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LETTER TO THE EDITOR

Effectiveness of a third dose of BNT162b2 anti-SARS-CoV-2 mRNA vaccine over a 6-month follow-up period in allogenic hematopoietic stem cells recipients

Abstract

This study reports the effectiveness of three injections of BNT162b2 anti-SARS-CoV-2 mRNA vaccine in 141 Allo-HSCT recipients with a median follow-up of 6 months post-third shot. We demonstrate a long-term high protection of Allo-HSCT recipients since only 2 infections and one death related to COVID-19 occurred.

Boosting immunity by providing a third dose of COVID-19 vaccine has now become crucial in the general population as it not only overcomes the waning of humoral immune responses after a few months but also restores efficacy against new variants such as Delta and Omicron. Data reporting the interest of a third-dose/boost vaccine in immunocompromized hosts, including solid tumor patients[1] or allogeneic hematopoietic stem-cell transplant (allo-HSCT) recipients,[2] are also progressively reported, yet with very short follow-up.

Since French authorities recommended boosts for high-risk patients in April 2021, we can report here the effectiveness of this strategy in 141 allo-HSCT recipients with a median follow-up of 6 months post-third shot. All received three injections of BNT162b2 anti-SARS-CoV-2 mRNA vaccine (V1 V2 V3) between January and September 2021. The median age of the cohort was 58 years old (range: 20–77) and the median delay between the graft and V1 was 33.5 months (3–282), with 28, 33 and 80 cases within the first year post-transplant, the second year of transplant or above, respectively. The study was approved by the review board of Nantes University Hospital and all participants provided informed consent. Patient characteristics are given in the Table 1. Detectable antibody responses, tested twice after V3 (early S1 $n = 124$, median 33 days from V3, and late S2 $n = 141$, median 193 days from V3) were classified as "weak" or "good". At S1 and S2, 83% and 82% of the patients had good responses, that is, above the 250 BAU/ml threshold, reported to correlate with neutralizing antibody levels.[2] For the 96 patients tested twice with the same assay, the proportions of good responders remained similar between S1 (81%) and S2 (79%), yet with a slight decrease of IgG titers for 29% of them (Table 1). Factors associated with good responses were, as expected,[2] a higher lymphocyte (median 2.84×10^9/L vs. 1.00×10^9/L, $p = 0.005$), CD4+ T cells (median 3.79×10^9/L vs. 2.05×10^9/L, $p = 0.001$) and B cells (median 3.12×10^9/L vs. 0.68×10^9/L, $p < 0.001$) counts at S2, absence of immunosuppressive drugs or chemotherapy (82% vs. 56%, $p = 0.01$), and being at least one year post-transplant (85.3% vs. 56%, $p = 0.002$). Effectiveness at S2 or after was investigated in terms of infection, hospitalization and COVID-19-related death. At last follow-up (18 January 2022), and in line with published preliminary results,2 only 2 mild COVID-19 infections occurred, both in patients with S2 ≥250 BAU/ml (+168 and +1042 days post-transplant). There was one COVID-19-related death (S2: 15.3 BAU/ml, +150 days post-transplant). The death rate is thus 0.7% versus 21%–25% for non-vaccinated allo-HSCT recipients.[3]

This observational study demonstrates a long-term high protection of Allo-HSCT recipients vaccinated three times with the BNT162b2 anti-SARS-CoV-2 mRNA vaccine. The median delay of 44 days after the second shot could be reconsidered as a longer interval between the second priming dose of vaccine and the booster dose appears to result in higher neutralizing antibody titers against all variants tested in a recent study.[4]

Waning of IgG titers concerns around 30% of our patients at 6 months but only a small proportion (19%) had IgG titers <250 BAU/ml, suggesting the possibility to propose a fourth injection to enhance protection in these cases. Of note, in healthy population, a 6-month long-term follow-up after the booster have been reported showing that neutralization titers against the omicron variant were 6.3 times lower than the peak titers assessed 1 month after the booster injection, but the titers remained detectable in all the participants.[5]

T-cell immunity may be also interesting to investigate at distance of the boost but this is currently challenging and not performed in routine practice. Finally, although the Delta variant was predominant during the period of our analyses, the lesser gravity of Omicron suggests that the same results should be observed, although this hypothesis has to be confirmed in the next few months.

TABLE 1 Patient characteristics, effectiveness and antibody levels

Patients *N* = 141[a]	
Median age: years (range)	58 (20–77)
<40/40–59/≥60	19/55/67
Gender: Male/Female	84/57
Underlying disease: Myeloid/Lymphoid	101/40
Donor type: sibling/MUD/haplo/9–10/cord blood	34/59/42/4/2
Conditioning: MAC/RIC/sequential	29/105/7
Previous GVHD: Yes/no	77/64
Ongoing treatment: Yes/no	32/109
Yes: Immunosuppressive drugs/Chemotherapy	27/5
Median lymphocyte count at S2: Range (x10^9/L)	1720 (121–6570)
</≥1 × 10^9/L *n* =	32/109
Vaccine and serology dates	
V1	Jan 14th–15 June 2021
V2	Feb 4th–15 July 2021
V3	Apr 2nd–24 Sept 2021
S1	May 3rd–25 Oct 2021
S2	Aug 8th–18 Jan 2022
Median delays	
Graft-V1: months (range)	33.5 (3–282)
<6 months *n*=	10
<12 months *n*=	18
12–24 months *n*=	33
>24 months *n*=	80
V1-V2: days (range)	23 (12–52)
V2-V3: days (range)	44 (20–205)
V1-S1: days (range)	121 (76–242)
V1-S2: days (range)	272 (154–363)
Early serology (S1) after V3 N = 124	
Median delay: days (range)	33 (13–139)
Tests	
Roche S tAb	92
Abbott S IgG	5
DiaSorin TriS	11
Atellica	13
Novalisa	3
IgG titers	
Negative	14 (11%)
Detectable <250 BAU/ml	7 (6%)
≥250 BAU/ml	103 (83%)
Late serology (S2) after V3 N = 141	
Median delay: days (range)	193 (94–263)
Techniques	
Roche S tAb	116
Abbott S IgG	7
DiaSorin TriS	14
Atellica	8
Novalisa	2
IgG titers	
Negative	13 (9.5%)
Detectable <250 BAU/ml	12 (8.5%)
≥250 BAU/ml	116 (82%)
Comparison of IgG titers between S1 and S2 n = 96[b]	
Negative/negative	10 (11%)
Decrease (<250 BAU/ml/≥250 BAU/ml at S2)	28 (9/19) (29%)
Increase (conversion)	4(1) (4%)
≥250 BAU/ml at S1 S2	54 (56%)
Total ≥250 BAU/ml at S1	78 (81%)
Total ≥250 BAU/ml at S2	76 (79%)
Effectiveness of the third vaccine with a median of 6 months follow-up	
COVID-19 infection	2 (1.4%)
Hospitalization due to COVID-19 infection	0
Death from COVID-19	1 (0.7%)

Abbreviations: GVHD, graft-versus-host disease; haplo, haploidentical; MAC, myeloablative; MUD, matched unrelated donor; RIC, reduced-intensity conditioning.

[a]Including 4 with a previous asymptomatic SARS-CoV-2 infection.

[b]Using the same serologic assays at S1 and S2 for comparison.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL STATEMENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

AUTHOR CONTRIBUTIONS

Patrice Chevallier, Maxime Jullien and Thierry Guillaume designed, performed, coordinated the research, analyzed, performed statistical analyses, interpreted the data, generated the figure, and wrote the manuscript. Marianne Coste-Burel performed serology tests, generated the virologic data and commented on the manuscript. Maxime Jullien and Marie C. Béné performed statistical analyses and commented on the manuscript.

STATEMENT OF INFORMED CONSENT

Informed consent was obtained from all participants for being included in the study.

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DATA AVAILABILITY STATEMENT

The principal investigator PC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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PEER REVIEW

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