Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Cancer Cell

CellPress

Letter

Antibody response against SARS-CoV-2 Delta and Omicron variants after third-dose BNT162b2 vaccination in allo-HCT recipients

Lorenzo Canti,[1,9] Kevin K. Ariën,[2,3,9] Isabelle Desombere,[4,9] Stéphanie Humblet-Baron,[5,9] Pieter Pannus,[4] Leo Heyndrickx,[2] Aurélie Henry,[6] Sophie Servais,[1,6] Evelyne Willems,[6] Grégory Ehx,[1] Stanislas Goriely,[7] Laurence Seidel,[8] Johan Michiels,[2] Betty Willems,[2] Maria E. Goossens,[4,10] Yves Beguin,[1,6,10] Arnaud Marchant,[7,10] and Frédéric Baron[1,6,10,*]

[1]Laboratory of Hematology, GIGA-I3, University of Liege and CHU of Liège, Liege, Belgium
[2]Virology Unit, Department of Biomedical Sciences, Institute of Tropical Medicine, 155 Nationalestraat, 2000 Antwerp, Belgium
[3]Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium
[4]Scientific Directorate Infectious Diseases in Humans, Sciensano, Brussels, Belgium
[5]Department of Microbiology, Immunology and Transplantation, Laboratory of Adaptive Immunology, KU Leuven, Leuven, Belgium
[6]Department of medicine, division of Hematology, CHU of Liège, Liège, Belgium
[7]Institute for Medical Immunology and ULB Center for Research in Immunology (U-CRI), Université Libre de Bruxelles (ULB), Gosselies, Belgium
[8]Department of Biostatistics, University Hospital of Liège, Liège, Belgium
[9]These authors contributed equally
[10]These authors contributed equally
*Correspondence: f.baron@uliege.be
https://doi.org/10.1016/j.ccell.2022.02.005

Allogeneic hematopoietic stem cell transplant (allo-HCT) recipients are particularly at risk of severe COVID-19. In addition, they have lower serological response to two doses of mRNA vaccines as compared to healthy individuals (Redjoul et al., 2021a; Canti et al., 2021; Maillard et al., 2022). Whether they are protected following vaccination against the Delta and Omicron variants remains to be established.

We previously reported a study of 40 allo-HCT recipients immunized with the BNT162b2 mRNA vaccine at 3 weeks apart (days 0 and 21) (Canti et al., 2021). Among the 37 SARS-CoV-2 naive patients, 32 (86%) had detectable RBD binding antibodies (Ab) and 18 (49%) neutralizing Ab (NAb) against wild-type (WT) SARS-CoV-2 following primary immunization (two doses of vaccination). Anti-RBD and NAb titers were significantly lower in allo-HCT recipients than in healthy adults. Furthermore, among allo-HCT recipients, serological responses were less frequent in patients with moderate/severe chronic graft-versus-host disease (GVHD) as well as in patients who had received the anti-CD20 monoclonal Ab rituximab in the year before vaccination. Based on these observations, the protocol was amended to provide a booster dose 14–26 weeks after primary immunization (EudractCT # 2021-000673-83).

Here, we report the waning of Ab after primary BNT162b2 immunization and the Ab response to booster immunization (a third dose of vaccination) in 38 of the 40 allo-HCT patients enrolled in our initial study (Canti et al., 2021). Thirty-seven patients were SARS-CoV-2 seronegative at first vaccination, and one patient (#25) was weakly seropositive at first vaccination and diagnosed with COVID-19 6 days after the first vaccine dose and did not receive the second dose (Table S1). RBD binding Ab and immune cell subsets at baseline were quantified as previously reported (Canti et al., 2021). Nab titers that reduced the number of infected wells by 50% (NT50) were used as a proxy for the NAb concentration in serum, as previously reported (Canti et al., 2021; Ariën et al., 2021).

While prior publications have reported the waning of Ab following two doses of mRNA vaccine in healthy subjects (Levin et al., 2021), Ab waning in allo-HCT recipients has not yet been well documented. The booster dose was administered a median of 153 (range, 146–174) days after the first vaccine dose. RBD binding Ab levels decreased from a median of 497 BAU/mL (geometric mean [geomean] 325.7 BAU/mL; 95% CI: 140.0–757.6 BAU/mL) 28 days after the second vaccine dose (49 days after first vaccine) to a median of 152 BAU/mL (geomean 106.8 BAU/mL; 95% CI: 53.1–214.7 BAU/mL) on the day of booster immunization ($p < 0.0001$; among patients with detectable Ab on day 28 after second vaccine, pre-booster values were a median of 24% of those from day 28 after second vaccine) (Figure S1). Nineteen patients had detectable NAb against WT SARS-CoV-2 at day 28 post-dose two (50%). Before booster, 15 patients had detectable NT50 titers (40%), including 1 patient without detectable NAb at day 28 post-dose two. Among them, only 5 patients had detectable NT50 against the Delta variant.

One possibly vaccine-related suspected unexpected serious adverse reaction was observed after the booster vaccination: patient 7 was diagnosed with transverse myelitis on day 72 after booster immunization. Other adverse events are described in the supplemental information.

Binding RBD Ab levels increased from a median of 152 BAU/mL (geomean 106.8 BAU/mL; 95% CI: 53.1–214.7 BAU/mL) on the day of the booster dose to a median of 2,955 BAU/mL (geomean 1,958 BAU/mL, 95% CI: 1,002–3,827 BAU/mL) 28 days later ($p < 0.0001$) (Figure S1A). Of note, 4 of the 5 patients who failed to seroconvert after the two first doses of the vaccine responded to the booster dose. These data are in line with prior reports assessing binding Ab responses to a third dose of mRNA vaccine in

allo-HCT patients (Redjoul et al., 2021a; Maillard et al., 2022).

To our knowledge, the NAb response against SARS-CoV-2 variants to a third-dose vaccine of mRNA vaccine in allo-HCT recipients has not yet been reported. SARS-CoV-2 WT NT50 titers increased from a geomean 52.5 (95% CI: 37.3–73.8) on the day of the booster dose to 566.8 (95% CI: 351.8–913.4) 28 days later ($p < 0.0001$) (Figure S1B). Geometric mean of Delta variant NT50 titers increased from 28.8 (95% CI: 25.4–32.6) on the day of the booster dose to 200.4 (95% CI: 129.3–310.7) 28 days later ($p < 0.0001$). After booster immunization, 33 (87%), 31 (82%), and 23 (60.5%) patients had detectable NAb against the WT, Delta, and Omicron variants, respectively. As previously observed in healthy individuals (Zeng et al., 2021; Gruell et al., 2022), patients had higher NT50 titers against the WT virus (median 1,078, geomean 566.8, $p < 0.0001$) than against the Delta (median 202, geomean 200.4) and the Omicron (median 80.5, geomean 74.4, $p < 0.0001$) variants following booster immunization. Furthermore, there were strong correlations between binding RBD Ab and NAb levels ($p < 0.001$; Figure S1C).

Moderate/severe chronic GVHD ($n = 10$) was significantly ($p < 0.05$) associated with lower levels of RBD binding Ab and of NAb to SARS-CoV-2 WT and Delta variant before and after booster immunization (Figures S1D–S1F). GVHD was also associated with lower NAb titers against the Omicron variant after booster immunization ($p = 0.0002$; only 1 of the 10 patients with chronic GVHD had detectable NAb against Omicron) (Figure S1G). Among patients without moderate/severe chronic GVHD, rituximab administration within the year before first vaccination was associated with lower RBD binding Ab levels before but not after booster immunization.

There was a correlation beween absolute counts of unswitched memory B cells ($r = 0.51$, $p = 0.001$), class-switched memory B cells ($r = 0.40$, $p = 0.01$), naive B cells ($r = 0.35$, $p = 0.03$), and follicular helper T cells ($r = 0.37$, $p = 0.027$) assessed at baseline of the first immunization and anti-RBD-Ab levels assessed after booster immunization.

Finally, we observed six cases of (mild) COVID-19 infection after third vaccination (see supplemental information).

Three prior studies have assessed the impact of a third dose vaccine in allo-HCT recipients (Redjoul et al., 2021b; Le Bourgeois et al., 2021; Maillard et al., 2022). Redjoul et al. assessed the efficacy of a third dose of vaccine in 42 patients with anti-spike RBD IgG < 4,160 AU/mL (as a surrogate for protection) following two doses of the BNT162b2 vaccine. The third dose was given 51 ± 22 days after the second vaccine. Following the third dose, binding Ab increased significantly from 737 ± 1,009 to 11,099 ± 18,607 AU/mL, with 20 patients reaching the 4,160 AU/mL threshold (Redjoul et al., 2021b). Similarly, Le Bourgeois et al. assessed the efficacy of a third dose of vaccine in 80 allo-HCT patients and observed that 9 patients failed to seroconvert after the third-dose regimen, while two patients seronegative after the second vaccine dose seroconverted with the third dose (Le Bourgeois et al., 2021). More recently, Maillard et al. investigated the impact of a third dose vaccine in 181 allo-HCT recipients (Maillard et al., 2022). The third vaccine was given a median of 54 days after dose 2. Twenty-nine of 70 patients (41%) with no Ab response after the first two doses seroconverted, while booster vaccine increased Ab titers in remaining patients. Unfortunately, none of these studies assessed the impact of the third dose vaccine on NAb. Our study observed that all but one patient seroconverted with the three-dose vaccine but that 18% of the patients failed to develop NAb against the Delta and 39.5% against the Omicron variant. Another difference between prior studies and ours is that the delay between second and third vaccine was significantly longer in our cohort. This might explain the high efficacy of the booster dose in our cohort. Further studies are needed to determine whether a forth vaccine dose is useful in patients who failed to achieve NAb after the first three doses.

There are limitations in our study, including the small sample size, the absence of data on T cell response to the vaccine, and the absence of Ab assessment at the time of COVID-19 onset in 5 of the 6 patients diagnosed with COVID-19 after third vaccination.

In conclusion, in contrast to what has been observed after solid organ transplantation (Jurdi et al., 2022), but as observed in solid cancer patients (Zeng et al., 2021), our data indicate that a majority of allo-HCT patients without active moderate/severe chronic GVHD are able to produce NAb against Delta and Omicron variants in response to a third dose of the BNT162b2 vaccine. Whether this response is sufficient to prevent severe COVID-19 remains to be established in larger studies.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2022.02.005.

ACKNOWLEDGMENTS

L.C. is Televie Research Fellow, F.B. is Senior Research Associate and AM is Research Director at the National Fund for Scientific Research (FNRS) Belgium. We are very grateful to Anne Lawarrée, Inès Fourneau, and Isabelle Bonivers for injecting the patients with the vaccines and performing the blood draws. We are also very grateful to the BHUL (“BHUL - Liege University Hospital Biobank - CHU of Liege & University of Liege, Belgium”) for great handling and strorage of the patients’ samples. We thank Caroline Rodeghiero, Fabienne Jurion, Felicie Chaumont, and Celien Van Oostveldt for performing binding Ab assays. This study was funded by the Belgian Federal Government through Sciensano, by the University of Liège through “Crédits Sectoriels de Recherche en Sciences de la Santé (FSR 2021)” awarded to F.B., by the Research Foundation – Flanders (grant FWO G0G4220N) through K.K.A., and by a KU Leuven starting grant (S.H.-B.).

DECLARATION OF INTERESTS

F.B. has received travel grants from Pfizer, Celgene, Abbvie, Novartis, and Sanofi as well as honoraria from Merck and Abbvie. The other authors declare no relevant conflict of interest.

REFERENCES

Ariën, K.K., Heyndrickx, L., Michiels, J., Vereecken, K., Van Lent, K., Coppens, S., Pannus, P., Martens, G.A., Van Esbroeck, M., Goossens, M.E., et al. (2021). Three doses of the BNT162b2 vaccine confer neutralising antibody capacity against the SARS-CoV-2 B.1.1.529 (Omicron) variant of concern. Preprint at MedRxiv, 2021.12.23.21268316.

Canti, L., Humblet-Baron, S., Desombere, I., Neumann, J., Pannus, P., Heyndrickx, L., Henry, A., Servais, S., Willems, E., Ehx, G., et al. (2021). Predictors of neutralizing antibody response to BNT162b2 vaccination in allogeneic hematopoietic stem cell transplant recipients. J. Hematol. Oncol. *14*, 174.

Gruell, H., Vanshylla, K., Tober-Lau, P., Hillus, D., Schommers, P., Lehmann, C., Kurth, F., Sander, L.E., and Klein, F. (2022). mRNA booster immunization elicits potent neutralizing serum activity against the SARS-CoV-2 Omicron variant. Nat. Med. https://doi.org/10.1038/s41591-021-01676-0.

Jurdi, A.A., Gassen, R.B., Borges, T.J., Lape, I.T., Morena, L., Efe, O., Solhjou, Z., Fekih, R.E.,

Deban, C., Bohan, B., et al. (2022). Diminished antibody response against SARS-CoV-2 Omicron variant after third dose of mRNA vaccine in kidney transplant recipients. MedRxiv, Preprint at 2022.01.03.22268649.

Le Bourgeois, A., Coste-Burel, M., Guillaume, T., Peterlin, P., Garnier, A., Imbert, B.-M., Drumel, T., Mahé, B., Dubruille, V., Blin, N., et al. (2021). Interest of a third dose of BNT162b2 anti-SARS-CoV-2 messenger RNA vaccine after allotransplant. Br. J. Haematol. https://doi.org/10.1111/bjh.17911.

Levin, E.G., Lustig, Y., Cohen, C., Fluss, R., Indenbaum, V., Amit, S., Doolman, R., Asraf, K., Mendelson, E., Ziv, A., et al. (2021). Waning Immune Humoral Response to BNT162b2 Covid-19 Vaccine over 6 Months. N. Engl. J. Med. *385*, e84.

Maillard, A., Redjoul, R., Klemencie, M., Labussiere-Wallet, H., Le Bourgeois, A., D'Aveni, M., Huynh, A., Berceanu, A., Marchand, T., Chantepie, S.P., et al. (2022). Antibody response after 2 and 3 doses of SARS-CoV-2 mRNA vaccine in allogeneic hematopoietic cell transplant recipients. Blood *139*, 134–137. https://doi.org/10.1182/blood.2021014232.

Redjoul, R., Le Bouter, A., Beckerich, F., Fourati, S., and Maury, S. (2021a). Antibody response after second BNT162b2 dose in allogeneic HSCT recipients. Lancet *398*, 298–299.

Redjoul, R., Le Bouter, A., Parinet, V., Fourati, S., and Maury, S. (2021b). Antibody response after third BNT162b2 dose in recipients of allogeneic HSCT. Lancet Haematol. *8*, e681–e683.

Zeng, C., Evans, J.P., Chakravarthy, K., Qu, P., Reisinger, S., Song, N.-J., Rubinstein, M.P., Shields, P.G., Li, Z., and Liu, S.-L. (2021). COVID-19 mRNA booster vaccines elicit strong protection against SARS-CoV-2 Omicron variant in patients with cancer. Cancer Cell *40*. https://doi.org/10.1016/j.ccell.2021.12.014.