Received: 13 December 2021 | Accepted: 10 January 2022

DOI: 10.1111/bjh.18055

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

LETTER TO THE EDITOR

Response to vaccination against SARS-CoV-2 in 168 patients with Waldenström macroglobulinaemia: A French Innovative Leukaemia Organization study

Patients with haematological malignancies have shown an increased risk of morbidity and mortality with regard to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1,2] Immunocompromised patients have been excluded from initial trials evaluating SARS-CoV-2 mRNA vaccines[3–5] and there is a crucial need to assess vaccine efficacy among these patients.

Underlying disease and B-cell-directed therapies might adversely affect the production of antibodies in response to SARS-CoV-2 vaccination in Waldenström macroglobulinaemia (WM) patients. Recent studies confirmed that antibody-mediated response to SARS-CoV-2 vaccine was impaired in several cohorts of immunocompromised populations including chronic lymphocytic leukaemia (CLL),[6,7] myeloma[8] and B-cell lymphoma[9] patients. A recent study evaluating the production of neutralizing antibodies (NAbs) against SARS-CoV-2 indicated that WM patients produced significantly lower levels of NAbs compared with controls.[10] While this type of evaluation is of great interest, anti-spike (anti-S) response rate is the evaluation that has been most widely reported and is currently routinely applicable .

In this study, we evaluated anti-S antibody response to anti-SARS-CoV-2 vaccination in 168 WM patients, provided information on the efficacy of a third booster dose in patients with suboptimal response after two doses of vaccines and on specific anti-SARS-CoV-2 T-cell responses. We conducted a prospective non-interventional study in the framework of the FILO group and the French patient associations SILLC and Waldenström France. Patients were eligible if they had a diagnosis of WM and were vaccinated through the French national vaccination programme. All patients provided written informed consent and the study was approved by the Health Data Hub. Patients received two vaccine doses, usually at a four-week interval, and a third booster dose (if seronegative) as recommended by the French Authority of Health. More details regarding methods are provided in the Supplementary data.

From March to July 2021, a total of 168 WM patients were included in this study. Main demographic, disease and treatment characteristics of this cohort are summarized in Table 1. A large majority of patients received BNT162b2 vaccine (n = 150/168, 89%). Median patient age was 72 years (range, 43–94). Median number of therapeutic lines for WM before vaccination was one (range, 0–4). Thirty-eight WM patients (22.5%) were treatment-naïve (TN), 96 (57%) had received prior therapy and were off therapy [including 29 (17%) and 67 (40%) patients with a time interval between last therapy and vaccination inferior or superior to one year (1 y) respectively], and 34 (20%) were on therapy at the time of vaccination.

After two doses of vaccination, anti-S response rate for the whole cohort was 67.5% (n = 113/168). This is in line with what has been reported for lymphoma (70%–75%)[11] but seems superior to what has been observed for CLL (43%–50%)[6,7] and myeloma patients (55%).[8] Main characteristics of patients with positive and negative (n = 55/168, 32.5%) antibody response are detailed in Table 1. Anti-SARS-CoV-2 antibody responses according to disease and treatment status are summarized in Figure 1. Evaluation of humoral response in Arbitrary Units (AU)/ml and standardized Binding Antibody Units (BAU) are available in Figure S1. TN patients had the highest response rate (94.7%, n = 36/38) compared to previously treated patients (66.7%, n = 64/96; p = 0.003), most of whom received chemoimmunotherapy (CIT) (Table 1), and to patients on therapy (38.2%, n = 13/34; p < 0.001) (Figure 1A). The 34 patients on therapy were receiving the Bruton tyrosine kinase inhibitor (BTKi) ibrutinib (n = 23, 67.5%) or anti-CD20 based-regimens (n = 11, 32.5%), either in monotherapy [n = 2] or in CIT (n = 9), and presented respective vaccination response rates of 43.5% (n = 10/23) and 27.5% (n = 3/11) (p = 0.49). Response rates were markedly different according to the time interval between last therapy and vaccination, as they were respectively 13.8% (n = 4/29) and 89.6% (60/67) (p < 0.001) for WM patients off therapy with a <1-year and >1-year time interval. The type of last therapy consisted mainly in anti-CD20-based-regimen (n = 87/96, 90%; Table 1). The proportion of patients with anti-S antibodies post dose 2 (D2) < 250 BAU/ml, the threshold used to consider patients eligible to prophylactic antibodies, was 44% (n = 74/168) for the whole cohort. Regarding subgroups of patients according to their therapy status, this proportion was distributed as follows: 16% (n = 6/38) for TN patients, 91% (n = 31/34) for patients on therapy, 93% (n = 27/29) for patients off therapy <1 year

TABLE 1 Main characteristics of the WM cohort

	Whole cohort	Post D2 positive antibody test	Post-D2 negative antibody test	
	n (%)	*n* (%)	*n* (%)	*p* value
Total	168 (100)	113 (67.5)	55 (32.5)	
Median age at vaccination, years (range)				NS
Sex, male	110 (65)	73 (64.5)	37 (67)	NS
Vaccination type				
Bnt162b2 (Pfizer)	150 (89)	101 (89.5)	49 (89)	NS
ARNm-1273 (Moderna)	4 (2)	1 (1)	3 (5.5)	NS
ChAdOx1-S (AstraZeneca)	13 (8)	11 (9.5)	2 (3.5)	NS
JNJ-78436735 (Janssen)	1 (1)	0 (0)	1 (2)	NS
Number of previous lines of therapies				
0	38 (23)	36 (32)	2 (3.5)	< 0.05
1	79 (47)	49 (43)	30 (54.5)	
2	29 (17)	14 (11,5)	15 (27.5)	
3 or more	22 (13)	14 (12.5)	8 (14.5)	
Therapy status				
On therapy	34 (20)	13 (11.5)	21 (38)	< 0.05
Off therapy <12 months	29 (17)	4 (3.5)	25 (45.5)	
Off therapy >12 months	67 (40)	60 (53)	7 (12)	
Delay between last treatment and vaccination, median (months)				< 0.05
Type of ongoing treatment	*n* = 34	*n* = 13	*n* = 21	< 0.05
Immunochemotherapy	9 (26.5)	3 (23)	6 (28.5)	
Dexamethasone–Rituximab–Cyclophosphamide (DRC)	2 (6)	0 (0)	2 (9.5)	
Bendamustine–Rituximab (BR)	4 (11.5)	1 (7.5)	3 (14.5)	
Others	3 (9)	2 (15.5)	1 (4.5)	
Rituximab monotherapy	2 (6)	0 (0)	2 (9.5)	
Ibrutinib	23 (67.5)	10 (77)	13 (62)	
Type of last line of treatment	*n* = 96	*n* = 64	*n* = 32	NS
Immunochemotherapy	82 (84.5)	55 (85.5)	27 (84.5)	
Dexamethasone–Rituximab–Cyclophosphamide (DRC)	27 (28)	20 (32)	7 (22)	
Bendamustine–Rituximab (BR)	41 (42)	21 (33.5)	20 (62.5)	
Fludarabine–Rituximab (FR) or Fludarabine–Cyclophosphamide–Rituximab (FCR)	14 (14.5)	13 (20)	1 (3)	
Bortezomib–Dexamethasone–Rituximab (BDR)	3 (3.5)	2 (3)	1 (3)	
Rituximab monotherapy	2 (2)	2 (3)	0 (0)	
Other	9 (10)	6 (9.5)	3 (9.5)	
Gammaglobulin level <6 g/l at vaccination	64/94 (68)	33/56 (59)	31/38 (81)	NS
Delay between vaccination and antibody test, median in days (range)				NS

Abbreviations: ICT, immunochemotherapy; NS, not significant; WM, Waldenström macroglobulinaemia.

and 15% (*n* = 10/67) for patients off therapy >1 year (Table S2). After a median follow-up of 122 days since dose 2 (D2), one patient (*n* = 1/168, 0.5%), receiving BTKi and with no detectable antibodies, developed COVID-19 that did not require hospitalization.

The highest response rate observed for TN patients was in line with the reported similar response rate observed between smouldering WM patients and healthy controls.[12] The negative influence of BTKi or anti-CD20-based regimen on antibody production was concordant with other vaccination

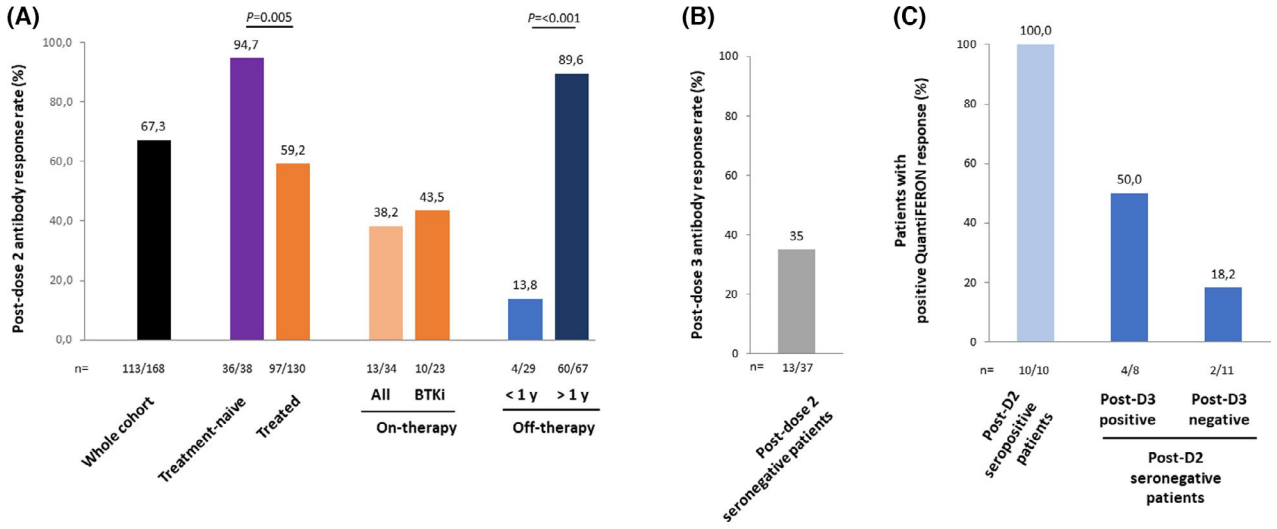

FIGURE 1 Anti-SARS-CoV-2 antibody responses in patients with WM according to disease status and treatment. (A) Antibody response rates after two doses of anti-SARS-CoV-2 vaccination. Antibody response rates are represented in percentages. The number of patients with a positive response rate and the total number of patients for each category are indicated below each histogram. Two subgroups of off-therapy patients are represented: those for whom the length of time between last treatment and vaccination was (i) shorter than one year and (ii) longer than one year. (B) Antibody response rates after a third booster dose of anti-SARS-CoV-2 vaccination for post-dose 2 seronegative patients. Data were available for 37 out 55 post-dose 2 seronegative patients. (C) (QuantiFERON SARS-CoV-2, Qiagen) response according to anti-S response vaccination after dose two (D2) and/or three (D3). Data were available for 29 WM patients. Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; D, dose; y, year

efficacy reports.[7,10,11] However, the response rate of WM patients treated with BTKi (43.5%) or anti-CD20-based regimen [ongoing (27.5%) or in the last 12 months (13.8%)] compared favourably with the response rates observed in CLL (respectively 16%–22%, 0% and 0%–5%).[6,7,13]

Among the 55 patients with post-D2 negative response, data regarding the efficacy of a third booster dose were available for 37. Post-D3 response rate was 35% (n = 13/37) (Figure 1B). This result is concordant with what has been reported in the French CLL cohort (35%).[13] Characteristics of post-D3 positive and negative groups are summarized in Table S3. All post-D3 negative patients were on therapy or received anti-CD20-based regimen for less than two years.

Considering the role of T-cell immunity in COVID-19,[14] we evaluated the anti-SARS-CoV-2 T-cell response in 29 WM patients. Among them, ten patients had positive post-D2 anti-S serologic tests and 19 post-D2 negative tests including eight who experienced post-D3 seroconversion and 11 who remained seronegative. Two of the 11 post-D3 seronegative patients harboured anti-SARS-CoV-2 T-cell response, whereas all post-D2 seropositive patients (n = 10/10) and one half (n = 4/8) of post-D2 seronegative/post-D3 seropositive patients had positive anti-SARS-CoV-2 T-cell response (Figure 1C).

To conclude, 67.5% of our WM cohort exhibited anti-SARS-CoV-2 anti-S humoral response after two vaccine doses, which increased to 75% (n = 126/168) after a third booster dose for seronegative patients. Ongoing BTKi treatment and anti-CD20 therapy in the last year were associated with the lowest response rates. Our results not only confirm the value of vaccination strategy, including the third booster dose for post-D2 seronegative patients, but also indicate that a fraction of WM patients still have partial or combined impaired anti-SARS-CoV-2 humoral/T-cell responses despite a complete vaccination schedule.

ACKNOWLEDGEMENTS

We would to thank all the patients along with the SILLC (association de Soutien et d'Information à la Leucémie Lymphoïde Chronique et la maladie de Waldenström) and Waldenström France patients' associations for their support and participation in this study. This study was supported by grants from INCA-DGOS-Inserm_12560 (SiRIC CURAMUS is financially supported by the French National Cancer Institute, the French Ministry of Solidarity and Health and INSERM with financial support from ITMO Cancer AVIESAN).

KEYWORDS

antibody response, COVID, SARS-CoV-2, vaccination, Waldenström

CONFLICT OF INTEREST

There is no conflict of interest.

AUTHOR CONTRIBUTIONS

Cécile Tomowiak, Véronique Leblond, Florence Cymbalista and Damien Roos-Weil designed the research and analysed data. Cécile Tomowiak and Damien Roos-Weil wrote the manuscript. Elodie Courret, Guy Gorochov and Delphine Sterlin performed experiments. Cécile Tomowiak, Véronique Leblond, Kamel Laribi, Marine Baron, Christian Puppinck, Elodie Courret, Olivier Tournilhac, Pierre Morel, Florence Cymbalista and Damien Roos-Weil recruited patients. All authors reviewed and approved the manuscript.

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