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Letter to the Editor

Three is better than two: humoral response in allogeneic HSCT after the third BNT162b2 SARS-CoV-2 mRNA vaccine

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Dear Editor,

In our previous study, we evaluated the humoral immune response in 31 patients who underwent hematopoietic stem cell transplantation for hematologic malignancy, after two BNT162b2 SARS-CoV-2 mRNA vaccine doses. We reported a positive humoral immune response (cut-off responders IgG SARS-CoV-2 > 15.0 AU/ml) in 23/31 patients (74%) with a median titer of 303 AU/mL. Factors associated with vaccination response failure were represented by the presence of severe chronic Graft vs Host-Disease (cGVHD) and Combined Antibody Deficiency (CAD)[1]. Between September 2021 and January 2022, 19/31 patients were considered eligible for and received the third BNT162b2 dose according to national guidelines[2]. We performed peripheral blood immunophenotyping (BD Biosciences FACSLyric System, Franklin Lakes, NJ, USA), and we tested neutralizing antibodies to the SARS CoV-2 using IgG anti-spike antibody assay (Liaison® TrimericS Diasorin, Rome, Italy) one month after the administration of the third dose, at a median time of 224 days after the second dose serology. Clinical and biological data were collected retrospectively from medical records. Continuous variables were compared using the Mann-Whitney test and the Wilcoxon test for paired and unpaired data. All analyses were performed using Prism 5.04 statistical software (GraphPad Software, La Jolla, CA, USA). Statistical significance was set at $p < 0.05$.

Because of the change in the unit of measurement between the second and the third dose, Arbitrary Units/mL (AU/mL) were converted to international standard units (BAU/mL) using a conversion factor of 2.6 according to the manufacturer's recommendations. Patients with BAU/mL < 33.8 were considered non-responders, while those with titer > 33.8 BAU/mL were defined as responders. As before the second dose, we performed immunophenotyping of peripheral blood before the third dose, but we could not detect any correlation between the T, B, and natural killer (NK) lymphocyte subsets and the immune response of the patients.

Administration of the third dose resulted in an increase in IgG SARS-CoV-2 titer in 18 out of 19 patients, from a median of 611 BAU/mL (min 10 - max 1,040) to 2,080 (min 22 - max 2,080) BAU/mL, [mean 537.9 BAU/mL (95% CI 322-753.7) *vs.* 632 BAU/mL (95% CI 1,442-2,051) $p = 0.0002$] (Figure 1). Considering the seroconversion rate, 6 out of 19 (32%) patients who received the third dose were considered non-responders, while 13 (68%) were considered responders after the third dose. In our cohort, 5 of the 6 patients who had not

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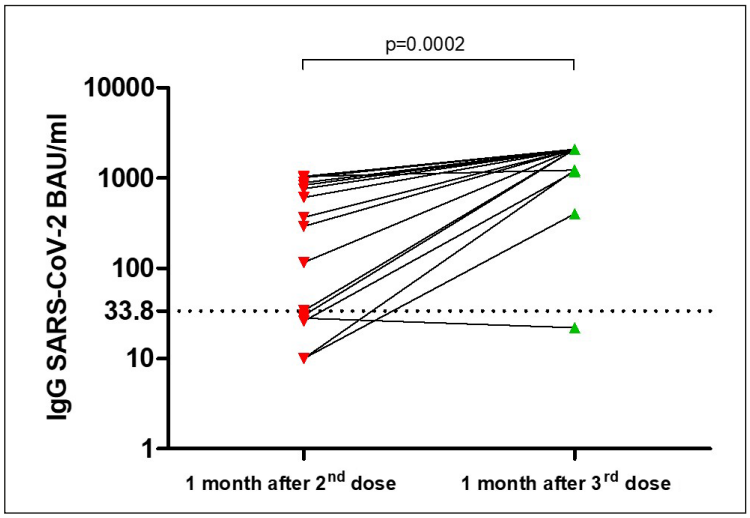

Figure 1. IgG SARS-CoV-2 median titer after 2nd and 3rd dose.

previously responded to the second dose had a seroconversion, with a median IgG SARS-CoV-2 titer of 1,230 (403-2,080) BAU/mL. Only one patient did not experience an increase in IgG SARS-CoV-2 titer after the third dose of vaccine (from 28 to 22 BAU/mL). He underwent a matched unrelated donor transplant in October 2020, and subsequently developed fungal pneumonia treated with voriconazole and discontinued immunosuppression 8 months before the administration of the third dose. At the time of the third dose, he had the following values: cluster of differentiation 4 (CD4) 326/μL, CD19 187 μL, with IgG 1,620 mg/dl, IgM 64 mg/dl, IgA 94 mg/dl.

Despite several studies[3,4] showing low seroconversion rates in certain hematologic disorders characterized by strong immunosuppression, rates of 75-86% have been reported in allogeneic hematopoietic stem cell transplantation (HSCT) patients after two doses of vaccine[5,6] and 89% after the third one[7].

In our cohort, 94.5% of allogeneic HSCT patients achieved seroconversion after the third dose with a rate of 83% (5/6). Our results are consistent with the previous findings reported in the literature[7,8] and highlight the benefit of the third dose in hematologic immunocompromised patients.

Further studies are needed to investigate the duration of the vaccine-induced immunity after HSCT transplantation and the resulting need for additional booster doses.

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Conflict of Interest
All the authors declare that they have no conflict of interest.

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Not applicable.

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References

1) Barabino L, Galitzia A, Murru R, Caocci G, Targhetta C, Greco M, Angioni G, Mulas O, Vacca A, Piras E, Frau V, Costa A, La Nasa G. Chronic graft vs. host disease and hypogammaglobulinemia predict a lower immunological response to the BNT162b2 mRNA COVID-19 vaccine after allogeneic hematopoietic stem cell transplantation. Eur Rev Med Pharmacol Sci 2022; 26: 8984-8989.
2) Girmenia C, Pagano L, Cesaro S, Ciceri F, Corradini P. COVID-19 vaccine in hematopoietic stem-cell transplantation recipients. Version 1.0, 5. Società Italiana di Ematologia (SIE) and Gruppo Italiano Trapianto di Midollo Osseo (GITMO) 2021. Available at: https://www.siematologia.it/storage/siematologia/article/pdf/22/2-documento-sie-gitmo_20210210-124518.pdf.
3) Galitzia A, Barabino L, Murru R, Caocci G, Greco M, Angioni G, Mulas O, Oppi S, Massidda S, Costa A, La Nasa, G. Patients with Chronic Lymphocytic Leukemia Have a Very High Risk of Ineffective Response to the BNT162b2. Vaccine 2022; 10: 1162.
4) Shen Y, Freeman, JA, Holland J, Solterbeck A, Naidu K, Soosapilla A, Downe P, Tang, C, Kerridge I, Wallman L, Van Bilsen N, Milogiannakis V, Akerman A, Martins Costa Gomes, G, Sandgren K, Cunningham AL, Turville S, Mulligan SP. COVID-19 vaccine failure in chronic lymphocytic leukaemia and monoclonal B-lymphocytosis; humoral and cellular immunity. Br J Haematol 2022; 197: 41-51.
5) Watanabe M, Yakushijin K, Funakoshi Y, Ohji G, Hojo W, Sakai H, Saeki M, Hirakawa Y, Matsumoto S, Sakai R, Nagao S, Kitao A, Miyata Y, Koyama T, Saito Y, Kawamoto S, Ito M, Murayama T, Matsuoka H, Minami H. The Safety and Immunogenicity of the BNT162b2 mRNA COVID-19 Vaccine in Japanese Patients after Allogeneic Stem Cell Transplantation. Vaccines (Basel) 2022; 21: 158.
6) Canti L, Humblet-Baron S, Desember I, Neumann J, Pannus P, Heyndrickx L, Henry A, Servais S, Willems E, Ehx G, Goriely S, Seidel L, Michiels J, Willems B, Liston A, Ariën K K, Beguin Y, Goossens ME, Marchant A, Baron F. Predictors of neutralizing antibody response to BNT162b2 vaccination in allogeneic hematopoietic stem cell transplant recipients. J Hematol Oncol 2021; 14: 174.
7) Kimura, M, Ferreira VH, Kothari S, Pasic I, Mattsson JI, Kulasingam V, Humar A, Mah A, Delisle J S, Ierullo M, Majchrzak-Kita B, Kumar D, Hosseini-Moghaddam SM. Safety and Immunogenicity After a Three-Dose SARS-CoV-2 Vaccine Schedule in Allogeneic Stem Cell Transplant Recipients. Transplant Cell Ther 2022; 28: 706-710.
8) Redjoul R, Le Bouter A, Parinet V, Fourati S, Maury S. Antibody response after third BNT162b2 dose in recipients of allogeneic HSCT. Lancet Haematol 2021; 8: 681-683.