

Interest of a third dose of BNT162b2 anti-SARS-CoV-2 messenger RNA vaccine after allotransplant

The efficacy of two doses of anti-severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) messenger RNA (mRNA) vaccines, successfully demonstrated in healthy populations,¹ is progressively reported in recipients of allogeneic haematopoietic stem cell transplant (allo-HSCT) with, surprisingly, high humoral antibody responses of ~80%.^{1–3} In our own experience based on an observational study of 117 allo-HSCT adult recipients, we found that 83% of them achieved a significant specific humoral response after two doses (V1 and V2) of BNT162b2 anti-SARS-CoV-2 mRNA vaccine (Pfizer BioNTech). However, although 61.5% of the patients achieved the highest detectable antibody level, this proportion remained significantly lower than what was observed in healthy controls, where 100% reached this result.⁴

In the present study, we investigated retrospectively whether a third dose of BNT162b2 vaccine (V3) would improve the anti-SARS-CoV-2 response in a cohort including most of our previously reported patients. Patients with clinical or asymptomatic biological coronavirus disease 2019 (COVID-19) infection before V1 were excluded from the study. A cohort of healthy volunteers (caregivers from the Clinical Hematology Department) who had also already received V1 and V2 was considered as controls. All participants were vaccinated between January 20 and June 1, 2021. The study was approved by the Ethic Review Board of Nantes University Hospital.

Antibody response to the SARS-CoV-2 Spike protein receptor-binding domain was tested after V2 for all subjects (Serology post V2, SpV2). All subjects benefited later from another evaluation of specific serum antibodies as monitoring (Serology post V2+, SpV2+) or after V3 (Serology post V3, SpV3). Antibody levels to the SARS-CoV-2 Spike protein receptor-binding domain were assayed in all participants using Roche Elecsys[®] (Rotkreuz, Switzerland) with titres ≥ 0.8 u/ml considered positive, the highest threshold being >250 u/ml.

Four subgroups could be identified: (i) negativity at both SpV2 and SpV2+/SpV3, (ii) increase of antibody levels between SpV2 and SpV2+/SpV3, including patients showing seroconversion, (iii) decreased or stable antibody levels between SpV2 and SpV2+/SpV3 and (iv) sustained highest antibody levels at both times. A cohort of 25 controls and 102 patients, including 80 who received V3 (V3+) and 22 who did not (V3–) was considered for the purpose of the present study. The characteristics of participants and delays

from SpV2 to SpV2+ or SpV2 to SpV3 are reported in Tables I and II. The V3+ and V3– subgroups shared similar characteristics except regarding the number of matched unrelated donors, which was significantly higher for the former (Table I). The reasons for not receiving V3 were forgetting or refusal. Moreover, although the French National Authority of Health had recommended the use of a third dose in immunocompromised hosts,⁵ surveillance after detection of the highest antibody level at SpV2 was retained for some patients.

Samples from controls showed that they reached and sustained the highest anti-Spike antibody values (>250 u/ml) at both SpV2 and SpV2+, suggesting a persistent response without the need of a third vaccine in this healthy population.

The proportion of allo-HSCT patients still negative at SpV2+ or SpV3 was not significantly different between V3– and V3+ patients (23% vs. 11%, $P = 0.30$). An increase in antibody levels between SpV2 and SpV3 was observed in 19 V3+ patients (24%), while none of V3– patients displayed higher levels than at SpV2 ($P = 0.02$). Among V3 patients, seroconversion occurred for two and 17 reached the highest antibody level, confirming the interest of a third booster. This led to 81% of V3+ patients with the highest antibody level *versus* 50% in the V3– group ($P = 0.006$), of note still significantly lower than in controls ($P = 0.04$). Only 5% of V3+ patients had stable/decreased antibody levels *versus* 27% of V3– subjects ($P = 0.006$) (Table II). Finally, the proportion of patients documented twice with the highest antibody level at SpV2 and SpV2+/SpV3 was similar between V3– and V3+ patients (50% vs. 60%, $P = 0.55$).

Of note, neither COVID-19 infection nor graft-*versus*-host disease (GVHD) reactivation were documented in any participant.

As already reported in solid organ transplant recipients,^{6–8} and in a recent report with allo-SCT recipients,⁹ this retrospective study demonstrates that the administration of a third vaccine dose to allotransplanted patients increases the humoral response and antibody levels.

One major limitation of the present retrospective study is the absence of antibody level values after serum dilution (not done routinely in our hospital) and assays for neutralising antibodies. This would have been of high interest as higher titres seems to correlate with higher vaccine efficacy,¹⁰ while virus neutralising response towards variants may depend on the number of vaccines and neutralising antibody titres.¹¹

Table I. Patients' characteristics.

Characteristic	Allotransplanted V3 received, <i>n</i> = 80	Allotransplanted V3 not received, <i>n</i> = 22	<i>P</i>
Age, years, median (range)	57 (20–75)	52 (24–75)	0.20
Gender, Male/Female, <i>n</i>	45/35	12/10	1
Time from transplant to Dose 1, days, median (range)	719 (91–6198)	765 (126–5775)	0.89
Underlying disease			
Myeloid/Lymphoid/others, <i>n</i>	56/20/4	10/11/1	0.07
Donor type, <i>n</i> (%)			
Geno-identical	17 (21)	8 (36)	0.03
Matched unrelated	40 (50)	5 (23)	
Haploidentical	23 (29)	8 (36)	
9/10 mismatch unrelated	0	1 (5)	
Conditioning, <i>n</i>			
Myeloablative	21	0	0.57
Reduced-intensity	67	20	
Sequential	3	3	
Previous GVHD, Yes/No, <i>n</i>	44/36	12/10	1
Ongoing treatment (chemotherapy or immunosuppressive drugs), Yes/no, <i>n</i>	19/61	10/12	0.08
Lymphocyte count at Dose 1, ×10 ⁹ /l, median (range)	1.390 (0.260–9.880)	1.505 (0.150–3.990)	0.62

GVHD, graft-versus-host disease; V3, third dose of vaccine.

Table II. Comparison of serology results after receiving or not a third dose of SAR-CoV-2 vaccine in allotransplanted patients and controls.

	Allotransplanted V3 received <i>n</i> = 80	Allotransplanted V3 not received <i>n</i> = 22	Controls V3 not received <i>n</i> = 25
SpV2			
Delay V2-SpV2, days, median (range)	35 (18–77)	32 (18–68)	58 (32–71)
Delay V2-SpV2+/SpV3, days, median (range)	94.5 (55–220)	101.5 (62–203)	130 (103–140)
Antibody levels: SpV2 vs SpV2+/SpV3, <i>n</i> (%)			
NN	9 (11)	5 (23) <i>P</i> = 0.30	
Increase	19 (24)*	0 (0) <i>P</i> = 0.02	
Decrease/stable	4 (5)	5/1 (27) <i>P</i> = 0.006	
HH	48 (60)	11 (50) <i>P</i> = 0.55	25 (100)
H at SpV2+/SpV3	65 (81)	11 (50) <i>P</i> = 0.006	25(100) <i>P</i> = 0.04
Delay V1– SpV2+/SpV3, days, median (range) = follow-up	119 (76–242)	119 (63–225)	154 (133–160)
COVID-19 infection or GVHD reactivation after V1	0	0	0

GVHD, graft-versus-host disease; SpV2, first serology after V2; SpV2+, second serology after V2 without receiving V3; SpV3, serology after V3; V1, first dose of vaccine; V2, second dose of vaccine; V3, third dose of vaccine.

NN: antibody levels negative at SpV2 and at SpV2+/SpV3.

Increase: increase of antibody levels between SpV2 and SpV2+/SpV3.

Decrease/stable: decrease or stability of antibody levels between SpV2 and SpV2+/SpV3.

HH: highest antibody level at SpV2 and at SpV2+/SpV3.

*Including two seroconversions.

In conclusion, the present study supports the interest of a third dose of BNT162b2 anti-SARS-CoV-2 mRNA vaccine after allo-HSCT. Prospective studies should confirm these results.

Conflict of interest

The authors declare no conflict of interest, except Dr Patrice Chevallier who received honoraria from Pfizer outside the submitted work.

Author contributions

Amandine Le Bourgeois, Patrice Chevallier and Thierry Guillaume designed, performed, co-ordinated the research, analysed, performed statistical analyses, interpreted the data, generated the figure, and wrote the manuscript. Marianne Coste-Burel performed serology tests, generated the virological data, and commented on the manuscript.

Marie C. Béné performed statistical analyses and commented on the manuscript.

Ethical standards 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.

Statement of informed consent

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

Additional contributions

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Data availability statement

The principal investigator (Amandine Le Bourgeois) and Patrice Chevallier had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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