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Short Communication

COVID-19 Vaccination does not Prevent Breakthrough Omicron Infection in 3-times Vaccinated Subjects due to Irrelevant Adaptive Immunity

Anat Achiron*, Mathilda Mandel, David Magalashvili, Sapir Dreyer-Alster, Polina Sonis, Rina Falb, Michael Gurevich

Department of Neurology, Laura Schwarz-Kipp Research of Autoimmune Diseases, Sackler School of Medicine Tel-Aviv University, Neuroimmunology Laboratory, Multiple Sclerosis Center, Sheba Medical Center, Ramat-Gann, Israel

ABSTRACT

We evaluated adaptive immune responses in three-time BNT162b2 mRNA vaccinated individuals that subsequently developed Omicron Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) breakthrough infections. Following the third mRNA booster, all subjects had protective IgG antibody response and memory B and T cells responses. However, these responses were not sufficient to prevent Omicron infection that occurred within a period of few months following the booster dose. Our findings suggest the need for a targeted vaccine against Omicron.

Keywords: COVID-19; Vaccination; Immunogenicity; Infections; Omicron; SARS-CoV-2; Receptor Binding Domain (RBD)

INTRODUCTION

Omicron (B.1.1.529), detected in November 2021, has emerged as a new SARS-CoV-2 Variant of Concern (VOC) and caused high infection rate over the world because its high transmissibility [1]. This SARS-CoV-2 variant is currently known to be the most mutated with nearly 50 mutations in its genome and more than 35 mutations in the viral spike (S) region, particularly at the Receptor Binding Domain (RBD) [2]. In the early stage of the Omicron pandemic wave, it was believed that fully vaccinated, and moreover triple vaccinated subjects, will maintain protective immunity against the virus. A contact tracing study for Omicron conducted in Israel demonstrated that from 51 contacts only one was infected [3]. Similarly, within three weeks of the Omicron-emerged wave in South Africa, epidemiological surveillance concluded that two vaccine doses protected individuals from severe disease [4]. However, in a live virus micro neutralization assay, Omicron variant tested with sera from BNT162b2 recipients demonstrated detectable neutralizing antibodies only in 20% of BNT162b2 recipients [5]. Additional *in-vitro* studies reported a reduction in the neutralization efficacy of infection and vaccine-elicited antibodies against Omicron [6-10], indicating a partial failure of the current vaccines to prevent the disease. Sera from Pfizer vaccine recipients, sampled after complete vaccination, barely inhibited Omicron, while administration of a booster Pfizer dose did generate an anti-Omicron neutralizing response, but with titers 4-6 folds lower than against that of the ancestral strain [11].

No data is available in relation to the immune status in-vivo in triple vaccinated subjects, prior to Omicron infection. In the current study we first report the occurrence of breakthrough symptomatic Omicron infection in m-RNA Pfizer BNT162b2 triple vaccinated subjects in spite of appropriate humoral and cellular immune responses to the vaccine.

METHODS

Subjects

Inclusion criteria:

- Symptomatic Omicron infection with confirmed SARS-CoV-2 infection by PCR;
- Previously received three intramuscular injections of 30 μg of Pfizer BNT162b2 (0.3 ml volume);
- All had appropriate humoral and cellular immune responses to the vaccine. Demographic and clinical symptoms were documented.

Correspondence to: Anat Achiron, Department of Neurology, Laura Schwarz-Kipp Research of Autoimmune Diseases, Sackler School of Medicine Tel-Aviv University, Neuroimmunology Laboratory, Multiple Sclerosis Center, Sheba Medical Center, Ramat-Gann, Israel, Tel: +972-3-5303932; Email: anat.achiron@sheba.health.gov.il

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Immunological evaluation

Adaptive immunity included the presence of humoral response by SARS-CoV-2 anti-spike S1 IgG antibodies performed using anti-SARS-CoV-2 QuantiVac ELISA IgG (Euroimmun, Lubeck, Germany) based on the S1 domain of the spike protein [12]. Cut-off for positive IgG level was determined as >35.2 binding antibody units (BAU)/ml. Cellular response was evaluated by the presence of COVID-19 memory B-cells detected by SARS-CoV-2-specific Receptor Binding Domain (RBD) ELISpot and Interferon gamma (IFN-γ), Interleukin 2 (IL2), and IFN-γ+IL2-secreting memory T cells in the presence of S1 peptide pools using FluoroSpot [13,14]. The results of the ELISpot and FluoroSpot assays were evaluated using an IRIS reader and analyzed using IRIS software version 1.1.9 (Mabtech AB).

Ethics

The study was approved by Sheba Medical Center Institutional Review Board. All subjects signed written informed consent. The study design is presented in Figure 1.

RESULTS

Sixteen healthy subjects, 9 females, mean ± SD age 52.7 ± 13.9 years, 3-times vaccinated by Pfizer BNT162b2 against COVID-19, who developed Omicron within 5.2 ± 0.8 months from the third booster vaccine dose were included in the study. All subjects had symptomatic Omicron infection in spite of protective humoral and adaptive immune responses to the Pfizer BNT162b2 vaccine. All subjects had positive anti-spike IgG, with an average titer of 1592.1 ± 988.6 BAU/ml, all were positive for COVID-19 RBD memory B-cells and all were positive for any COVID-19 memory T-cells. The circulating SARS-CoV-2-reactive cytokine-producing memory T-cell frequencies were: 87.5% IFN-γ, 56.3% IL2, and 56.3% IFN-γ/IL-2 secreting memory T cells in the presence of S1 peptide pools. The results of the immune profiles are presented in Figure 2.

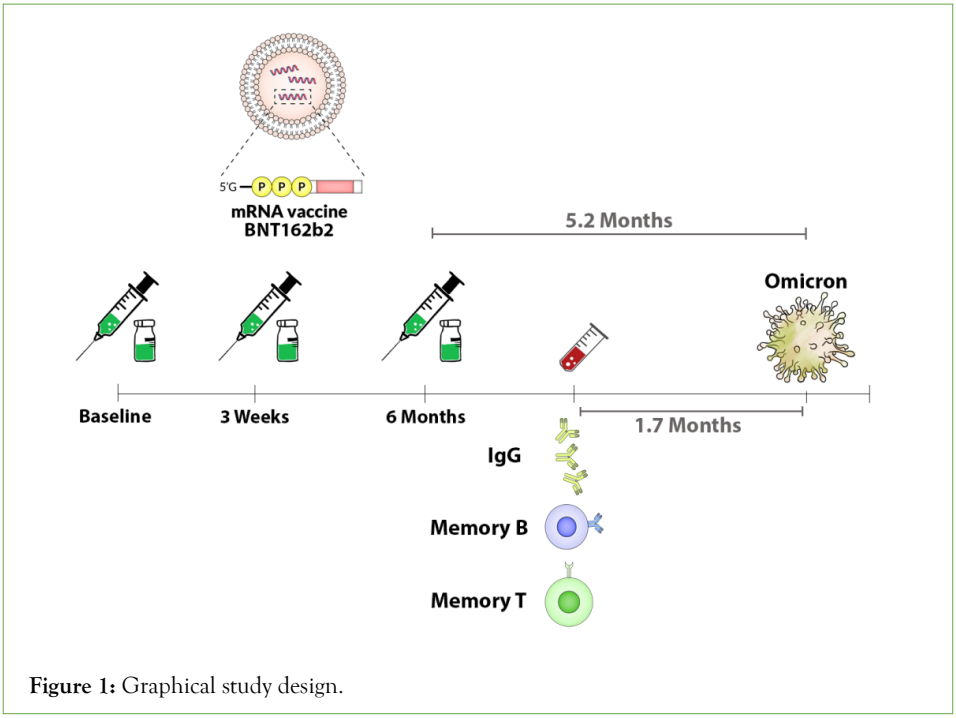

Figure 1: Graphical study design.

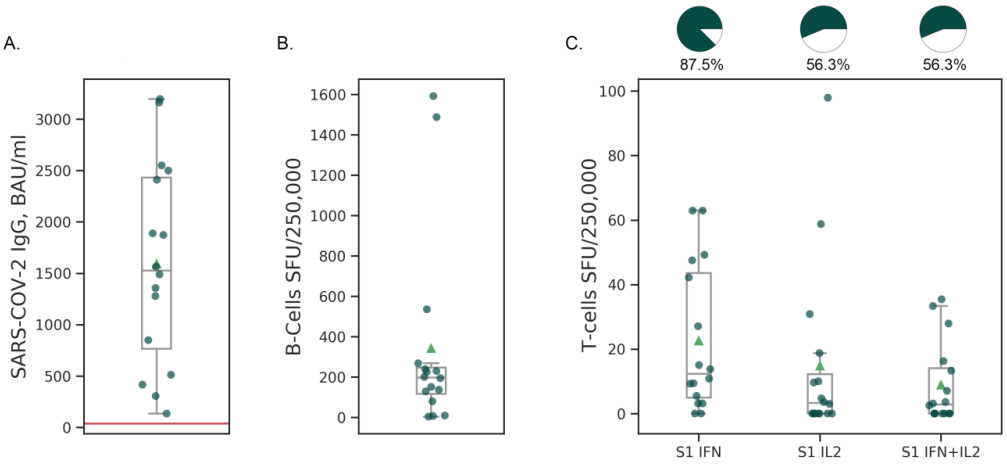

Figure 2: Immune response to SARS-CoV-2 in 3-time COVID-19 vaccinated subjects that developed Omicron. (Note: A) SARS-CoV-2 IgG; B) SARS-CoV-2-specific memory B-cells and memory T-cells; C) Pies depict the proportion of subjects exhibiting a detectable cytokine-producing memory T-cell response.)

DISCUSSION

In the current study we first demonstrated that the immune response against COVID-19 in triple vaccinated subjects was insufficient to prevent symptomatic Omicron infection. Our findings demonstrate that the Pfizer BNT162b2 vaccine that was highly efficient against previous delta and alpha COVID-19 variants did not prevent symptomatic Omicron in real life. These findings are already known in the community as the Omicron infection has spread in the world in-spite of appropriate vaccination. A large Canadian epidemiological study reported that two vaccine doses were not protective against Omicron at any point in time, and similarly the third COVID-19 vaccine dose did not offer much protection compared to the Delta variant [13]. The immunological results of our study demonstrate that both humoral and cellular adaptive responses developed after the third vaccine doses were not sufficient to prevent symptomatic Omicron.

Related to humoral immunity, the anti-spike S1 antibodies present in high levels in our subjects, are known to fail to neutralize Omicron, though Omicron neutralizing antibody titers were reported to increase *in-silico* after a third vaccine immunization [10,12,14,15].

A key question in human vaccination studies is whether the ex-vivo activated cells or the memory cells measured in the cultured assays are of greater protective importance [16]. In this respect, the occurrence of both memory B and T cells was suggested to protect against the new variant.

Kotaki, et al. showed in an *in-vitro* study, that more than one third of RBD-binding IgG+ memory B cells bound Omicron variant, and as a result Omicron-neutralizing antibodies were detected when stimulated *in-vitro* [17].

However, regarding SARS-CoV-2-specific RBD memory B-cells, our findings demonstrate in-vivo that their presence did not restrain the occurrence of Omicron infection. Similarly, a recent study reported that COVID-19 fully vaccinated subjects had reduced memory B cells against the Omicron variant, and that memory B cell recognition of Omicron RBD was substantially diminished [7].

The cellular response of memory T-cells against COVID-19 m-RNA vaccine in our triple vaccinated subjects was not helpful to prevent Omicron. Several studies that have cross-referenced the mutations in Omicron with sites in the SARS-CoV-2 genome known as targets of T cells, found that the majority of sites recognize Omicron [18-20]. Overall, it was reported that at least 83% of the CD4+ T-cell responses and 85% of the CD8+ T-cell responses remained [18]. It is of importance to note that these T-cell studies did not investigate subjects following natural infection, and the assays used tested peptide-based responses rather than the responses that will occur in-vivo, as in real-life the variant might change multiple features of epitope presentation. We observed the presence of SARS-CoV-2-reactive cytokine-producing memory T-cells to the vaccine in all subjects, including T-cells for the effector IFN-γ which was the majority, proliferative IL-2, and IFN-γ/IL-2 Th1 memory responses. A recent study that assessed the resilient T-cell responses to Omicron variant reported that the number of IFN-γ producing T-cells was equal between the ancestral SARS-CoV-2 spike proteins to those against Omicron. However, similarly to our findings there was a decrease in the number of IL-2 producing T-cells against Omicron [21]. In a review from 32 scientific articles from Omicron databases, it was suggested that the third dose will be the solution to defeat SARS-CoV-2 Omicron [22]. Based on our findings we propose a different solution. The administration of a fourth dose of the current COVID-19 vaccine is not expected to be translated into a substantial extra-protection against Omicron [23], therefore, to overcome the new Omicron or other variants, targeted m-RNA vaccines against the RBD-S1 new mutations are needed.

CONCLUSION

This study highlights the need for targeted vaccination against the COVID-19 Omicron variant in three-time BNT162b2 mRNA vaccinated individuals.

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