Letter to the Editor

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Assessment of antibody titer after third doses of COVID-19 mRNA vaccination in healthy volunteers

https://doi.org/10.1515/labmed-2022-0008
Received January 25, 2022; accepted February 18, 2022; published online March 16, 2022

Keywords: BNT162b2 vaccine; humoral response; SARS-CoV-2; third doses; vaccination.

To the Editor,

As of the end of January 2022, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected over 351 million individuals worldwide and caused more than 5.6 million deaths. In the year of 2021, numerous groups, including us, have been reported about humoral responses and side effects after two doses of BNT162b2 vaccinations [1–4]. Subsequently, third dose of SARS-CoV-2 vaccination have just started from December 1, 2021 in Japan. Currently, several groups have started to report humoral responses after third doses of vaccinations, indicating an efficacy of a third dose [5–7]. However, further studies are warranted to verify these findings. Our group have recently reported antibody titers and side effects after two doses of BNT162b2 vaccination [4], and subsequent study of antibody decline 6 months after first vaccination [8]. In the current study, we examined levels of SARS-CoV-2 antibodies among healthy volunteers at Tohoku Medical and Pharmaceutical University Hospital, before and after vaccination with the Pfizer/BioNTech BNT162b2 mRNA vaccine for the third time.

Antibody titers were evaluated using a newly established, highly sensitive, fully automated chemiluminescent enzyme immunoassay (CLEIA) designed to specifically detect IgG and IgM against the SARS-CoV-2 spike protein receptor-binding domain (RBD) as described [4, 8]. Of 41 volunteers who received two doses of BNT162b2 at our hospital, all completed 9 months of follow-up after the first dose. At the time of writing, all 41 participants have completed this period, and none experienced SARS-CoV-2 infections prior to third vaccination or during post-third vaccination follow-up. Serum samples were obtained on average 279.5 days (SD 5.5 days) after the first dose of BNT162b2 (Figure 1A). 264.4 days (SD 5.8 days) after the first dose of BNT162b2, mean anti-RBD IgM was 0.3 C.O.I. (SD 0.3), which was baseline level and equal to day 0 and 180 days after first vaccination [4] (Figure 1B). Additionally, mean anti-RBD IgG antibodies was 17.3 AU/mL (SD 13.1) at 264.4 days after vaccination (Figure 1C), which was 6.36% of the antibody after the second dose. At 15 days after the third vaccination (day 279.5), anti-SARS-CoV-2 IgM was modestly but significantly increased (average, 1.7 C.O.I. [SD 3.9], 5.7-fold increase) (Figure 1B), while anti-SARS-CoV-2 IgG was more markedly increased (average, 702.9 AU/mL [SD 402.9], 40.6-fold increase) (Figure 1C).

Quite recently, the antibody titers before and after a third dose of the SARS-CoV-2 BNT162b2 vaccine in adults aged more that 60 years (n=97) have been published [7]. In their study, median IgG titer was increased from 440 to 25,468 (AU/mL), with no major adverse events. From the retrospective cohort study, Saciuk et al. [9], concluded that the third dose provides added protection against SARS-CoV-2 infection for those vaccinated 6 months ago. Barda et al. [10], recently demonstrated that using data from mandatory health-care coverage for over half of the Israeli population, and compared 0.728 million individuals receiving a third vaccine dose to demographically and clinically similar controls who did not receive a third dose. As a result, admission to hospital (231 vs. 29), severe disease (157 vs. 17) and death (44 vs. 7) is significantly reduced in the population vaccinated with three doses [10].

The long-term efficacy of BNT162b2 vaccination remains to be determined. Our current study may have limitations, such as small sample size, lack of cellular immunity testing and neutralizing antibody testing. However, based on our observations of dramatic increase of IgG

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titers after third vaccination, third doses of BNT 162b2 is effective to protect against SARS-CoV-2.

Acknowledgments: The authors gratefully acknowledge the generous help of all members of the Department of Clinical Laboratory in Tohoku Medical and Pharmaceutical Hospital including Ms. Yuri Sato, Ms. Mei Takahashi, Ms. Nodoka Chida, Ms. Mizue Takahashi, and Ms. Shukuko Iwabuchi. The authors also thank members of the Product Planning Department in Fujirebio for helpful discussions and support.

Research funding: This work was supported in part by the Shino-Test Corporation Research Fund.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: RK: provision of reagents (FUJIREBIO), KH, YI: no potential competing interest, ST: granted from Shino-Test Corp. research fund.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and has been approved by the Ethics Committee in Tohoku Medical and Pharmaceutical University Hospital in the 2020 fiscal year (2020-2-256).

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