DOI: 10.1111/ajt.16998

Waning humoral immune response to the BNT162b2 vaccine in heart transplant recipients over 6 months

To the Editor:

A third booster dose of mRNA vaccines, shown to elicit enhanced immune responses in solid organ transplant (SOT) recipients,[1,2] has been recommended for immunocompromised patients, but the optimal interval between doses to ensure long-lasting protective immunity has not been determined. We therefore conducted a six-month longitudinal prospective study of antibody kinetics in heart transplant (HT) recipients with positive antibody responses after two doses of the BNT162b2 vaccine (Pfizer BioNTech), given at a mean interval of 21.8 (±1.3) days. The study was approved by our institutional review board (8314-21-SMC).

The cohort comprised 20 adult HT recipients (mean age 54 [±16] years; 16 [80%] male, median time from transplant to vaccination 8.5 [3.8–15.8] years). None had previously suffered from or developed COVID-19 during the study period. Hypertension (65%) and diabetes mellitus (45%) were the most common comorbidities. Immunosuppression with a calcineurin inhibitor and mycophenolate was the most frequently followed protocol (50%). Beginning two weeks after the second vaccination, patients were assessed for receptor-binding domain (RBD) IgG and neutralizing antibody responses (Figure 1).[3] Blood samples were obtained every 28 ± 14 days such that there were four sampling periods: period 1 (P1), days 14–56; period 2 (P2), days 57–99; period 3 (P3), days 100–141; and period 4 (P4), days 142–184.

We found a significant waning of the humoral response within the 6 months after the second vaccine dose (Figure 1, Figure S1). While both RBD IgG and neutralizing antibody titers declined significantly, the patterns of decline were different: After peaking during P1, the titers of RBD IgG antibodies decreased gradually at a consistent rate, with an overall decrease by a factor of 1.8. The geometric mean titer (GMT) for IgG anti-RBD antibodies declined from 2.50 (95% CI, 1.86–3.35) in P1 as follows: to 2.06 (95% CI, 1.32–3.19) in P2, to 1.66 (95% CI, 1.03–2.66) in P3, and to 1.40 (95% CI, 0.80–2.45) in P4 (Figure 1A). In contrast, neutralization titers peaked later (from P1 to P2), remained stable for a longer period (in P3), and then declined sharply (in P4), with an overall decrease by a factor of 4.9 (Figure 1B): GMTs for neutralizing antibodies were 34.30 (95% CI, 14.32–82.16) in P1, 55.17 (95% CI, 18.35–165.9), in P2, 57.97 (95% CI, 23.57–142.5) in P3, and 11.31 (95% CI, 3.42–37.38) in P4.

Importantly, there was a strong correlation between IgG anti-RBD antibody and neutralizing antibody titers during P2-P4 (Spearman's rank correlation 0.7–0.9). These findings have important clinical implications in the management of the COVID-19 pandemic, since functional neutralization assays (the gold standard for evaluation of vaccine efficacy) are expensive and time-consuming[4,5] and are thus often unavailable in clinical practice.

Information on the duration and breadth of activity afforded by the mRNA vaccines is a key factor in establishing immunization protocols, especially for high-risk populations. We present here the first study of the kinetics of neutralizing antibody activity in SOT recipients. 6 months after the second dose of the BNT162b2 vaccine, the humoral response had waned substantially, suggesting that the timing of the third mRNA vaccine dose in immunocompromised populations should be 6 months at the latest from the second dose.

Among the limitations of this study is the relatively small number of subjects; nevertheless, following the second vaccine dose, neutralizing antibodies were detectable in only 9% of HT recipients.[1] Thus, our cohort comprises the largest cohort of HT recipients reported to date. Also, there is not yet an established threshold for vaccine-induced immune responses and protection from SARS-CoV-2 infection, and the study was not designed to establish the vaccine clinical efficacy or the role of the T cell response.

KEYWORDS

clinical research/practice, heart transplantation/cardiology, infection and infectious agents—viral, infection and infectious agents—viral: SARS-CoV-2/COVID-19

ACKNOWLEDGMENTS

The authors gratefully acknowledge the invaluable contribution of Ms. Hana Algazi-Patal, the coordinator of heart transplants at the Sheba Medical Center, Ms. Sarit Skiano, Ms. Michal Kelishek, Ms. Merav Moreno, Ms. Tal Aharon, Ms. Eitana Mor, Ms. Ravid Amitai, and Mr. Aharon Greitzer of the Heart Transplant Unit, Sheba Medical Center, for organizing the vaccination effort for our cohort. We thank our editor, Ms. Inez Mureinik, for critical reading of the manuscript.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

Abbreviations: COVID-19, coronavirus disease 2019; ELISA, enzyme-linked immunosorbent assay; GMT, geometric mean titer; HT, heart transplantation; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SOT, solid organ transplants.

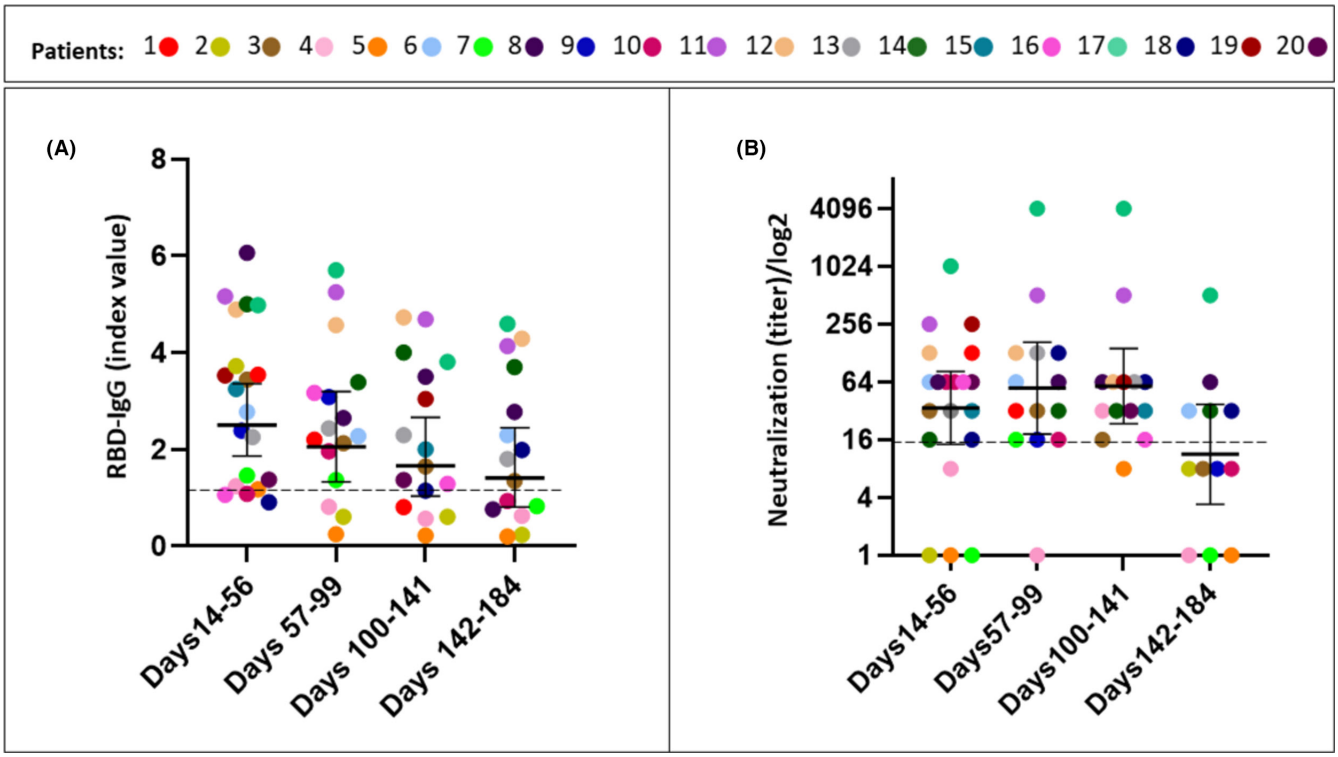

FIGURE 1 Quantification of receptor-binding domain (RBD) IgG (A) and neutralizing antibodies (B) throughout the 6 months following the second dose of the BNT162b2 vaccine. An ELISA assay was used to detect IgG antibodies against the RBD of SARS-CoV-2, and a SARS-CoV-2 pseudo-virus neutralization assay was performed to detect SARS-CoV-2 neutralizing antibodies.[3] Dashed line indicates the limit level of positive antibodies. Solid lines and numbers indicate the geometric mean titer, and error bars show the 95% confidence interval

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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