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**B-cell aplasia is the most powerful predictive marker for poor humoral response after BNT162b2 mRNA SARS-CoV-2 vaccines in recipients of allogeneic hematopoietic stem cell transplantation**

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

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## Highlights

- 1- Two injections of BNT162b2 mRNA SARS-CoV-2 vaccine allow to reach specific anti Spike (S) antibody responses in 83% of recipients of allogeneic stem cell transplantation (Allo-HSCT).
- 2- B-cell aplasia is the only factor statistically associated with the absence of antibody response after two vaccine injections.
- 3- The interval between Allo-HSCT and first vaccination, the donor source or current immunosuppressive/chemotherapy treatment do not impact the humoral response after two vaccine injections in this series.

## **Abstract**

**Background:** Little is known on the immune response to SARS-CoV-2 vaccination in recipients of allogeneic hematopoietic stem cell transplantation (Allo-HSCT). However, a few studies have reported that adequate protection could be provided to this population.

**Objective(s):** The purpose of this study was to evaluate which factors can predict the efficacy of SARS-CoV-2 vaccination in these specifically immunosuppressed patients.

**Study design:** Specific anti Spike (S) antibody responses were assessed in a cohort of 117 Allo-HSCT recipients after two injections of BNT162b2 mRNA SARS-CoV-2 vaccine (V1 and V2). Factors considered liable to influence the antibody response and analyzed in this series were the interval between Allo-HSCT and V1, donor source, recipient and donor age, current immunosuppressive/chemotherapy (I/C) treatment and levels of CD4<sup>+</sup> and CD8<sup>+</sup> T-cells, B-cells and NK-cells at the time of V1.

**Results:** Overall, the S-antibody response rate, evaluated at a median of 35 days after V2, was 82.9% for the entire cohort, with 71 patients (61%) reaching the highest titre. In univariate analysis, a lower pre-V1 median total lymphocyte count, lower CD4<sup>+</sup> T-cell and B-cell counts as well as ongoing I/C treatment and a haploidentical donor were characteristic of non-humoral responders. However, multiparameter analysis showed that B-cell aplasia was the only factor predicting the absence of a specific immune response (Odd Ratio 0.01, 95%CI [0.00 – 0.10],  $p < 10^{-3}$ ). Indeed, the rate of humoral response was 9.1% in patients with B-cell aplasia, vs 95.9% in patients with a B-cell count higher than 0 ( $p < 10^{-9}$ ).

**Conclusion(s):** These results advocate for the prescription of anti-SARS-CoV-2 vaccination in Allo-HSCT recipients as early as peripheral B-cell levels can be detected, suggesting also a need for a close monitoring of B-cell reconstitution after Allo-HSCT.

## Introduction

COVID-19 due to infection by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been responsible for over 4 million of deaths worldwide. Immunocompromised patients such as patients treated for hematologic malignancies,<sup>1-4</sup> including recipients of allogeneic hematopoietic stem cell transplantation (Allo-HSCT),<sup>5</sup> represent a particularly high-risk population with mortality rates comprised between 25 and 40%. The results of anti-SARS-CoV-2 vaccination are now progressively reported in such patients, showing surprisingly high efficacy around 70-80%, a rate yet lower than that observed in the general population.<sup>6-8</sup>

Recently, Ram *et al.*<sup>9</sup> published a study dealing with immune responses after anti-SARS-CoV-2 vaccination in a cohort of patients having received infusion of Allo-HSCT or anti-CD19 CAR T-cells. These authors reported a better post-vaccination humoral response in patients with higher levels of peripheral B-cells. In fact, data remain scarce regarding factors predicting the humoral response after such vaccines in immunocompromised hosts. As a consequence, here we retrospectively investigated which factors, including immune status at time of vaccination, might influence the post-vaccination antibody response after Allo-HSCT.

## Material and Methods

The main objective of the study was to decipher which factors can predict the humoral response after two injections (V1 and V2) of BNT162b2 (Pfizer-BioNTech) vaccine in a cohort of 117 Allo-HSCT recipients. The characteristics and outcomes of these patients have been already reported.<sup>7,8</sup>

Antibody response to the SARS-CoV-2 spike (S) protein receptor-binding domain was tested (Roche Elecsys®, Rotkreuz, Switzerland) at a median of 35 days (range: 18-77) post-V2. As recommended by the manufacturer, titres  $\geq 0.8$  U/mL were considered positive, the highest value being  $>250$  U/mL.

Factors considered for analyses were gender, underlying disease (myeloid vs lymphoid), recipient/donor ABO blood type, donor type (matched vs haploidentical), conditioning regimen (myeloablative vs reduced-intensity vs sequential), graft-versus-host-disease (GVHD) history, current

immunosuppressive/chemotherapy (I/C) treatment, delay between the graft and V1 as well as pre-V1 CD3, CD4 and CD8+ T cells, B and NK cells counts. Total lymphocyte counts and quantitative lymphocyte subsets were evaluated by flow cytometry before V1.

Statistical analyses were performed with R (version 4.0.3) software. Patient characteristics were compared by using the  $\chi^2$  test for discrete variables and the Wilcoxon test for continuous variables, and generalized linear models were used to conduct multivariate analyses. All participants provided informed consent and the study was approved by the Ethic Review Board of Nantes University Hospital.

## Results

The 117 Allo-HSCT recipients enrolled (**Table 1**) were vaccinated between January 20 and April 17, 2021. Briefly, their median age was 57 years, with a predominance of male subjects (60%) and treatment for a myeloid disease (66%). Donor source was matched in 67.5% of cases, and haploidentical in 30.8%. Two patients who received a graft from a 9/10 mismatched unrelated donor were not considered for univariate analysis. At the time of V1, 62/117 (53%) patients had a previous history of graft versus host disease (GVHD), and 32/117 (27.4%) were receiving ongoing I/C therapy. The average interval from Allo-HSCT (Day 0) to V1 (D0-V1) was 654 (IQR: 372–1367) days. As previously reported,<sup>8</sup> the S-antibody response rate post-V2 was 82.9% for the entire cohort, with 71 patients (61%) reaching the highest titre for this assay. Non-humoral responders (NHR) post-V2 (n = 20) had a lower D0-V1 interval (median 271 vs 914 days,  $p < 10^{-5}$ ) and lower pre-V1 median total lymphocyte counts ( $0.62$  vs  $1.61 \times 10^9/L$ ,  $p < 10^{-4}$ ). Regarding lymphocyte subsets, NHR displayed lower median CD3 ( $0.39$  vs  $0.97 \times 10^9/L$ ,  $p = 0.01$ ), CD4 ( $0.13$  vs  $0.35 \times 10^9/L$ ,  $p \leq 10^{-3}$ ), and B-cell ( $0.00$  vs  $0.28 \times 10^9/L$ ,  $p < 10^{-6}$ ) counts. NK and T CD8 counts were not statistically lower in NHR (respectively  $0.14$  vs  $0.21 \times 10^9/L$ ,  $p=0.14$  and  $0.23$  vs  $0.45 \times 10^9/L$ ,  $p=0.06$ ). No influence either was observed when considering the age of donors ( $p=0.39$ ) or recipients ( $p=0.55$ ), underlying disease ( $p=1$ ), Allo-HSCT conditioning ( $p=0.11$ ), blood groups (donor,  $p=0.55$ ; recipient,  $p=0.39$ ) or a previous history of GVHD ( $83.1$  vs  $83.6\%$ ,  $p=1$ ). Conversely, ongoing I/C treatment and a haploidentical source of graft were associated with lower responses to vaccination (respectively  $62.5$  vs

90.5%,  $p < 10^{-3}$ , and 69.4 vs 88.6% for patients with matched donors,  $p = 0.02$ ). These data are shown in **Table 1**.

In multivariate analysis (**Figure 1**) also including D0-V1 interval, donor source, current I/C treatment and TCD4 lymphocyte count, only B-cell aplasia remained statistically associated with lack of antibody response after two vaccine injections (Odd Ratio 0.01, 95%CI [0.00 – 0.10],  $p < 10^{-3}$ ). The rate of humoral response was 9.1% in patients with B-cell aplasia, vs 95.9% in patients with a B-cell count higher than 0 ( $p < 10^{-9}$ ).

The characteristics of patients with B-cell aplasia ( $n = 11$ ) were compared to those of patients with a documented B-cell count above 0 ( $n = 73$ ). B-cell aplasia was mainly due to rituximab administration post-Allo-HSCT but not to BTK inhibitor or CD19-directed treatments, which both represent only 4 patients. Indeed, more patients with B-cell aplasia had received rituximab post Allo-HSCT (63% vs 24.7%,  $p = 0.01$ ). The indication for rituximab was EBV reactivation, except for 2 patients where it was as part of chemotherapy for relapse. The median number of rituximab infusions was not statistically different between patients with or without B-cell aplasia: 6 (IQR: 3.5-6.5) vs 3 (IQR: 2-4),  $p = 0.06$ , but, as expected, time from the last rituximab infusion was shorter in patients with B-cell aplasia: 6 months (IQR: 5.2-8.8) vs 32.3 months (IQR 17.0-43.8),  $p < 0.001$ . No difference was observed regarding the number of patients who had received rituximab before Allo-HSCT (18% vs 8.2%,  $p = 0.28$ ).

## Discussion

This study attempted at identifying factors impairing a protective immune response after anti-SARS-CoV-2 vaccination in Allo-HSCT recipients. The S-antibody response rate post-V2 is high reaching 82.9% for the entire cohort, 61% reaching the highest titre for this assay and thus probably much higher protective levels.<sup>10</sup> B-cell aplasia clearly appeared as the major predictor of the absence of antibody response after two doses of anti SARS-CoV-2 mRNA vaccine in this population. The overall response rate (83%) in our cohort is similar to that reported by Ram *et al.*<sup>9</sup> when taking into account the real population of 47 responders among 57 patients actually tested for humoral response in the Israeli

cohort of Allo-HSCT patients. Of note, although B-cell levels were correlated with humoral response, the cohort of Ram *et al.*<sup>9</sup> included only 1 Allo-HSCT patient with total B-cell aplasia. Similarly, in a recent study by Malard *et al.*,<sup>11</sup> including 41 allografted patients, those with B-cells <120 / $\mu$ L had significantly lower anti-Spike IgG levels at day 42 after the second vaccine. One explanation is of course that low B-cell numbers, as a reflection of immunodepression and/or previous anti-B-cell therapy, may prevent antibody production after transplant. As we know that, in healthy populations, SARS-CoV-2 mRNA vaccines induce persistent human germinal centre responses,<sup>12</sup> it can be also hypothesized that, in immunocompromised hosts, these specific responses are abolished. Finally, the possibility that these patients have developed a cellular response, which has not been studied here but was demonstrated by Ram *et al.*<sup>9</sup> in 7/37 patients, should be considered. In any event, these results advocate for a close immune monitoring after Allo-HSCT to administrate the vaccine immediately upon B-cell detection, and without waiting for a defined period of time as is currently the case. For patients with B-cell aplasia or about to receive post-Allo-HSCT rituximab therapy, other strategies such as neutralizing antibodies for the prevention of COVID-19 infection should be also explored.<sup>13</sup>



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**Table 1:** Patient characteristics.

Characteristics	All (n = 117)	Responders (n=97)	Non-responders (n=20)	p value
<b>Recipient age (yo)</b>	57.1 (44.2 - 65.9)	56.4 (44.1 - 65.9)	60.8 (45.3 - 65.1)	0.55
<b>Gender</b>				
Male	70 (59.8%)	56 (57.7%)	14 (70%)	0.44
Female	47 (40.2%)	41 (42.3%)	6 (30%)	
<b>Underlying disease</b>				
Myeloid	77 (65.8%)	63 (64.9%)	14 (70%)	1
Lymphoid	36 (30.8%)	30 (30.9%)	6 (30%)	
<b>Recipient blood type</b>				
O	55 (47.0%)	46 (47.4%)	9 (45.0%)	0.39
A	43 (36.8%)	37 (38.1%)	6 (30.0%)	
B	12 (10.3%)	9 (9.3%)	3 (15.0%)	
AB	2 (1.7%)	1 (1.0%)	1 (5.0%)	
<b>Donor blood type</b>				
O	56 (47.9%)	47 (48.5%)	9 (45.0%)	0.55
A	45 (38.5%)	37 (38.1%)	8 (40.0%)	
B	11 (9.4%)	10 (10.3%)	1 (5.0%)	
AB	2 (1.7%)	1 (1.0%)	1 (5.0%)	
<b>Donor type *</b>				
Matched	79 (67.5%)	70 (72.2%)	9 (45.0%)	<b>0.02</b>
Haploidentical	36 (30.8%)	25 (25.8%)	11 (55.0%)	
<b>Donor age (yo)</b>	38.6 (28.2 - 48.7)	37.8 (28.1 - 46.4)	42.4 (30.7 - 52.5)	0.39
<b>Conditioning</b>				
Reduced intensity	87 (74.4%)	70 (72.2%)	17 (85.0%)	0.11
Myeloablative	23 (19.7%)	22 (22.7%)	1 (5.0%)	
Sequential	7 (6.0%)	5 (5.2%)	2 (10.0%)	
<b>D0V1 interval (d)</b>	654 (372 - 1367)	914 (454 - 1455)	271 (198 - 395)	<b>&lt; 10<sup>-5</sup></b>
<b>GVHD history</b>				
Yes	62 (53.0%)	51 (52.6%)	11 (55.0%)	1
No	55 (47.0%)	46 (47.4%)	9 (45.0%)	
<b>Current IS/chemo treatment</b>				
Yes	32 (27.4%)	20 (20.6%)	12 (60.0%)	<b>&lt; 10<sup>-3</sup></b>
No	85 (72.6%)	77 (79.4%)	8 (40.0%)	
<b>Pre-V1 Ly count (x10<sup>9</sup>/L)</b>	1.40 (0.71 - 2.27)	1.61 (1.01 - 2.33)	0.62 (0.47 - 1.24)	<b>&lt; 10<sup>-4</sup></b>
<b>T Ly</b>	0.82 (0.42 - 1.32)	0.97 (0.49 - 1.39)	0.39 (0.15 - 0.85)	<b>0.01</b>
TCD4	0.31 (0.16 - 0.49)	0.35 (0.22 - 0.52)	0.13 (0.08 - 0.23)	<b>&lt; 10<sup>-3</sup></b>
TCD8	0.38 (0.19 - 0.86)	0.45 (0.21 - 0.87)	0.23 (0.07 - 0.52)	0.06
<b>B Ly</b>	0.24 (0.08 - 0.46)	0.28 (0.16 - 0.51)	0.00 (0.00 - 0.00)	<b>&lt; 10<sup>-6</sup></b>
<b>NK</b>	0.20 (0.14 - 0.30)	0.21 (0.15 - 0.30)	0.14 (0.10 - 0.23)	0.14

**Abbreviations:** y: years old. d: days. GVHD: graft versus host disease. IS: immunosuppressive drug; chemo: chemotherapy; Ly: lymphocytes. DOV1: delay between day O (day of the graft) and first anti-SARS-CoV-2 vaccine after the graft; d: days.

Continuous variables are given in median (interquartile range), categorical variables are given as number (percent).

\*2 patients received a graft from a 9/10 mis-matched unrelated donor and were not considered for univariate analysis.

**Figure 1:** Multivariate analysis.

