Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Case Report

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

Makoto Inada, Masahiro Ishikane, Mari Terada, Akihiro Matsunaga, Kenji Maeda, Noriko Iwamoto, Mugen Ujie, Satoshi Kutsuna, Shinichiro Morioka, Yukihito Ishizaka, Hiroaki Mitsuya, Norio Ohmagari

A R T I C L E   I N F O

Article history:
Received 24 February 2022
Revised 10 March 2022
Accepted 12 March 2022

Keywords:
COVID-19
SARS-CoV-2
re-infection
antispoke protein IgG antibody
neutralizing antibody vaccine

A B S T R A C T

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 antispoke protein and neutralizing activity from the first infection before and after 2 doses of vaccine. Both antispoke 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.

© 2022 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

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 antispoke 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 antispoke 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...
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 3rd and on August 2nd, 2021. Two NT50 values after vaccination were above the upper limit (NT50 > 1,000).

Discussion

Here, we have shown the trend of antispike protein antibody titers and NT50 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 NT50 (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 SARS-CoV-2, the antispike protein IgG antibodies and NT50 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 NT50 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 NT50 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 NT50 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 NT50 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 NT50 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.

Acknowledgments

We would like to thank Drs. Okba N.M.A. and Haagmans B.L. (Department of Viroscience, Erasmus Medical Center, NL) for providing the plasmid encoding full-length SARS-CoV-2 spike protein and Drs. Teratake Y. and Ueno M. (Department of Intractable Diseases, NCGM) for preparing the spike protein.
Funding

This work was supported by the Ministry of Health, Labour and Welfare Policy Research Grants, Research on Emerging and Reemerging Infectious Diseases and Immunization [grant number 20HA1006], Japan Agency for Medical Research and Development [grant numbers JP19fk0108163, JP20fk0108160, and JP20fk108262, JP20fk0108502h001], and the NCGM Intramural Research Fund [grant numbers 20A2003D and 21A006]. These funding sources had no involvement in the content of this study.

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.

References

Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C; et al. Covid-19 breakthrough infections in vaccinated health care workers. N Engl J Med 2021;385(16):1474–84.
Chen J, Liu X, Zhang X, Lin Y, Liu D, Xun J; et al. Decline in neutralising antibody responses, but sustained T-cell immunity, in COVID-19 patients at 7 months post-infection. Clin Transl Immunology 2021;10(7):e1319.
Doria-Rose N, Suthar MS, Makowski M, O’Connell S, McDermott AB, Flach B; et al. Antibody persistence through 6 months after the second dose of mRNA-1273 vaccine for Covid-19. N Engl J Med 2021;384(23):2259–61.
Golob J, Lugogo N, Lauring AS, Lok AS. SARS-CoV-2 vaccines: a triumph of science and collaboration. JCI Insight 2021;6(9).
Hansen CH, Michlmayr D, Gubbelis SM, Mbibak K, Ethelberg S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. Lancet 2021;397(10280):1204–12.
Hasanazadeh S, Shariatzamghani SS, Yavilin A, Javan A, Rahmani M, Ganjoo S; et al. Amel Jameh Dar. Case series: Reinfection of recovered SARS-CoV-2 patients for the third time. Case Series. Clin Case Rep 2021;9(10):e04936. doi:10.1002/ccr3.4936.
Hayakawa K, Kutsuna S, Kawamata T, Sugiki Y, Nonaka C, Tanaka K; et al. SARS–CoV-2 infection among returnees on charter flights to Japan from Hubei, China: a report from National Center for Global Health and Medicine. Glob Health Med 2020;2(2):107–11.
Inada M, Ishikane M, Terada M, Matsuura A, Maeda K, Tsuchiya K; et al. Asymptomatic COVID-19 re-infection in a Japanese male by elevated half-maximal inhibitory concentration (IC50) of neutralizing antibodies. J Infect Chemother 2021;27(7):1063–7.
Krammer F, Srivastava K, Alishammary H, Amoako AA, Awawda MH, Beach KF; et al. Antibody responses in seropositive persons after a single dose of SARS-CoV-2 mRNA vaccine. N Engl J Med 2021;384(14):1372–4.
Maeda K, Amano M, Uemura Y, Tsuchiya K, Matsushima T, Noda K; et al. Correlates of neutralizing/SARS-CoV-2-S1-binding antibody response with adverse effects and immune kinetics in BNT162b2-vaccinated individuals. Sci. Rep. 2021a;11:22848.
BNO news. COVID-19 reinfection tracker. 2022. https://bnonews.com/index.php/2020/08/covid-19-reinfection-tracker/ (Accessed 20 February 2022)
Maeda K, Hijashiki-Kuwata N, Kinoshita N, Kutsuna S, Tsuchiya K, Hattori S; et al. Neutralization of SARS-CoV-2 with IgG from COVID-19-convalescent plasma. Sci. Rep.:5563. Sci Rep. 2021b;11(1):5563.
Sekizuka Y, Itohara K, Hashino M, Okubo K, Ohnishi A, Goto K; et al. A discernable increase in the severe acute respiratory syndrome coronavirus 2 R1 lineage carrying an E484K spike protein mutation in Japan. Infect Genet Evol 2021;94 Oct.
Terada M, Kutsuna S, Togano T, Saito S, Kinoshita N, Shimamushi Y; et al. How we secured a COVID-19 convalescent plasma procurement scheme in Japan. Transfusion 2021;61(7):1998–2007.
Ministry of Health, Labour and Welfare, Japan. COVID-19 vaccine Q&A. 2022. https://www.cov19-vaccine.mhlw.go.jp/qa/0028.html. (Accessed 20 February 2022)
Centers for Disease Control and Prevention, United States. Interim clinical considerations for use of COVID-19 vaccines currently approved or authorized in the United States. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. (Accessed 20 February 2022)

M. Inada, M. Ishikane, M. Terada et al.

International Journal of Infectious Diseases 119 (2022) 18–20