



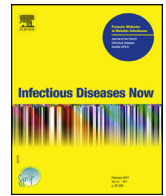
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Original article

# The humoral response of mRNA COVID-19 vaccine in hematological diseases: The HEMVACO study



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## ARTICLE INFO

### Article history:

Available online 3 June 2022

### Keywords:

SARS-CoV-2 vaccine  
 Anti-CD20 monoclonal antibody  
 Hematologic diseases  
 Hypogammaglobulinemia  
 Booster immunization

## ABSTRACT

**Objectives:** The HEMVACO study evaluated the humoral response after mRNA anti-SARS-CoV-2 vaccination in an hematological cohort.

**Methods:** HEMVACO was a prospective, multicentric study registered in ClinicalTrials.gov, number NCT04852796. Patients received two or three doses of BNT162b2 vaccine or mRNA-1273 vaccine. The SARS-CoV-2 TrimericS IgG titers were measured 1, 3, 6 and 12 months after the second dose.

**Results:** Only 16 patients (11.6%) were naive of hematological treatment and 77 patients (55.8%) were on active treatment for hemopathy. Among the 138 analyzed patients, positive antibody titer at 1 month was obtained in 68.1% of patients with mean serology at  $850 \pm 883$  BAU/ml. Risk factors for vaccine failure were anti-CD20 therapy (OR = 111 [14.3–873];  $P < 0.001$ ), hypogammaglobulinemia under 8 g/L (OR = 2.49 [1.05–5.92];  $P = 0.032$ ) and lymphopenia under 1.5G/L (OR = 2.47 [1.18–5.17];  $P = 0.015$ ). Anti-CD20 therapy induced no anti-SARS-CoV-2 seroconversion (96%). Seventy-eight patients (56.5%) received a third dose and could reach the SARS-CoV-2 TrimericS IgG titer of high-risk patients ( $P = 0.54$ ). The median titer at 379 BAU/ml distinguished two groups of vaccine response ( $99 \pm 121$  BAU/ml versus  $1,109 \pm 678$  BAU/ml).

**Conclusion:** Vaccination should be performed before anti-CD20 therapy if the hemopathy treatment can be delayed. Administration of the third vaccine dose was interesting for patients with suboptimal response, defined by a 379 BAU/ml titer in our study.

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## 1. Introduction

Since the first report of COVID-19 in December 2019 in Wuhan, China [1], many cases of fatal pneumonia have been reported with higher mortality rate in hospitalized patients with hematological malignancies (62% vs. 8% in patients without hematological malignancies) [2]. Although hematological diseases were heterogeneous, post-vaccinal immunization appeared to be less effective than in the general population [3]. Anti-CD20 therapy used in B-cell lymphoid hemopathies, through rapid and prolonged depletion of B cells, could for instance prevent the development of a specific anti-SARS-CoV-2-antibody response but few publications were available in hematological populations [4–6].

The HEMVACO study aims to evaluate the humoral response 1 month after mRNA anti-SARS-CoV-2 complete vaccination in a cohort of patients with hemopathies (primary objective). Our secondary objectives were to evaluate the persistent humoral response over a year, the safety of mRNA vaccines and the clinical effectiveness of COVID-19 vaccine in an hematological cohort.

## 2. Methods

HEMVACO was a prospective, observational, multicentric, open, non-randomized study, approved by the Institutional Ethics Committee and registered in ClinicalTrials.gov, number NCT04852796. The inclusion period ran from February 1, 2021 to August 31, 2021 in the Department of Internal Medicine, Infectious Diseases and Hematology from Quimper, Concarneau and Vannes hospitals, France. All adult patients followed in the departments could be enrolled after mRNA COVID-19 vaccine eligibility according to

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French guidelines. Oral and written information was delivered, and written consent was collected.

According to the successive French guidelines of the Vaccine Strategy Guidance Council (Conseil d'Orientation de la Stratégie Vaccinale), some patients were defined as priority for COVID-19 vaccine: cancer patients, hematological disease patients, and transplant recipients [7]. Patients received two doses of the Pfizer-BioNTech COVID-19 (BNT162b2) vaccine (Pfizer, Inc; Philadelphia, Pennsylvania) or the Moderna COVID-19 (mRNA-1273) vaccine (ModernaTX, Inc; Cambridge, Massachusetts) 1 month apart starting from January. Since the beginning of May 2021, French guidelines recommend a third dose to be administered at least 1 month after the second dose, for patients at very high-risk of severe COVID-19 disease [8]. These patients were defined by auto- or allogeneic stem cell transplant, lymphoid hemopathy (lymphoma, myeloma), in particular treated by anti-CD20 antibody, Burton tyrosine inhibitors or CAR-T cells and primary immunodeficiency diseases. High-risk patients for severe COVID-19 disease were represented by other hematological conditions.

Recent COVID-19 disease (< 1 year), previous positive serology, palliative care patients, and patients under legal protection were excluded.

Antibody titers were measured before each mRNA COVID-19 vaccine and 1, 3, 6 and 12 months after the second dose administration, with anti-Trimeric Spike protein titers (BAU/ml), according to the WHO international standard (NIBSC 20-136) with the LIAISON SARS-CoV-2 TrimericS IgG kit from DiaSorin (Stillwater, MN 55082). This titer was considered negative with a concentration of < 31 BAU/ml and positive with > 36 BAU/ml result. Positive results were limited to 2,080 BAU/ml. For the primary objective of the study, the main outcome was the SARS-CoV-2 TrimericS IgG titer 1 month after the second dose administration.

For the secondary objective, all other measures (at 3, 6 and 12 months) were analyzed, and many pieces of data were collected, including demographic, clinical, and biological characteristics of patients. Adverse events of mRNA vaccine and COVID-19 disease were self-reported during the follow up.

Continuous variables were described with mean and SD values or median and interquartile ranges (IQRs). We compared means and proportions between groups using Mann-Whitney test and Fisher's exact test. All statistical tests were two-sided, and probability values <0.05 were considered significant. A patient was excluded from the analysis if data or value were lacking for the variable of interest. Univariate and multivariate logistic regression analysis was used to identify variables associated with a negative antibody response. Covariates of interest for the multivariate logistic regression analysis were selected based on a *P* value <0.2 in univariate analysis. Hosmer-Lemeshow test was used with *P*=0.58 for the fit test. Analyses were performed using Stata version 16.1 (StataCorp).

### 3. Results

One-hundred and eighty-nine (*n* = 189) patients were included (Table 1). Nineteen patients were excluded (five deaths and 14 patients lost to follow-up). One-hundred and thirty-eight (*n* = 138) adult patients were assessed for the primary objective (preliminary results). The sex ratio males (*n* = 71)/females (*n* = 67) was 1.06 and the mean age was 65.01 years ( $\pm$  standard deviation 12.1 years). They harbored heterogeneous hematological malignancies: 56 cases of B lymphoma (40.57%), 41 cases of plasma cell dyscrasias (29.71%), 28 cases of myeloid malignancy (20.29%), five cases of Hodgkin lymphoma (3.63%), five cases of T cell lymphoma (3.63%), two cases of immune deficiency (1.45%) and one case of immune thrombocytopenic purpura (0.72%).

**Table 1**  
Characteristics of study patients.

Characteristics of patients	No.	%
Total patients (No.)	189	
Excluded patients	19	
Death	5	
Lost to follow-up	14	
Included patients	170	
Intermediate analysis 1 month after vaccination	138	
Gender male, No. (%)	71	51.45
Age (years), mean (SD)	65.01	12.1
Body mass index (kg/m <sup>2</sup> ), mean (SD)	25.21	4.53
Hematological malignancies		
B lymphoma	56	40.57
Plasma cell dyscrasias	41	29.71
Myeloid malignancy	28	20.29
Hodgkin lymphoma	5	3.63
T cell lymphoma	5	3.63
Immune deficiency	2	1.45
Immune thrombocytopenic purpura	1	0.72
Comorbidity		
Autoimmune disease	16	11.59
Solid cancer	25	18.12
Hypertension	49	35.8
Diabetes	12	8.7
Ischemic cardiopathy	10	7.25
GFR <60 ml/min	10	7.25
Autologous transplantation	22	15.94
Allogeneic stem cell transplant	3	2.17
Treatment	16	
None	45	11.6
Finished	77	32.6
Ongoing	16	55.8
Anti-CD20 therapy	9	11.6
Anti-CD20 therapy <6 months	15	6.5
Anti-CD38 therapy	1	10.87
CAR-T cells		0.72
Lymphocyte count (10 <sup>9</sup> /L), mean (SD)	3.28	10.40
Albuminemia (g/L), mean (SD)	40.3	4.82
Gammaglobulinemia	38	
5-8 g/L	36	31.15
<5 g/L		29.5

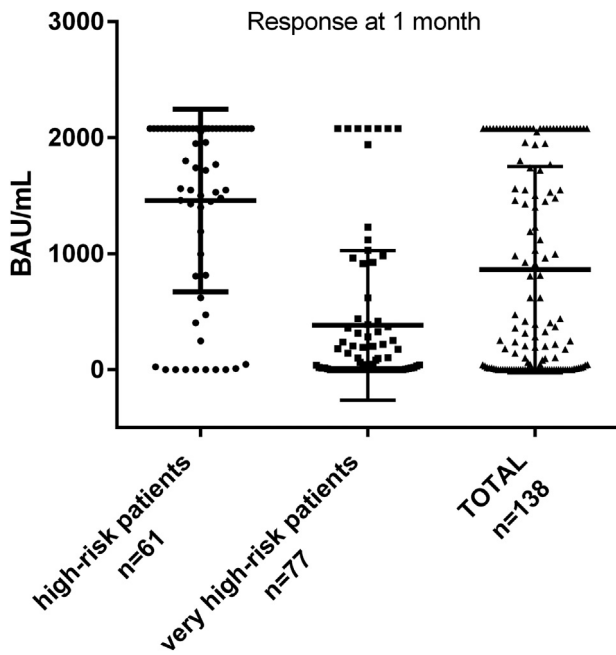
GFR: glomerular filtration rate; SD: Standard Deviation.

Only 16 patients (11.6%) were naive of hematological treatment and 77 patients (55.8%) were on active treatment for their hemopathy, including 16 (11.6%) on ongoing anti-CD20 antibody therapy and nine who (6.5%) recently (< 6 months) received anti-CD20 antibodies.

No positive serology was detected before the first vaccine dose. Positive serologies were observed in 43 patients after one injection (32.5%) and in 94 patients after the second dose (68.1%); negative for 43 patients (31.1%) and undetermined for one patient (0.7%). At 1 month, the mean positive SARS-CoV-2 TrimericS IgG titer was 850  $\pm$  883 BAU/ml (Fig. 1).

In univariate analysis (Table 2), risk factors for vaccine failure were ongoing or recent anti-CD20 therapy (OR = 111 [14.3–873]; *P* < 0.001), hypogammaglobulinemia under 8 g/L (OR = 2.49 [1.05–5.92]; *P* = 0.032 and lymphopenia under 1.5G/L (OR = 2.47 [1.18–5.17]; *P* = 0.015). In multivariate analysis, anti-CD20 therapy (OR = 196 [19.1–2020]; *P* < 0.001) and hypogammaglobulinemia (OR = 6.5 [1.41–30.1]; *P* = 0.017) were confirmed as poor risk factors. Among the cohort, 24/25 (96%) patients under ongoing or recent (< 6 months) anti-CD20 therapy did not show evidence of anti-SARS-CoV-2 seroconversion. The other patients with lack of seroconversion were represented by heterogeneous pathology and treatment (Table 3). No additional risk factors for non-response have been demonstrated (age, sex, anti-CD38 antibody, autologous of allogeneic transplantation, solid cancer, chronic renal insufficiency, diabetes, autoimmune diseases).

Three months after the second dose, the mean SARS-CoV-2 TrimericS IgG titers decreased to 29.7% with a mean of



**Fig. 1.** Distribution of anti-Trimeric Spike protein (mean) titers at 1 month, according to the risk factors for severe COVID-19 disease. Very high risk patients were represented by auto or allogeneic stem cell transplant, lymphoid hemopathy (lymphoma, myeloma), in particular treated by anti-CD20 antibody, Burton tyrosine inhibitors or CAR-T cells, and primary immunodeficiency diseases. High-risk patients were represented by other hematological diseases or non-immunosuppressive therapy.

598±727 BAU/ml (Fig. 2). Seventy-eight patients (56.5%) received a third dose in a median time of 2 months (range 1–4). These patients were defined as being at very high risk of severe COVID-19 disease. Vaccination response at 1 and 3 months was significantly reduced ( $P < 0.0001$ ) in the very high risk group (with three injections) versus in the group with other hematological conditions (with two injections). The third vaccination dose could have helped reach the SARS-CoV-2 TrimericS IgG titer of high-risk patients ( $P = 0.54$ ), but only four (4/44, 9%) patients with vaccine failure at 1 month increased their antibody titer (330 BAU/ml±211).

No major adverse event of mRNA COVID-19 vaccine nor SARS-CoV-2 disease were reported at the time of the intermediate analysis.

#### 4. Discussion

We presented the preliminary results of the HEMVACO study. To our knowledge, it is the largest study performed on COVID-19 vaccination in an hematological population in real-life situation. The seroconversion rate after two doses of mRNA COVID-19 vaccine was achieved in 94 patients (68.1%). Despite the heterogeneity of hematological diseases, we highlighted a significant association between a history of anti-CD20 therapy and a lack of response to mRNA COVID-19 vaccine (96%; OR = 111 [14.3–873];  $P < 0.001$ ), which was consistent with a recent publication [9]. Hypogammaglobulinemia under 8 g/L (OR = 2.49 [1.05–5.92];  $P = 0.032$ ) and lymphopenia under 1.5G/L (OR = 2.47 [1.18–5.17];  $P = 0.015$ ) were the other risk factors for vaccine failure in univariate analysis. These circumstances mostly represented B cell lymphoma.

The selected biological test for this study was performed according to the WHO international standard (NIBSC 20-136)

**Table 2**  
Risk factors for vaccine failure.

Univariate analysis		Number of patients	Number of events (vaccine failure)	OR	95% CI	P
Age (years)	≤65	58	17 (29.3%)	1	–	
	>65	80	27 (33.7%)	1.23	(0.59 to 2.55)	0.58
Sex	Female	67	19 (28.3%)	1	–	
	Male	71	25 (35.2%)	1.37	(0.67 to 2.82)	0.39
Solid cancer	No	113	37 (32.7%)	1	–	
	Yes	25	7 (28%)	0.80	(0.31 to 2.08)	0.64
Autoimmune disease	No	122	39 (31.9%)	1	–	
	Yes	16	5 (31.2%)	0.97	(0.31 to 2.94)	0.95
GFR	≥60	128	42 (32.8%)	1	–	
	<60	10	2 (20%)	0.51	(0.10 to 2.52)	0.38
BMI	≤25	72	21 (29.1%)	1	–	
	>25	62	23 (37%)	1.43	(0.69 to 2.56)	0.33
Hypertension	No	88	28 (31.8%)	1	–	
	Yes	49	16 (32.6%)	1.04	(0.49 to 2.19)	0.92
Diabetes	No	126	42 (33.3%)	1	–	
	Yes	12	2 (16.6%)	0.4	(0.08 to 1.91)	0.21
Anti-CD20 therapy	No	113	20 (17.7%)	1	–	
	Yes, <6 months	25	24 (96%)	111	(14.3 to 873)	<0.001
Anti-CD38 therapy	No	123	41 (33.3%)	1	–	
	Yes	15	3 (20%)	0.5	(0.13 to 1.87)	0.28
Lymphocyte count (10 <sup>9</sup> /L)	≥1.5	71	16 (22.5%)	1	–	
	<1.5	67	28 (41.8%)	2.47	(1.18 to 5.17)	0.015
Albuminemia (g/L)	≥35	122	38 (31.1%)	1	–	
	<35	16	6 (37.5%)	1.33	(0.45 to 3.91)	0.61
Gammaglobulinemia (g/L)	≥8	48	9 (18.7%)	1	–	
	<8	74	27 (36.4%)	2.49	(1.05 to 5.92)	0.032
Multivariate analysis			OR	95% CI	P	
Anti-CD20 therapy	No	101	16 (15.8%)	1	–	
	Yes	21	20 (95.2%)	196	(19.1 to 2020)	<0.001
Gammaglobulinemia (g/L)	≥8	48	9 (18.7%)	1	–	
	<8	74	27 (36.4%)	6.5	(1.41 to 30.1)	0.017

OR: Odds Ratio; GFR: glomerular filtration rate; BMI: Body Mass Index.

**Table 3**  
 Characteristics of patients with negative serology after two doses of mRNA COVID-19 vaccine.

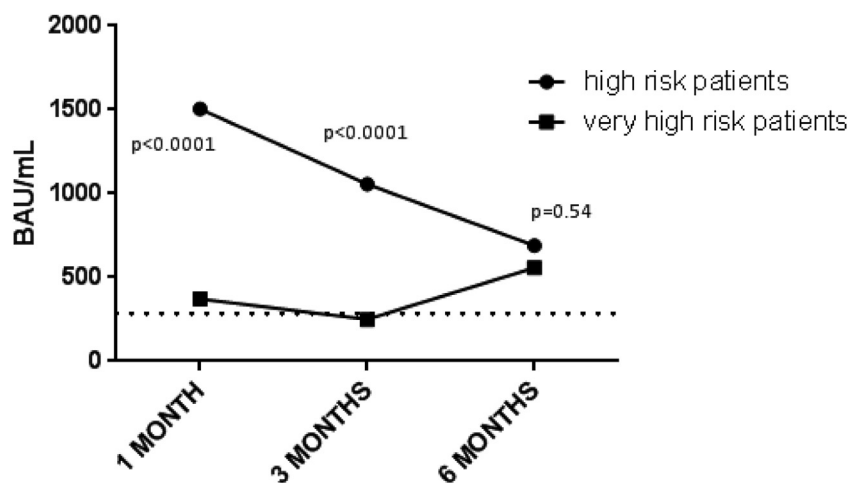
No.	Age	Gender	Hematological diseases	Current therapy	Treatment detail	SARS-CoV-2 TrimericS IgG (BAU/ml)
2	64	M	Myelodysplastic syndrome	Yes	5-azacytidine	<5
8	69	F	Follicular lymphoma	Yes	Rituximab maintenance	<5
10	69	M	Follicular lymphoma	Yes	Obinutuzumab maintenance	<5
12	70	M	Chronic lymphoid leukemia	Yes	Ibrutinib	<5
13	61	M	Diffuse large B-cell lymphoma	No		<5
17	75	F	Diffuse large B-cell lymphoma	No	(CAR-T cells)	<5
18	63	M	MALT lymphoma	Yes	Bendamustine-rituximab	9
22	68	M	Follicular lymphoma	Yes	Rituximab maintenance	<5
30	56	M	Diffuse large B-cell lymphoma	Yes	Rituximab -CHOP	<5
32	77	M	Waldenström macroglobulinemia	Yes	Rituximab-cyclophosphamide-dexamethasone	<5
33	72	M	Follicular lymphoma	Yes	Obinutuzumab maintenance	<5
38	71	M	Follicular lymphoma	Yes	Obinutuzumab maintenance	<5
41	70	F	Follicular lymphoma	Yes	Obinutuzumab maintenance	<5
45	19	F	Diffuse large B-cell lymphoma	Yes	Dose-adjusted-EPOCH-rituximab	<5
51	74	M	Waldenström macroglobulinemia	No		<5
52	46	F	Diffuse large B-cell lymphoma	No		19
53	80	F	Diffuse large B-cell lymphoma	Yes	Rituximab -mini-CHOP	<5
56	83	M	Mantle cell lymphoma	Yes	Rituximab maintenance	<5
62	70	M	Multiple myeloma	Yes	Isatuximab-pomalidomide-dexamethasone	16
68	63	F	Mantle cell lymphoma	Yes	Ibrutinib	<5
72	65	M	Multiple myeloma	Yes	Daratumumab-bortezomib-thalidomide dexamethasone	16
73	53	F	Chronic lymphoid leukemia	Yes	Obinutuzumab-venetoclax	<5
76	66	F	Multiple myeloma	Yes	Isatuximab-pomalidomide-dexamethasone	<5
84	59	M	Diffuse large B-cell lymphoma	No		<5
85	48	M	Follicular lymphoma	No		<5
87	75	M	Multiple myeloma	Yes	Daratumumab-bortezomib-dexamethasone	8
92	72	M	Transformation follicular lymphoma into diffuse large B-cell lymphoma	Yes	Rituximab maintenance	<5
104	60	F	Follicular lymphoma	Yes	Obinutuzumab maintenance	<5
107	81	F	Follicular lymphoma	Yes	Obinutuzumab maintenance	<5
115	74	F	Chronic lymphoid leukemia	Yes	Venetoclax	<5
121	64	F	Follicular lymphoma	Yes	Rituximab maintenance	<5
122	69	M	Chronic lymphoid leukemia	Yes	Venetoclax	<5
132	67	F	Follicular lymphoma	No		10
134	72	M	Transformation follicular lymphoma into diffuse large B-cell lymphoma	Yes	Rituximab maintenance	<5
152	85	F	Waldenström macroglobulinemia	Yes	Ibrutinib	14
157	83	F	Myeloid acute leukemia	Yes	5-azacytidine - venetoclax	<5
159	64	M	Primary central nervous system lymphoma	Yes	Ibrutinib	<5
160	65	M	Diffuse large B-cell lymphoma	Yes	Rituximab -CHOP	<5
161	81	F	T-cell lymphoma	No		<5
163	37	F	Diffuse large B-cell lymphoma	No		<5
166	71	H	Myeloid acute leukemia	Yes	5-azacytidine	<5
167	60	M	Transformation follicular lymphoma into diffuse large B-cell lymphoma	Yes	Rituximab maintenance	25
168	73	F	Mantle cell lymphoma	Yes	Rituximab -DHAC	19

F: Female–M: Male–CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone–Dose-adjusted EPOCH: dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) - DHAC: dexamethasone, high-dose cytarabine carboplatin.

to discriminate SARS-CoV-2 disease history and vaccination effectiveness. Recent COVID-19 disease (< 1 year) and positive pre-vaccination serology were noted to avoid confusion bias. Previous studies reported that immunocompromised patients could not synthesize many post-vaccine antibodies, due to impaired B cell memory lymphocytes and plasmablasts [4]. Recent studies showed that mRNA vaccination induced persistent germinal center B cell response and specific T cells enabling a robust immunity response [10,11]. This study was unable to measure the cellular immunity, but clinical effectiveness will be recorded in case of SARS-CoV-2 disease during the one-year follow-up. At the time we submitted the article, no case of SARS-CoV-2 disease occurred in our cohort, probably due to a weak COVID-19 incidence in our region and an

efficient patient training for self-protection (hand washing, mask wearing, avoiding sick people, avoiding crowds, cocooning strategy of vaccination, etc.).

International guidelines recommended to vaccinate immunocompromised patients to offer a minimum protection. Currently, most learned societies added a third dose of anti-COVID-19 vaccine for patients at very high risk. In the general population, the antibody response after mRNA COVID-19 vaccine declined after 3 months [12,13]. We observed a similar result with a mean decrease of 29.7% of antibody rate in our patients. Some patients became serologically negative, leading to considering a boosted strategy with a third dose of the vaccine. Overall, 56.5% of our patients received a third dose in a median time of 2 months, as per the



**Fig. 2.** Anti-Trimeric Spike protein (mean) titers evolution. Very high-risk patients received three doses of mRNA COVID-19 vaccine (auto or allogeneic stem cell transplant, lymphoid hemopathy [lymphoma, myeloma], in particular treated by anti-CD20 antibody, Burton tyrosine inhibitors or CAR-T cells, and primary immunodeficiency diseases). The mean ( $\pm$  SD) anti-Trimeric Spike protein were 371 ( $\pm$  641), 249 ( $\pm$  493) and 557 ( $\pm$  776) BAU/mL at 1, 3 and 6 months respectively, for 77, 50 and 40 patients, respectively. High-risk patients received two doses of mRNA COVID-19 vaccine and were represented by other hematological diseases or non-immunosuppressive therapy. The mean ( $\pm$  SD) anti-Trimeric Spike protein were 1,504 ( $\pm$  756), 1,056 ( $\pm$  784) and 689 ( $\pm$  778) BAU/mL at 1, 3 and 6 months respectively, for 61, 59 and 18 patients, respectively.

French Guidelines. Four patients with negative serology seroconverted (9%), and some patients ( $n = 7/19$ , 36.8%) with a suboptimal response (defined by Feng and al. study [14]) had a greater benefit as described in a solid organ transplant recipients study [15]. The diversity of biological tests has made it difficult to compare studies. The effectiveness of anti-COVID-19 vaccine boosted strategy was confirmed by the increase (+55%) of antibody level at 6 months (Fig. 2) which completely erased differences between high risk and very high risk patients ( $P = 0.54$ ).

At this stage, we are not sure that an additional third dose will be able to improve SARS-CoV-2 TrimericS IgG titers for patients without response ( $< 5$  BAU/ml) 1 month after two doses of mRNA COVID-19 vaccine. Would higher doses benefit these patients? The additional dose could be discussed for patients with positive but suboptimal SARS-CoV-2 TrimericS IgG titer to boost their humoral immunity. In our study, the suboptimal response at 1 month could be defined with the median titer: 379 BAU/ml. Two groups of patients were also distinguished. Below this threshold, SARS-CoV-2 TrimericS IgG titer decreased at 3 months with  $99 \pm 121$  BAU/ml contrasting with the most elevated threshold, for whom the SARS-CoV-2 TrimericS IgG did not vary as much ( $1,109 \pm 678$  BAU/ml). Nevertheless, these results should be confirmed in a larger study of hematological patients. At last, another vaccine dose beyond 6 months should improve long-term immunity [16].

The mortality rate of patients with hematological malignancies contracting COVID-19 disease could be 37% [17]. Thus, these patients should be treated promptly by subcutaneous REGEN-COV (casirivimab/imdevimab) or COVID-19 convalescent plasma therapy to avoid poor prognosis [18,19].

## 5. Conclusion

Our study reported a seroconversion rate of 68.1% in an hematological cohort. We confirmed anti-CD20 antibody strongly impaired the humoral response to anti-COVID-19 vaccination, as well as hypogammaglobulinemia and lymphopenia. We recommend performing vaccination before anti-CD20 therapy when the hemopathy treatment can be delayed—especially for indolent lymphomas. Hematological patients contracting SARS-CoV-2 disease should be treated by convalescent plasma therapy or REGEN-COV. The third (boosted) dose of vaccine should be monitored by SARS-CoV-2 TrimericS IgG titer 1 month after mRNA injection, but

suboptimal response should be defined by another hematological cohort. Those preliminary results will have to be further supported by final results and larger studies.

## Ethics committee approval

Yes.

## Disclosure of interest

The authors declare that they have no competing interest.

## Acknowledgement

The authors thank all the members of the Centre Hospitalier de Vannes and the Centre Hospitalier Intercommunal de Cornouaille de Quimper and Concarneau who helped to include patients. The authors also thank all patients involved in the study for their active participation and the interesting discussions about the vaccination. We would like to thank Pascaline Rameau and Emmanuel Nowak from the Centre d'Investigation Clinique, INSERM CIC-1412, CHRU de Brest and Quimper.

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