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Letter to the Editor

Humoral and cellular responses to the third COVID-19 BNT162b2 vaccine dose in research institute workers in Japan

Editor: Prof. R. Read

Dear Editor

We read with interest the article on SARS-CoV-2 antibody and T cell responses after first and second vaccination among healthcare workers by Mak et al. [1]. Cellular immunity was reportedly not necessarily related with humoral immunity, while T cell responses and anti-spike IgG (S-IgG) levels increased after vaccination. SARS-CoV-2 T cell response and S-IgG levels were also investigated before and after the third BNT162b2 (Pfizer-BioNTech) vaccine dose with an employee cohort of the National Center for Geriatrics and Gerontology (NCGG), consisting of a hospital and a research institute in Japan.

The S-IgG levels were reported to dramatically increase after the second BNT162b2 dose and reduced to about 10% for a period of 7–8 months as part of a repeated cross-sectional study [2,3]. In contrast, T cell responses were maintained even after 130–164 days post vaccination, although the sample size was small ($N = 11$). In this study, the cellular immunity kinetics induced by the third dose using a larger cohort were analyzed.

As summarized in Table S1, 86 NCGG employees who had received the second BNT162b2 dose in April–June 2021 were enrolled. The mean age ± SD was 46.69 ± 10.11 years and 38.4% were women. Clinical staff (doctors, nurses, and allied healthcare professionals) accounted for 34.9%, while the rest were engaged in basic research and investigation, general office duties, and other non-clinical work. Only three participants were N-IgG positive (≥10.0 SU/ml) at day 0 and two participants were seroconverted during the survey period.

Blood samples were obtained on days 0, 15, 29, and 61 after the third dose. Residual blood samples of annual health checkups 130–164 days after the third dose held in June 2022 were also used in the survey. Chemiluminescence enzyme immunoassays from Sysmex were used to measure S-IgG and anti-nucleocapsid IgG (N-IgG). QuantiFERON SARS-CoV-2 RUO kit (Qiagen) was used to evaluate SARS-CoV-2 T cell response by measuring interferon-γ (IFN-γ) produced in response to $CD4^+$ T cell epitopes (Ag-1) and $CD4^+$ and $CD8^+$ T cell epitopes (Ag-2). Values (IU/ml) were obtained by subtracting the negative control (Nil) value from the row data. The cutoff to positivity was set at 0.15 IU/ml according to the previous report [4].

The S-IgG levels kinetics are shown in Fig. 1A. The median S-IgG value was 152.6 BAU/mL (IQR 87.75–266.9) before the third dose. S-IgG value dramatically increased to 5690 BAU/mL (IQR 3531–8282) throughout the 15-day vaccination period, which was about 2.2 times greater than the 2636 BAU/mL value obtained after 6–20 days following the second dose in the previous survey [3]. The values at day 29 and 61 were 4626 (IQR 2498–7317) and 3065 BAU/mL (IQR 1718–4671), respectively, indicating the S-IgG induced by the third dose remained high for at least 2 months. On days 130–164, the level decreased to 1748 BAU/mL (IQR 987.8–2997), which was 29.3% compared to the day 15 value.

On day 0, Ag-1- and Ag-2-induced T cell response median values were 0.125 IU/mL (IQR 0.0375–0.3775, 41/86 positives) and 0.25 IU/mL (IQR 0.0675–0.64, 53/86 positives), respectively (Fig. 1B). IFN-γ response to Ag-1 significantly increased to 0.59 IU/mL (IQR 0.2425–1.598, 68/84 positives) at day 15 ($p < 0.0001$, Kruskal–Wallis test) and maintained until day 61 (0.48 IU/mL, IQR 0.190–1.800, 66/78 positives). After 130–164 days, the level contracted to 0.25 IU/mL (IQR 0.068–0.785, 52/77 positives), similar to those at day 0 ($p = 0.3218$). The Ag-2 response also showed a comparable trend. The level increased to 1.18 IU/mL (IQR 0.4500–2.413, 76/84 positives) on day 15 ($p < 0.0001$) and maintained until day 61 (0.86 IU/mL, IQR 0.2900–2.640, 76/83 positives). On day 130–164, the level decreased to 0.49 IU/mL (0.100–1.280, 52/78 positives), similar to the day 0 level ($p = 0.2474$).

A previous study among workers of a similar institute in Japan exhibited no correlation between humoral and T cell immunity after the first and second BNT162b2 doses [5]. In contrast, we observed significantly weak correlations between S-IgG and IFN-γ levels on days 0–61, and significantly moderate correlations on days 130–164 (Spearman's rank correlation coefficients $r = 0.4859$ $p < 0.0001$ and $r = 0.4075$, $p < 0.0002$, for Ag-1 and Ag-2, respectively) (Fig. 2). Our data suggested that S-IgG titer remained high when higher T cell response levels are maintained for an extended period, although the correlation between humoral and cellular immunity in response to COVID-19 mRNA vaccine remains controversial [1,5,6,7].

In conclusion, the present study demonstrated that the third BNT16b2 dose induced SARS-CoV-2 humoral and cellular responses. The antibody responses, where all participants obtained higher S-IgG levels after vaccination, indicated the efficacy of the booster dose. Conversely, individual differences were observed in the T cell responses. About half of the survey participants responded positively to the antigen on day 0, whereas about 20% and 10% missed to respond to Ag-1 and Ag-2 even after the dose, respectively. While breakthrough Omicron variant infections are reported worldwide despite the high antibody levels, T cell immunity importance is underscored by its contribution to prevent severe disease where most epitopes are conserved among variants

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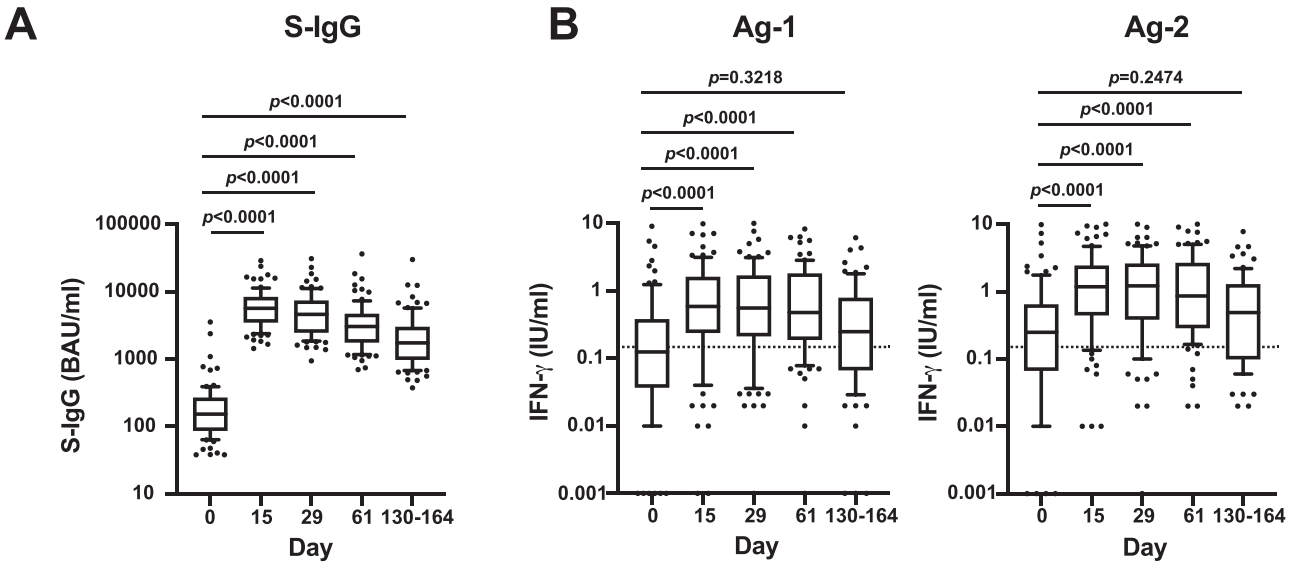

Fig. 1. Humoral and cellular response before and after the third BNT162b2 vaccination dose. (A) Levels of S-IgG in serum on day 0 ($n = 86$), day 15 ($n = 84$), day 29 ($n = 85$), day 61 ($n = 83$), and day 130–164 ($n = 78$) after inoculation. (B) Levels of IFN-γ released in response to Ag-1 and Ag-2. Dotted lines indicate the positivity cutoff values. Data are expressed as box plots: middle line, median; box edges, 25th–75th percentile. Statistical comparisons were performed by nonparametric ANOVA, Kruskal–Wallis test.

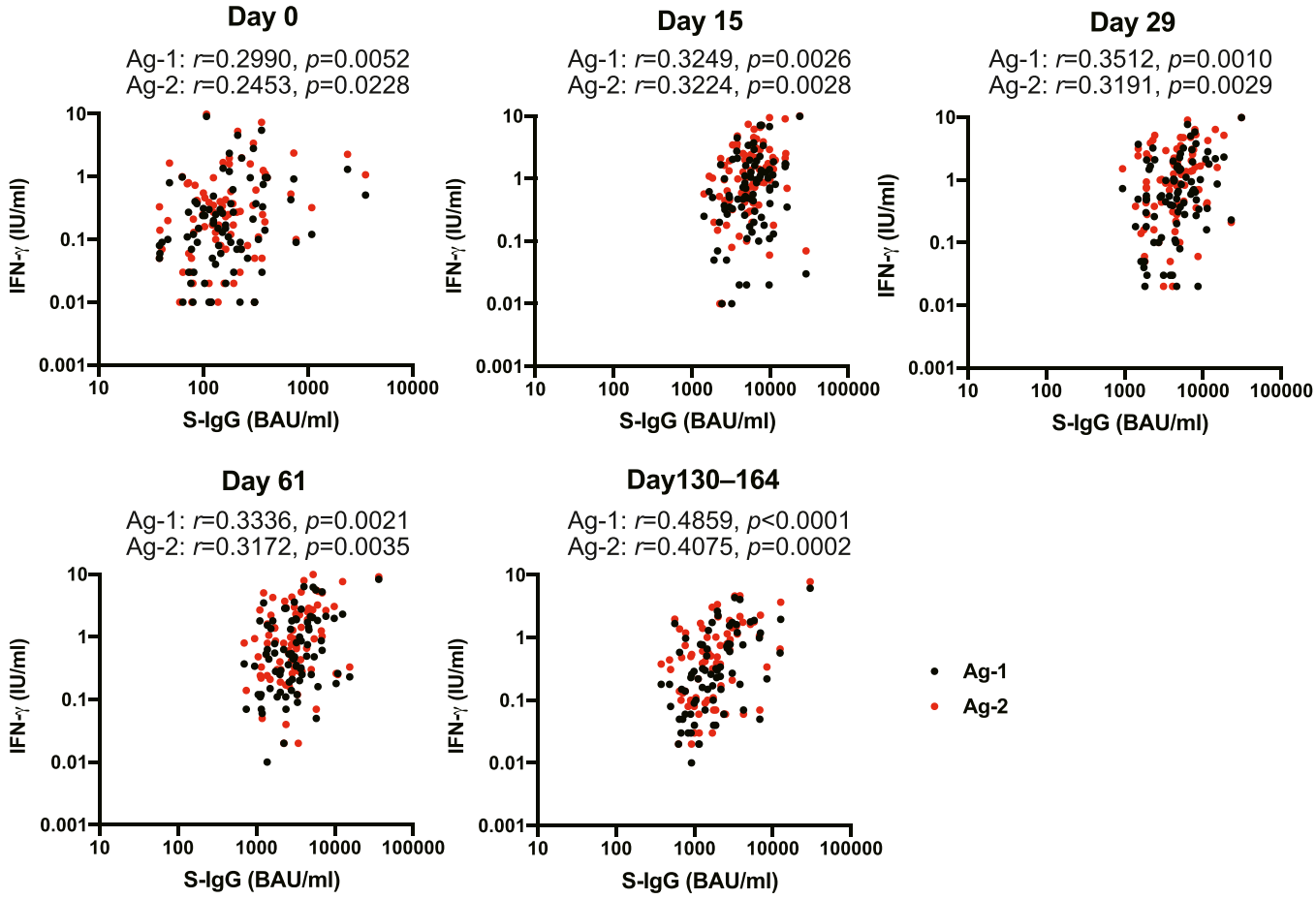

Fig. 2. Correlation between S-IgG titer and T cell responses before and after the third dose. Correlation between S-IgG levels and IFN-γ levels induced by Ag-1 and Ag-2, respectively, at each point were analyzed by Spearman's rank correlation test. Spearman r and p-values are presented in each graph.

[8]. T cell response analyses in addition to antibody levels are required to allude to vaccination efficiency.

Data sharing statement

Datasets used in the present study are available upon reasonable requests.

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Ethical approval

The Institutional Review Board of the Ethics and Conflicts of Interest Committee (No. 1481) approved this study. All participants provided written informed consent.

Declarations of Competing Interest

The authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.10.026.

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