Immune Netw. 2022 Aug;22(4):e31
https://doi.org/10.4110/in.2022.22.e31
pISSN 1598-2629·eISSN 2092-6685

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Comparison of Waning Immunity Between Booster Vaccination and 2-Dose Vaccination With BNT162b2

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Received: Jun 3, 2022
Accepted: Jun 8, 2022
Published online: Jun 17, 2022

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Conflict of Interest
The authors declare no potential conflicts of interest.

Booster vaccination has been implemented worldwide due to the emergence of the delta variant and waning immunity following the primary series of coronavirus disease 2019 (COVID-19) vaccination. However, there is limited data on the duration of protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the possibility of waning immunity following booster vaccination. Longer intervals between booster doses are required because longer intervals are associated with generally greater immune responses (1). Therefore, a 6-month interval between booster vaccinations of BNT162b2 after two 3-wk intervals of BNT162b2 induces stronger immune responses (2). However, it is unknown whether waning immunity after a booster dose of BNT162b2 with longer intervals is comparable to that after a 2-dose BNT162b2, despite the fact that significant waning immune response has been observed in several studies (3-5). Therefore, in this study, we compared the slope from the peak Ab titer (2-wk post immunization level) to the lowest Ab titer (23 wk after the second vaccination) and that from the peak Ab titer (2-wk post immunization level) to the Ab titer 12 wk after the booster vaccination. In addition, the slope of T cell responses from peak to lowest value after the second vaccination and that after booster vaccination was compared.

Healthcare workers (HCWs) who received BNT162b2 vaccination and agreed to blood sampling at Asan Medical Center were prospectively enrolled. They were given two doses of BNT162b2 separated by 3 wk, followed by a booster dose of BNT162b2 6 months later. Blood samples were collected from vaccinated HCWs 2, 9, and 23 wk after the second dose of BNT162b2, as well as 2 and 12 wk after the booster dose of BNT162b2. Asan Medical Center's Institutional Review Board (IRB Nos. 2020-0297 and 2021-0170) reviewed and approved this study, and all participants provided written informed consent.

The titer of anti-SARS-CoV-2 S1 specific IgG Ab was measured using an in-house developed ELISA, and the data are presented in IU/ml. The interferon-gamma ELISPOT assay was used to assess the SARS-CoV-2-specific T cell response in isolated PBMCs. T cells were stimulated using SARS-CoV-2 spike-overlapping peptides (Miltenyi Biotec, Bergisch Gladbach, Germany), and the number of spot-forming cells per 5.0×10^5 PBMCs were counted with an automated ELISPOT reader (AID iSPOT; Autoimmun Diagnostika GmbH, Strassberg, Germany).

A linear mixed regression model was used to compare the slope from the peak Ab titer to the lowest Ab titer (23 wk after the second vaccination) and the slope from the peak Ab titer

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Abbreviations

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Author Contributions

Conceptualization: Kim SH; Data curation: Yun SC; Formal analysis: Kim JY, Kwon JS, Yun SC; Funding acquisition: Kim SH; Investigation: Jung J, Kim JY, Kwon JS; Methodology: Kim JY, Kwon JS; Software: Yun SC; Visualization: Yun SC; Writing - original draft: Jung J; Writing - review & editing: Kim SH.

to the Ab titer 12 wk after the booster vaccination and the length of observation period was adjusted. We compared the slopes of IgG Ab titer and T cell responses. We then performed a sex-based stratified analysis.

A total of 49 HCWs were enrolled in the study. Thirty-four of these (69%) were available for immunogenicity analysis both after the second vaccination and after booster vaccination, while 15 (31%) were only available for immunogenicity analysis after booster vaccination. The median (interquartile range) age of the 49 HCWs was 29 years (26–35), with 32 (65%) being females.

The estimated (±SE) the slope of log value of the IgG titer after the second vaccination was −0.061±0.002 and that after booster vaccination was −0.062±0.003 (p=0.86) (**Supplementary Table 1**). In subgroup analysis, the estimated (±SE) log value of slope after second vaccination in female participants was −0.063±0.003 and that after booster vaccination was −0.069±0.003 (p=0.14) (**Fig. 1A** and **Supplementary Table 1**). Furthermore, the estimated (±SE) log value of slope after second vaccination in male participants was −0.060±0.004 and that after booster vaccination was −0.056±0.004 (p=0.40).

The estimated (±SE) slope of T cell responses after the second vaccination was −4.149±0.854 and that after booster vaccination was −3.505±1.508 (p=0.71) (**Supplementary Table 1**). In subgroup analysis, the estimated (±SE) slope after second vaccination in female participants was −2.860±0.969 and that after booster vaccination was −5.566±1.718 (P=0.17) (**Fig. 1B** and **Supplementary Table 1**). Furthermore, the estimated (±SE) slope after second vaccination in male participants was −5.439±1.407, and that after booster vaccination was −1.444±2.478 (p=0.16).

We found a similar waning Ab response after the booster dose at a 6-month interval, so vaccine effectiveness against symptomatic COVID-19 by omicron or new variant is expected to be significantly reduced 6 to 12 months after the booster dose. Therefore, our findings may be useful in preparing for the upcoming fall-winter season against COVID-19.

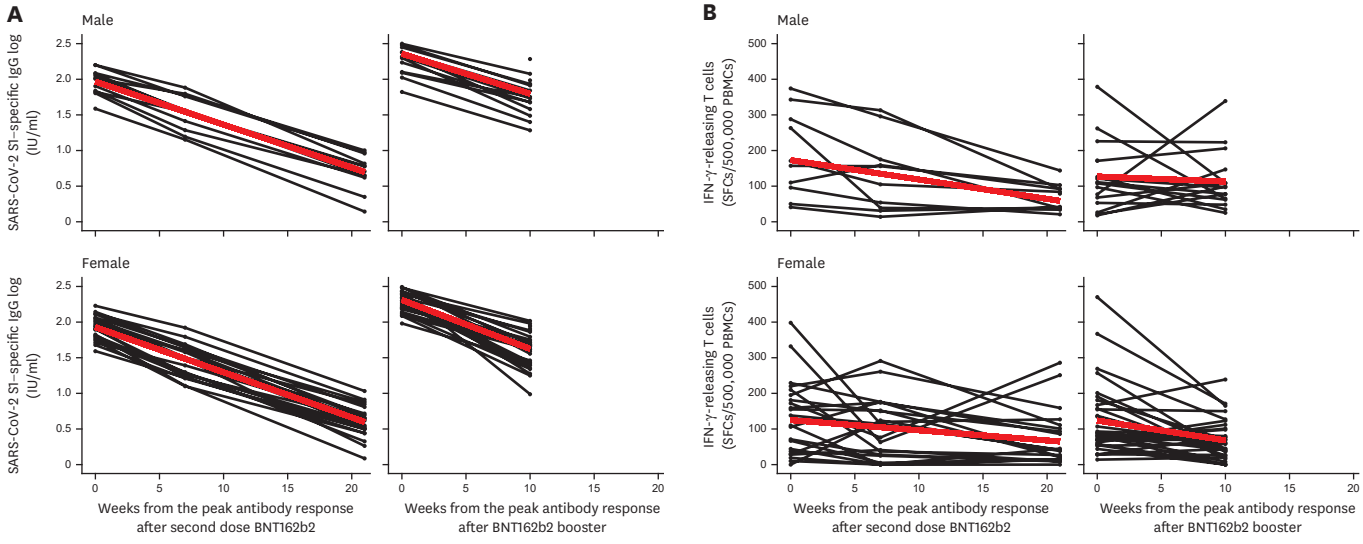

Figure 1. The estimated value of slope (red line) of anti-SARS-CoV-2 specific IgG Ab and T cell response. (A) The estimated value of slope (red line) of anti-SARS-CoV-2 specific IgG Ab by linear mixed regression model stratified by sex. (B) The estimated value of slope (red line) of SARS-CoV-2 specific T cell response by linear mixed regression model stratified by sex. The slope was from the peak level (2 wk after second vaccination) to the lowest level (23 wk after the second vaccination) after the second vaccination and that from the peak level (2 wk after second vaccination) to the level of 12 wk after the booster vaccination.

https://doi.org/10.4110/in.2022.22.e31

The experience with the emergence of the delta variant revealed a significant waning of vaccine effectiveness against severe COVID-19, particularly in the elderly population, as well as symptomatic COVID-19 (5). Despite waning humoral immunity, vaccine-induced protection against severe disease is likely to persist because cellular immunity is likely to persist. We found that cellular immune response after the booster dose BNT162b2 vaccination showed a similar waning pattern compared with that after the 2-dose BNT162b2 vaccination, although the slope of waning cellular immune response was gentle. Therefore, we anticipate that some significant waning of vaccine effectiveness against severe COVID-19 by omicron or a new variant may occur 6 to 12 months after booster BNT162b2 vaccination, particularly in the elderly population.

Only 3-month follow-up data after the booster dose were included in our study. Therefore, the possibility of different waning kinetics from 3 to 6 months after the booster dose cannot be ruled out, despite the lack of biologic plausibility. This study enrolled a lot of young adults. Therefore, more study in the elderly population, as well as longer-term follow-up after the booster dose, is required. Despite these limitations, our data provide important information on the preparedness for additional booster doses at least 6 to 12 months after the third dose vaccination.

ACKNOWLEDGEMENTS

This study was supported by grants from the Korea Advanced Research Program through the National Research Foundation of Korea (NRF), which is funded by the Ministry of Science and ICT, Republic of Korea (grant no. 2020M3H8A1115041).

SUPPLEMENTARY MATERIAL

Supplementary Table 1

The estimated (and SE) log value of peak Ab and T-cell response after second vaccination and booster vaccination, and the slope from peak Ab titer (or T-cell response) to lowest Ab titer (T cell response) after second vaccination and booster vaccination. Analysis was stratified by sex

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