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1 **Anti-SARS-CoV-2 antibody response after 2 and 3 doses of BNT162b2**
2 **mRNA Vaccine in patients with lymphoid malignancies.**

3
4 Running title: COVID-19 vaccine in lymphoid malignancies

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26

27 **Abstract**

28 **Objectives**

29 COVID-19 patients affected by hematological malignancies have a more severe course of the
30 disease and higher mortality, prompting for effective prophylaxis. The present study aims to
31 evaluate the humoral response after mRNA vaccination as well as the impact of a third vaccine
32 dose in patients with lymphoid malignancies

33 **Methods**

34 We conducted a single center study, evaluating the serological responses of mRNA vaccination
35 amongst a cohort of 200 patients affected by lymphoid malignancies after two or three doses
36 using an industrial SARS-CoV-2 serology assay for anti-RBD Spike IgG detection and
37 quantification.

38 **Results**

39 Among patients with plasma cell disorders, 59/96 (61%) had a seroconversion (anti-RBD > 50
40 AU/mL), and recent anti-CD38 therapies were associated with lower serological anti-RBD IgG
41 concentrations (median IgG concentration 137 (IQR 0-512) AU/mL vs 543 (IQR 35-3496) AU/mL,
42 $p < 0.001$). Patients with B-cell malignancies had a lower seroconversion rate (20/84, 24%)
43 mainly due to the broad usage of anti-CD20 monoclonal antibodies, only 2/53 (4%) patients
44 treated by anti-CD20 antibodies during the last 12 months experienced a seroconversion. A
45 total of 78 patients (44 with plasma cell disorders, 27 with B-cell malignancies and 7 with other
46 lymphomas) received a third dose of vaccine. The seroconversion rate and antibody

47 concentrations increased significantly, especially in patients with plasma cell disorders where
48 an increment of anti-RBD IgG concentrations was observed in 31/44 (70%) of the patients, with
49 an anti-RBD concentration median-fold increase of 10.6 (IQR 2.4-25.5), while its benefit in B-
50 cell malignancies is uncertain, only 2/25 (8%) patients having seroconverted after the vaccine
51 booster, without increased median antibody concentration.

52 **Conclusions**

53 A third mRNA vaccine dose improved significantly humoral responses among patients with
54 plasma cell disorders, while the effect was limited among patients with B-cell malignancies.

55 Key words: third dose, COVID-19, immunocompromised, vaccine, hematological malignancies

56 **BACKGROUND**

57 Early in the COVID-19 pandemic a more severe course of the disease and higher mortality were
58 reported among patients with malignant hemopathies[1]. Current French guidelines advise a
59 third dose with prioritization to immunocompromised recipients[2]. A third dose of vaccine in
60 solid organ transplant recipients was able to significantly improve its immunogenicity[3], but
61 available data among hematological patients remain scarce and incomplete. Previous reports
62 showed particularly low response rates (especially with anti-CD20 therapy) among patients with
63 lymphoid malignancies, and the effect of treatment such as anti-plasma cell drugs remains
64 controversial[4]. Here, we report the anti-SARS COV-2 antibody (anti-receptor binding domain
65 (RBD) IgG) response in vaccinated patients with lymphoid hematological malignancies in a
66 tertiary center, and immunogenicity of a third dose as boost in a subgroup of this population.

67 **METHODS**

68 We conducted a single center cohort study evaluating immunological responses among patients
69 treated for lymphoid malignancies in a tertiary center. All patients with an active follow-up in
70 our center were offered an on-site vaccination by BNT162b2 mRNA vaccine since January 1st
71 2021 (2 injections scheduled 21 days apart). Since March 2021, patients were advised to receive
72 a third injection of vaccine. Humoral response was evaluated by SARS-CoV-2 serology using the
73 IgG II Quant Assay (Abbot Laboratories, Wiesbaden, Germany) for anti-RBD Spike (S) IgG
74 detection and quantification. A quantifiable anti-RBD IgG concentration above the
75 manufacturer defined threshold (50 AU/mL) was considered as seroconversion. We stratified
76 samples by anti-RBD IgG concentrations above or below 1000 AU/mL and 4160 AU/mL,
77 associated with a high probability of virus neutralization in *in-vitro* plaque reduction assays
78 against several variants of concern[5,6]. The study was approved by local ethics committee and
79 in accordance with the 1964 Helsinki declaration. Categorical variables were expressed as
80 percentages, quantitative variables as median (interquartile range, IQR). Statistical comparisons
81 were performed using the Wilcoxon test and the Kruskal-Wallis non-parametric tests as
82 appropriate. Additional details regarding immunological response evaluation, statistics and
83 ethics are available in the Supplemental appendix.

84 **RESULTS**

85 The study included a total of 200 non-selected patients consecutively followed in our center
86 between January 1st 2021 and July 14th 2021. Baseline characteristics are shown in Table 1.
87 Seroconversion rate ranged from 3/20 (15%) patients with follicular lymphoma to 8/9 (89%) in
88 Hodgkin lymphoma patients (Figure 1A). Aiming to assess factors affecting vaccine response,
89 we clustered lymphoid diseases into groups based on common ontogeny and treatment type.
90 Plasma cell disorders (PCD) included multiple myeloma, plasma cell leukemia and light chain
91 amyloidosis; B-cell malignancies (BCM) included aggressive, indolent B-cell non-Hodgkin
92 lymphomas and chronic lymphocytic leukemia; while other lymphomas included Hodgkin and T
93 cell lymphomas.

94 In the 96 patients with PCD, 59/96 (61%) seroconverted and the median anti-RBD concentration
95 was 223.5 (IQR 0-2011) AU/mL (Figure 1b). Being actively treated in the previous six months
96 (83/96) was associated with a lower anti-RBD IgG concentration (147 (IQR 0-978) vs 5245 (IQR
97 297-8534) AU/mL, $p=0.001$). More specifically, the use of anti-CD38 antibodies in the last 12
98 months (54/96 (56%) patients, including 52 in the last 6 months) was not associated with lower
99 seroconversion rates (seroconversion observed in 29/54 (54%) vs 31/42 (73%) among patients
100 with or without such treatment respectively ($p=0.07$)), but fewer patients reached the
101 thresholds of 1000 (10/54 (19%) vs 18/48 (43%), $p=0.005$) and 4160 AU/mL (4/54 (7%) vs 11/42
102 (26%), $p=0.008$).

103 In the 84 patients with BCM, 20/84 (24%) seroconverted and the median anti-RBD
104 concentration was 0 (IQR 0-40) AU/mL (Figure 1B). We observed a seroconversion in 18/31

105 (51%) patients who did not receive anti-CD20 treatment in the 12 months prior to vaccination,
106 but only in 1/46 (2%) patients who received anti-CD20 antibodies in the last 6 months (with
107 anti-RBD concentration <1000 AU/mL). Although limited by a small number of patients, a
108 similar magnitude of seroconversion was observed when anti-CD20 was administered 6 to 12
109 months before vaccination (1/7 (14%) p=0.7). On the other hand, 7/10 (70%) patients who
110 received at least one vaccine dose before starting any treatment (n=10) had a seroconversion,
111 the median time before treatment being 16 days (IQR 5-29).

112 In a multivariate analysis, factors affecting vaccine humoral response in patients with lymphoid
113 malignancies were age (p<0.001), number of prior lines of therapy (p=0.01) and recent
114 treatment by anti-CD20/CD38 antibodies (<12 months) (p=0.007) (supplemental Table).

115 A total of 78 patients received a third BNT162b2 dose. Forty-four PCD patients (46%) received a
116 third dose of mRNA vaccine (median time from second dose: 70 days (IQR 47-87), median anti-
117 RBD concentration after 2 doses 146 (IQR 0-543] AU/mL). An increment of IgG anti-RBD
118 concentration was observed in 31 patients (70%), with a median-fold increase of 10.6 (IQR 2.4-
119 25.4), p<0.001), while 14 patients (32%) who had undetectable levels of anti-RBD antibodies
120 after 2 doses seroconverted (figure 1C). Treatment with anti-CD38 antibody did not alter the
121 response improvement (median increase of 450 (IQR 0-2204) vs 466 (IQR 77-5791) AU/mL,
122 p=0.8).

123 A total of 27 patients with BCM received a third dose of BNT162b2 vaccine (median time from
124 second dose: 58 days (IQR 43-88), median anti-RBD concentration after 2 doses: 0 (IQR 0-0)

125 AU/mL). Seroconversion rate increased modestly (4/27 (15%) to 6/27 (22%), and only 2/27
126 patients (without anti-CD20 treatment in the last year) reached the 1000 AU/mL threshold.

127 **DISCUSSION**

128 The results of the present study show a large heterogeneity in anti-RBD IgG concentration
129 levels among patients with lymphoid malignancies, reflecting the diversity of malignancies and
130 treatments [7,8]. Anti-CD20 immunotherapies were associated with negligible serological
131 responses. The extent of anti-CD38 treatments impairment on vaccine immunogenicity is
132 unclear[9,10]. Our study showed a significantly reduced proportion of patients with anti-RBD
133 concentrations above predefined thresholds compared to patients receiving only cytotoxic
134 chemotherapy.

135 To our knowledge, this is the first available study evaluating the effect of a third vaccine dose in
136 a significant number of patients affected by lymphoid malignancies. We showed a relevant
137 humoral response improvement in patients affected by PCD, including patients treated by anti-
138 CD38 therapies. In contrast, the effect of the third dose in BCM patients appeared limited [11].
139 It remains crucial to determine the timing of the booster dose from last administration of anti-
140 CD20, which could be guided by monitoring B cell restoration[12].

141 Our study bears some limitations. First, some analyses were limited by a small number of
142 patients. Second, while persistence of specific antibodies in COVID-19 patients with
143 hematologic malignancies have been reported[13], the dynamic of vaccine induced-antibodies
144 across time has yet to be explored. Third, predefined antibody concentration thresholds have

145 been established among healthy people after natural infection, and no clear correlation with
146 clinical protection has been demonstrated. The thresholds used in this study encompass a
147 rather large range of antibody concentrations and should be evaluated through neutralization
148 capacity of the antibodies obtained in this population, as well as the incident infections rate.
149 Fourth, our study did not evaluate T cell responses which could carry an important role in
150 controlling infection[14,15].

151 As new variants of concerns continue to emerge worldwide, updated data regarding the
152 efficacy of the available vaccine in one of the most vulnerable population is critical. Our study
153 suggests that a third vaccine dose could increase the seroconversion rate and antibody
154 concentrations, especially in patients with PCD; whereas its benefit among patients receiving
155 anti-CD20 therapy is uncertain, prompting for alternative protective strategies.

156

157 **Table. Baseline characteristics**

	All (n=200)	Plasma cell dyscrasias (n=96)	B-cell malignancies (n=84)	Other hematological malignancies (n=20)
Age (years, median [interquartile range])	70 [59 ; 76]	70 [61.5 ; 76]	71 [59 ; 76]	56.5 [46.25 ; 70.75]
BMI (kg/m ² , median [interquartile range])	24.00 [22.00 ; 27.00]	23.50 [22.00 ; 27.00]	24.00 [22.00 ; 26.25]	24.00 [20.50 ; 26.00]
Female gender (%)	83 (42%)	43 (45%)	33 (38%)	7 (35%)
Disease response status (%)				
Partial/complete responses (PR/CR)	136 (68%)	70 (73%)	53 (63%)	13 (65%)
Stable disease	8 (4%)	6 (6%)	2 (2%)	0 (0%)
Progressive disease	36 (18%)	16 (17%)	16 (20%)	7 (35%)
Treatment status (n)				
Naïve	16 (8%)	4 (4%)	10 (12%)	0 (0%)
On therapy	151 (76%)	83 (87%)	53 (63%)	18 (90%)
Off therapy – complete/partial response	22 (11%)	8 (8%)	12 (14%)	1 (5%)
Off therapy – relapse	11 (6%)	1 (1%)	9 (11%)	1 (5%)
Number of prior lines of therapy (n)	5 [3 ; 5]	5 [3 ; 6]	3 [3 ; 5]	1 [1 ; 2]
Previous autologous hematopoietic stem cell transplantation (n)	39 (19%)	29 (30%)	6 (7%)	4 (20%)
<12 months before vaccination	5 (2%)	4 (4%)	0	1 (5%)
≥12 months before vaccination	34 (17%)	25 (26%)	6 (7%)	3 (15%)
Malignancy type (%)	-	Multiple myelomas 68 (71%) Amyloidosis 28 (29%)	CLL 12 (14%) FL 20 (24%) MCL 9 (11%) MZL 12 (14%) DLBCL 31 (37%)	Hodgkin lymphomas 9 (45%) T cell lymphomas 10 (50%) Others 1 (5%)
Receiving specific immunological therapy (%)	-	Anti-CD38 therapy: 66 (69%)	Anti-CD20 therapy :70 (83%)	Anti-CD20 therapy: 4 (20%)
In the last 6 months previous vaccination		52 (54%)	46 (55%)	1 (5%)
6-12 months before vaccination		2 (2%)	7 (10%)	1 (5%)
More than 12 months before vaccination		12 (13%)	16 (19%)	2 (10%)
Third vaccine injection (n)	78 (36%)	44 (46%)	27 (32%)	7 (35%)

158 DLBC: diffuse large B cell lymphoma; FL: follicular lymphoma; MCL: mantle cell lymphoma; MZL:
159 marginal zone lymphoma and lymphoplasmocytic lymphoma/Waldenström macroglobulinemia; CLL:
160 chronic lymphoid leukemia
161

162 **Figure 1. Immunogenicity of two and three mRNA vaccines doses among patients with lymphoid**
163 **malignancies.**

164 Graphics display a representation of the median anti-RBD IgG concentration value (IQR) through boxplot
165 representation. In order to appreciate the data dispersion, interquartile range was included in the
166 attached tables.

167 **Panel A.** Anti-RBD IgG concentration (AU/mL) according to underlying hematological pathology, after 2
168 mRNA vaccine doses. **Panel B.** Anti-RBD IgG concentration (AU/mL) according to main pathology groups
169 and treatment characteristics, after 2 mRNA vaccine doses: “Naïve” condition represents patients who
170 received at least one vaccine dose before initiation any treatment; “Chemotherapy” condition
171 represents patients who only received in the previous year standard cytotoxic chemotherapy as
172 treatment; “Immunotherapy” condition represents patients who received in the previous year either
173 anti-CD20 or anti-CD38 therapy (accordingly to the underlying disease); “Post-treatment” condition
174 represent patients who had their last treatment at least 12 months before vaccination. Statistical
175 analyzes were made by comparing each group to the other three. **Panel C.** IgG anti-RBD IgG
176 concentrations (AU/mL) after 2 and 3 mRNA vaccine doses, according to main pathology groups and
177 stratified into sub-groups based on the use of immunotherapy in last 12 months (anti-CD20 or anti-CD38
178 accordingly to the underlying disease).

179 DLBC: diffuse large B cell lymphoma; FL: follicular lymphoma; MCL: mantle cell lymphoma; MZL:
180 marginal zone lymphoma and lymphoplasmocytic lymphoma/Waldenström macroglobulinemia; CLL:
181 chronic lymphoid leukemia; HL: Hodgkin’s lymphoma; TCL: T cell lymphoma.

182 †: graphic displays the whole population vaccinated with 2 doses, in order to identify the patients
183 selected for a third vaccine dose (44 and 27 patients in PCD and BCM groups respectively), attached
184 table describes the population who received 3 vaccine doses.

185 §: 3 patients affected by plasma cell disorders did not have clear or available treatment information

186 * p-value <0.05, ** p-value <0.01, *** p-value <0.001, ns: not statistically significant

187

188	Authors' contributions
189	S.B. Gressens: conceptualization, formal analysis, investigation, data curation, writing – original draft,
190	visualization. S. Fourati: conceptualization, methodology, investigation, writing – review and editing,
191	supervision. A. Le Bouter, F. Le Bras, J. Dupuis, M. Hammoud, T. El Gnaoui, R. Gounot, L. Roulin, K.
192	Belhadj : investigation, resources, writing – review and editing. C. Haioun: investigation, resources,
193	project administration, writing – review and editing. S. Gallien: investigation, resources, project
194	administration, supervision, writing – review and editing. G. Melica: conceptualization, investigation,
195	resources, supervision, writing – review and editing, project administration. F. Lemonnier:
196	conceptualization, investigation, resources, supervision, writing – review and editing, project
197	administration.
198	
199	

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249

250

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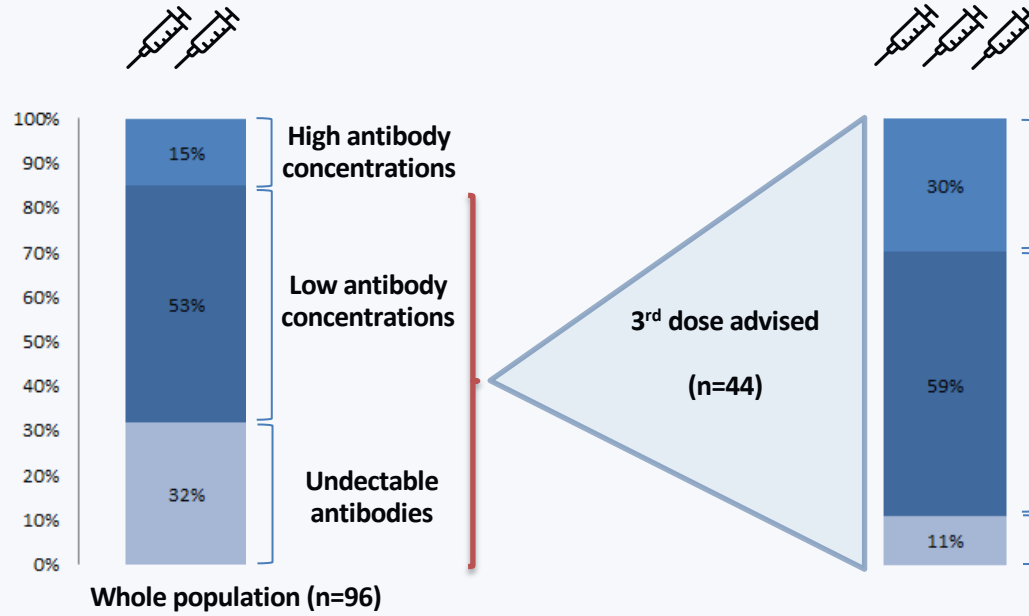
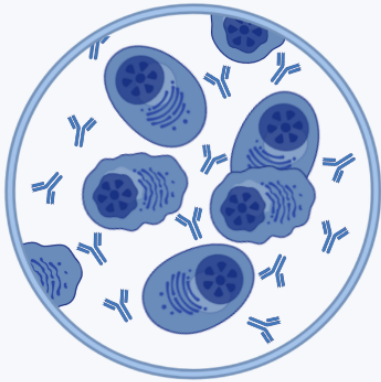
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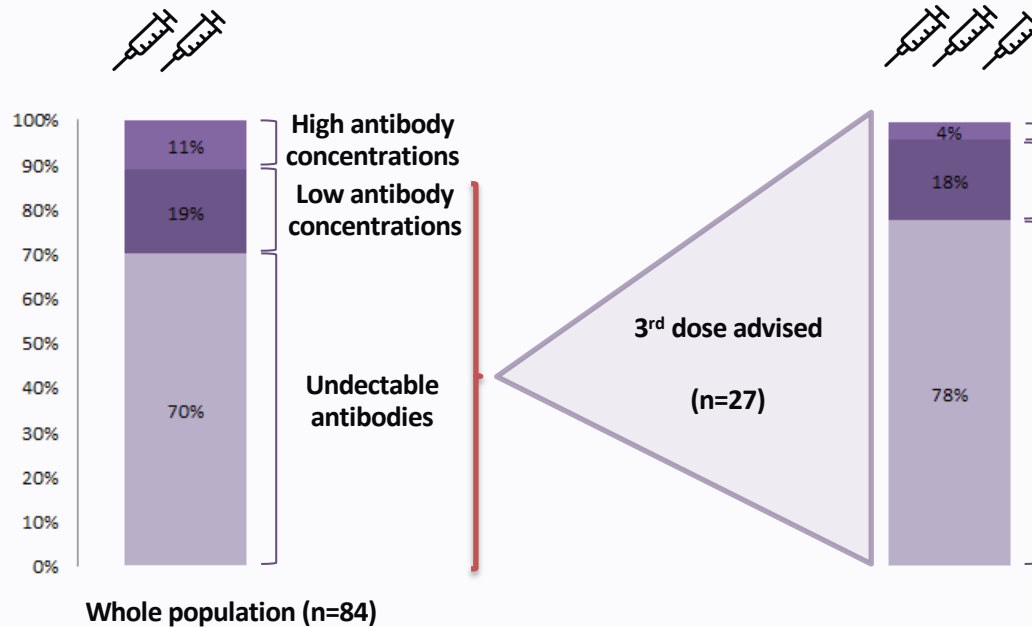
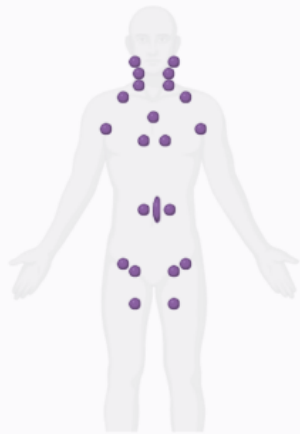
271

Plasma Cell Disorders



Anti-CD38 therapeutics did not impact improvement after booster dose

B-Cell Malignancies



Anti-CD20 therapeutics impaired humoral responses after 2 or 3 mRNA vaccine doses