

Safety and antibody response after one and/or two doses of BNT162b2 Anti-SARS-CoV-2 mRNA vaccine in patients treated by CAR T cells therapy

The efficacy of anti-SARS-CoV-2 messenger RNA vaccines was first demonstrated in healthy populations.¹ It was later progressively reported in immunocompromised hosts, including patients with solid tumours,² haematological malignancies, especially B-cell chronic lymphocytic leukaemia,^{3,4} as well as solid organ transplants.^{5,6} Surprisingly, the antibody response has been shown to be impressive (around 80%) only in recipients of allogeneic haematopoietic stem cells transplant.^{7–9}

Another immunocompromised population is patients who have received chimeric antigen receptor-T (CAR T) cell therapy. Two small studies, both including 14 patients, have reported humoral response rates of 36% and 21% respectively.^{8,9} Here we report on the efficacy and safety of one and/or two injections of the BNT162b2 (Pfizer-BioNTech) vaccine in 23 patients who had received CAR T-cell therapy in our Haematology Department. They were compared to a cohort of 25 volunteer healthy controls (caregivers from the Hematology Department) vaccinated concomitantly. All participants were vaccinated between 28 January and 31 May 2021. None of them had a previous clinical history of COVID-19. Antibody response to the SARS-CoV-2 spike protein receptor-binding domain was tested using several serological techniques but mainly the Roche Elecsys assay. Patients answered a questionnaire aimed at assessing vaccination safety within the 7 days following the first (D1) and second (D2) doses, while controls completed the same questionnaire directly in our Department. All patients gave informed consent and the study was approved by the Ethics Review Board of the CHU of Nantes.

Overall, 23 patients (14 males, nine females) with a median age of 62 years (range, 21–79) were enrolled. These patients had received CAR T-cells for high-grade lymphoma ($n = 20$) or acute lymphoblastic leukaemia ($n = 3$). Eight and three patients respectively had been previously autografted or allografted. All patients were submitted to lymphodepletion by fludarabine + cyclophosphamide before CAR T-cell infusion. Moreover, two patients had been allografted after CAR T-cell infusion failure. CAR T-cells were axicabtagene ciloleucel (Yescarta, Kite/Gilead) in 16 cases, tisagenlecleucel (Kymriah, Novartis Pharma) in five and KTE-X19 (Kite/Gilead) in one. An additional patient received allogeneic UCART19 (Servier). The median delay between CAR T-cell administration and D1 was 401 days (range, 113–819).

All except two patients were in complete remission at the time of first vaccine, while three patients were still on therapy (revlimid $n = 1$, tafasitamab $n = 1$, chemotherapy $n = 1$). Antibody response to the SARS-CoV-2 spike protein receptor-binding domain after D1 was tested by the Roche Elecsys assay at a median time of 29 days (range, 16–32) in 19 patients and of 23 days (range, 18–32) in controls. At that time, only 4 of 23 patients (21%) had a positive anti-spike antibody response, while the response was 100% for controls ($P < 0.001$). Among seropositive cases, median IgG titers were higher in controls (35.1 U/ml, range, 2.2 to >250) than in patients (5.9 U/ml range, 4.1–41.6, $P = 0.06$). The highest possible IgG titer (>250) was obtained in two controls.

The median delay between D1 and D2 of the vaccine was 28 days (range, 14–46). Among the 20 patients tested after D2, 17 had also been tested after D1 while three were tested only after D2. All controls were tested after D2. The second serology assay was performed at a median interval from D2 of 52 days (range, 21–99) for patients and 58 days (range, 32–71) for controls. This serology assay was positive in six patients (30%), while all controls (100%, $P < 0.001$) had a positive response. Three out of the six patients (15%) achieved the highest IgG titer, according to the serology assay used. Among the four patients with significant antibody titers after D1, three remained positive including one reaching the highest possible titer. The fourth patient has not yet received D2. Median IgG titers could not be compared with controls because various methods of detection were used after D2. However, all controls tested again by Roche Elecsys displayed the highest IgG titer (>250) after D2. The two patients in relapse and treated by chemotherapy or tafasitamab did not develop antibodies after D2, conversely to patients under maintenance by revlimid.

The delay between CAR T-cell infusion and the vaccine did not influence the antibody response in this small series. The influence of lymphopenia could not be evaluated as almost all patients remained under the threshold of $1 \times 10^9/l$ lymphocytes at the time of analysis.

Vaccine injections appeared to be safe both in patients and controls as only grade 1 or 2 adverse events were observed. Surprisingly, reported reactions were significantly less frequent in patients than in controls, both after D1 and D2. Only pain incidence was reported to be significantly more frequent in controls after D1 and D2, the use of

Table I. Vaccine-related adverse effects within 7 days after the first and second doses in patients and controls.

	Dose 1 Patients <i>n</i> = 20 <i>n</i> (%)	Dose 1 Controls <i>n</i> = 25 <i>n</i> (%)	<i>P</i> value	Dose 2 Patients <i>n</i> = 14 <i>n</i> (%)	Dose 2 Controls <i>n</i> = 25 <i>n</i> (%)	<i>P</i> value
Any reaction	5 (25)	17 (68)	0.01	3 (21.4)	22 (88)	0.0001
Injection-site reactions						
Pain	3 (15)	16 (64)	0.002	1 (7.1)	13 (52)	0.01
Redness	1 (5)	1 (4)	NS	1 (7.1)	3 (12)	NS
Swelling	0	1 (4)	NS	0	5 (20)	NS
Systemic reactions						
Fever	1 (5)	0	NS	0	1 (4)	NS
Chills	1 (5)	0	NS	0	2 (8)	NS
Fatigue	0	3 (12)	NS	1 (7.1)	8 (32)	NS
Myalgia	0	1 (4)	NS	0	3 (12)	NS
Headache	1 (5)	3 (12)	NS	0	7 (28)	NS
Nausea	0	0		0	2 (8)	NS
Medication (paracetamol)	1 (5)	10 (40)	0.01	0	13 (52)	0.003
Medical attention required	0	0		0	0	

NS, not significant.

medication by paracetamol being statistically higher in these subjects after D1 and D2 (Table I).

Finally, with a median follow up from D1 of 77 days (range, 49–127) in patients and 81 days (range, 62–95) in controls, no COVID-19 infection has been documented in participants. One patient died of sepsis 3.5 months after D2 without being tested for serology.

This study, the largest one currently, confirms that the administration of one and/or two doses of BNT162b2 anti-SARS-CoV-2 messenger RNA vaccine is safe, but provides a low rate (~30%) of seroconversion in recipients of CAR T-cell therapy, even at a distance from the administration of CAR T-cells and even after a second vaccine. The role of a persistent lymphopenia, especially B-cell lymphopenia, as already reported by Ram *et al.*,⁸ may explain this poor antibody response. Unfortunately, we have no information on B cell counts in our cohort. These results, however, should be mitigated by the fact that 50% of CAR T-cell recipients may achieve cellular response after vaccine, as demonstrated again by Ram *et al.*,⁸ for an overall rate of 57% of patients developing either or both immune/cellular responses. Overall, as a majority of CAR T-cell patients remains at risk of COVID-19 infection, and to improve their protection, the role of a third dose is warranted. The duration of this protection should also be explored in the future, to determine whether or not an annual booster is necessary.¹⁰

Acknowledgements

We acknowledge the following individuals for their assistance with the study, none of whom was compensated for his or her contributions: Hematology Department nurses, Patricia Lespart, Ghislaine Francois, and Katia Godart for administering vaccines and their help in collecting samples and

questionnaires. The paramedical staff of the Hematology Department and of the Virology Department.

Author contributions

T.G., A.L.B. and P.C. designed, performed and coordinated the research, performed statistical analyses, interpreted the data, generated the figure, and wrote the manuscript. M.C. performed serology tests, generated the virologic data and commented on the manuscript. M.C.B. performed statistical analyses and commented on the manuscript. All authors read and approved the final 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.

Conflict of interest

Patrice Chevallier received honoraria from Pfizer outside of the submitted work. All other authors declare no conflicts of interest.

Data availability statement

The principal investigator (TG) and PC 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.

Thomas Gastinne¹
 Amandine Le Bourgeois¹
 Marianne Coste-Burel²
 Thierry Guillaume^{1,3} 
 Pierre Peterlin¹
 Alice Garnier¹
 Berthe-Marie Imbert²
 Thomas Drumel²
 Beatrice Mahe¹
 Viviane Dubruille¹
 Nicolas Blin¹
 Anne Lok¹
 Cyrille Touzeau¹ 
 Benoit Tessoulin¹ 
 Maxime Jullien¹ 
 Sophie Vanthygem¹
 Marie C. Béné^{3,4} 
 Philippe Moreau¹ 
 Steven Le Gouill¹
 Patrice Chevallier^{1,3} 

¹Hematology Department, Nantes University Hospital, ²Virology Department, Nantes University Hospital, ³INSERM UMR1232, CRCINA IRS-UN, University of Nantes and ⁴Hematology Biology, Nantes University Hospital, Nantes, France.
 E-mail: patrice.chevallier@chu-nantes.fr

Keywords: COVID 19, vaccine, CAR-T cells, BNT162b2, SARS-CoV-2 mRNA

First published online 2 September 2021
 doi: 10.1111/bjh.17818

The 12-week kinetics of anti-SARS-CoV-2 antibodies in different haematological cancers after vaccination with BNT162b2

To date, studies on anti-severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccine efficacy in blood cancers show that different responses may be observed according to the haematological malignancy diagnosis, stage of disease and ongoing treatment. Immune responses are often lower compared to healthy controls, second doses appear to be crucial, and most of the evidence rely on tests of neutralising antibody response, not the full range of immune response or clinical outcomes.^{1–10} We do not know how long immunity lasts in such patients, and there is uncertainty about the

References

- Walsh EE, Frenck RW, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. *N Engl J Med*. 2020;**383**(25):2439–50.
- Barriere J, Chamorey E, Adjoutah Z, Castelnau O, Mahamat A, Marco S, et al. Impaired immunogenicity of BNT162b2 anti-SARS-CoV-2 vaccine in patients treated for solid tumors. *Ann Oncol*. 2021;**32**(8):1053–5. <https://doi.org/10.1016/j.annonc.2021.04.019>
- Agha ME, Blake M, Chilleo C, Wells A, Haidar G. Suboptimal response to coronavirus disease 2019 messenger RNA vaccines in patients with hematologic malignancies: a need for vigilance in the postmasking era. *Open Forum Infect Dis*. 2021;**8**(7):ofab353. <https://doi.org/10.1093/ofid/ofab353>
- Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood*. 2021;**137**(23):3165–73. <https://doi.org/10.1182/blood.2021011568>
- Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA*. 2021;**325**(21):2204–6.
- Ou MT, Boyarsky BJ, Motter JD, Greenberg RS, Teles AT, Ruddy JA, et al. Safety and reactogenicity of 2 doses of SARS-CoV-2 vaccination in solid organ transplant recipients. *Transplantation*. 2021. <https://doi.org/10.1097/TP.0000000000003780>. Epub ahead of print. PMID: 33859151.
- Redjoul R, Le Bouter A, Beckerich F, Fourati S, Maury S. Antibody response after second BNT162b2 dose in allogeneic HSCT recipients. *Lancet*. 2021;**398**(10297):298–9.
- Ram R, Hagin D, Kikozashvili N, Freund T, Amit O, Bar-On Y, et al. Safety and immunogenicity of the BNT162b2 mRNA COVID-19 vaccine in patients after allogeneic HCT or CD19-based CART therapy—a single-center prospective cohort study. *Transplant Cell Ther*. 2021:S2666–6367 (21)01027-7. <https://doi.org/10.1016/j.jct.2021.06.024>. Epub ahead of print. PMID: 34214738; PMCID: PMC8242200.
- Dhakal B, Abedin SM, Fenske TS, Chhabra S, Ledebner N, Hari P, et al. Response to SARS-CoV-2 vaccination in patients after hematopoietic cell transplantation and CAR-T cell therapy. *Blood*. 2021;Epub ahead of print. PMID: 34339501; PMCID: PMC8332674.
- Dan JM, Mateus J, Kato YU, Hastie KM, Yu ED, Faliti CE, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. *Science*. 2021;**371**(6529):eabf4063.

most reliable serological tests and cut-off values by which to identify the responders and track the putatively neutralising antibodies' titres.

To address some of these questions, we prospectively analysed the anti-SARS-CoV-2 spike (S) protein immunoglobulin G (IgG) titres over multiple time-points (TPs), and monitored clinical outcomes [asymptomatic infections and coronavirus disease 2019 (COVID-19)], after two doses of 30 µg 3 weeks apart of BNT162b2 in 182 consecutive patients with different malignancies [chronic myeloid leukaemia (CML),