value was x140).

However, after the first mRNA-1273 vaccination, the anti-SARS-CoV-2 spike protein IgG antibody level and NT_{50} increased rapidly and were higher than their original levels at the time of infection (anti-SARS-CoV-2 spike protein IgG antibody level = 3.29, NT_{50} >1,000). Furthermore, the titer remained high after the second vaccination (anti-SARS-CoV-2 spike protein IgG antibody level = 3.24, NT_{50} >1000) (Figure 1).

Discussion

Here, we have shown the trend of antispike protein antibody titers and NT_{50} against COVID-19 re-infection, about 1 year after initial infection and after 2 doses of mRNA-1273 vaccine. An individual with previous COVID-19 infection is less likely to experience re-infection (Hansen et al., 2021), but it is not clear whether an individual with 2 previous infections of COVID-19 may experience a third infection. An anecdotal case series has shown the occurrence of a third infection (Hasanzadeh et al., 2021). According to a study of vaccine breakthrough, participants who had a breakthrough infection tended to have a lower IgG level and lower NT_{50} (Bergwerk et al., 2021), suggesting that an individual who has a lower antibody titer might be more easily re-infected.

Our report highlights 2 important considerations. First, even if an individual has a history of re-infection with SASR-CoV-2, the antispike protein IgG antibodies and NT_{50} decrease approximately 1 year after initial infection. This suggests the possibility of a third infection. Second, after the first vaccination, the anti-SARS-CoV-2 spike protein IgG antibody level and NT_{50} increase rapidly and are higher than at the time of infection. The antibody titer after vaccination is higher than in those who had been infected only once (Terada et al., 2021). This may suggest that SARS-CoV-2 re-infection before a mRNA vaccination could induce robust antibody response, and sufficient immunity could be obtained without a second vaccination. Some experts suggest that a single mRNA vaccine dose may provide effective protection, even in previously infected persons (Krammer et al., 2021). At present, however, evidence to support this idea is lacking in the real world. It requires further examination whether individuals with history of COVID-19 re-infection need less doses of vaccination.

Our study has several limitations. First, this study evaluated antispike antibodies and NT_{50} in a single case of re-infection. However, this antibody response seems similar to the trend among individuals with past infection or 2 doses of vaccination. Namely, antibody titers decrease after a single infection event (Chen et al., 2021) or 2 doses of vaccination (Doria-Rose et al., 2021) and increase rapidly and strongly in response to vaccination after a single infection (Krammer et al., 2021) or a booster after 2 doses of vaccination. Therefore, although this study describes the antibody trend of a single case, the tendency is consistent with previous reports and plausible. Second, we evaluated the tendency of the antibody titer and NT_{50} in vitro, but the relationship between antibody trend and disease prevention or severity is still unclear. Despite these limitations, to the best of our knowledge, this report is the first to evaluate the trend in antispike protein antibody titers and NT_{50} in a patient re-infected with COVID-19 after 2 doses of mRNA vaccination.

In conclusion, the antiSARS-CoV-2 spike protein IgG antibody level and NT_{50} increase rapidly after the first mRNA vaccination, and this high antibody titer is maintained after the second vaccination in a previously re-infected individual. There are clear implications of vaccination in such re-infected patients and by increasing the number of cases, the postvaccination response in those who have recovered from re-infection will be further clarified.

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Ethical approval and informed consent

This study was approved by the ethics committee of the National Center for Global Health and Medicine (NCGM) (approval no: NCGM-G-003536-03 and NCGM-G-004136-00) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of the paper.

Disclosures

The authors have no conflicts of interest to declare.

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