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Short communication

B-cell cytopenia and time to last B-cell-depleting therapy predict response to SARS-COV-2 vaccines in patients with lymphoproliferative disorders

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ABSTRACT

Patients with B-non-Hodgkin lymphoma (NHL) are at increased risk of morbidity and mortality from SARS-CoV-2. We investigated the relationship between B cell cytopenia and the SARS-CoV-2 vaccine response in B-NHL patients. We measured anti-RBD antibodies and the lymphocyte immunophenotype in 19 controls, 22 lymphoma patients on observation (cohort 1) and 55 lymphoma patients receiving their vaccines post B-cell depleting therapy (cohort 2). Half of the lymphoma patients in both cohorts achieved seropositivity compared to 100% of controls. In cohort 2, only 5% achieved an antibody response in the first year post B-cell depleting treatment, vs 88% treated >2 years prior. Also, 28% of patients with <50 B cells/μl achieved a serologic response vs 86% of patients with B-cell >50 B cells/μl. B-cell cytopenia is profound within the first year of exposure to B-cell depleting treatment, therefore an additional dose of vaccine within that timeframe is unlikely to raise antibody levels.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection created a pandemic that has killed more than 5 million people [1]. This RNA virus uses the receptor binding domain (RBD) of its Spike glycoprotein to enter host cells, which is the target of neutralizing antibodies acquired from natural infection [2,3] and vaccines [4,5]. Vaccination against SARS-CoV-2 decreases COVID-19 related mortality and hospitalizations. However, patients with B-non-Hodgkin lymphoma (NHL) experience suboptimal antibody responses to COVID-19 vaccines, before and after B-cell-targeted therapies, such as the anti-CD20 antibody rituximab [6–11]. We investigated the relationship between B cell cytopenia and vaccine response in B-NHL to identify the best time for "booster" doses in patients receiving B cell-depleting therapies.

2. Methods

We measured anti-RBD antibodies and the absolute number of B cells in the peripheral blood (PB) of 77 patients with lymphoma and compared them to 19 healthy controls. This project was approved by our research ethics board (REB#2022–3008, REB11-047,2012–95). Participants consented to PB collection prior to the first vaccine dose, two to five weeks after the first dose and second doses. Cohort 1 comprised 22 lymphoma patients on observation or receiving their vaccine at least 2 weeks prior to initiating treatment. Cohort 2 included 55 patients who received their 2 doses after exposure to B-cell depleting treatment (<1 year

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(n = 22), 1–2 year (n = 16) and >2 years (n = 17)). Baseline immune profile, available in 69 participants, was determined using the complete blood cell count (CBC) at the time of the first vaccine dose. The absolute lymphocyte count on the CBC was multiplied by percentages of CD19, CD4, CD8 and CD56 determined by flow cytometry to obtain the absolute number of cell subsets. For CLL, the absolute number of normal B cells was estimated using the percentage of B cells expressing the alternate light chain of the malignant clone (see flow cytometry supplemental methods). The levels of anti-RBD antibodies at each time point were determined as described (see ELISA supplemental methods) [12–15].

2.1. Statistical analysis

Statistical calculations were performed using SPSS (version 27) and SAS (version 9.4). We compared the variables in different cohorts using Pearson Chi square test and Levene's test for equality of variances (differences in mean antibody levels), using a $p < 0.05$ as the level of significance.

To evaluate the association between the timing of the last rituximab dose and antibody response, we restricted to the cohort that received rituximab prior to the vaccine and estimated crude odds ratios for antibody response for three categories of rituximab dose timing (up to 1 year before vaccine receipt, 1–2 years before vaccine receipt, and 2 or more years before vaccine receipt as the referent), as well as odds ratios for a ten year increase of age, a one week increase in time between doses, and current disease status (active vs in remission). Multivariable logistic regression was then used to determine if the association between the last dose of rituximab and the antibody response changed when holding age, current disease status and time between vaccine doses were constant. P values for the rituximab timing group were obtained from Type 3 tests. To assess whether damage to B cells by recent rituximab therapy was a potential mechanism for this effect, we also estimated the association between CD19 levels < 50 B cells/μl and antibody production from a crude odds ratio and after multivariable regression adjusting for age and time between vaccine doses. Unfortunately, rituximab timing and disease status could not be included in this model without severe overfitting.

3. Results

Baseline characteristics of participants are outlined in Table 1. Controls were younger (56 years vs 66 years for patients, p = 0.03) and had a longer time between vaccine doses compared to patients (93 days vs 77 days, p = 0.02). Patients in cohort 1 had mostly indolent lymphoma under observation (59%) or were vaccinated prior to chemotherapy (41%). Patients in cohort 2 were all treated with rituximab-based chemotherapy, but two patients received anti-CD20/CD3 bispecific T-cell engager (BiTE) antibody at relapse < 6 months of their vaccine and one patient was previously treated with an anti-CD19 chimeric antigen receptor (CAR)-T cell therapy > 4 years prior to her vaccine. Only 28% of cohort 2 patients had active disease at the time of vaccination. There were no differences in the immune profiles of controls pre vaccine, post dose 1 and post dose 2, thus the immune profile pre-vaccine was used for this analysis. There was significant B-cell cytopenia in patients (median 50 B cells/μl and 40 B cells/μl cells in cohorts 1 and 2) compared to controls (median 179 B cells/μl (both $p < 0.05$). Patients in cohort 2 had CD4 T cytopenia compared to controls (median 426.8 vs 924.35 cells/μl, $p < 0.001$) that resolved with the first 3 months of therapy.

Antibody responses were significantly impaired in lymphoma patients compared to controls, with less than half of the lymphoma

Table 1
Patient characteristics.

	Controls	Lymphoma Group 1 Vaccine received pre-chemo or on observation	Group 2 Vaccine post B cell depleting therapy
N (total = 102)	19	22	55
Age	56	69 **(p = 0.01)**	64 **(p = 0.07)**
Sex			
Female	12	8	28
Male	7	14	27
Diagnosis			
DLBCL		2	24
FL		3	26
MCL/MZL/LPL		6	3
CLL		10	1
Other		1	1
Treatment			
Observation only		13 (59%)	0
RCHOP-like		4 (18%)	36
BR		2 (9%)	13
Other		3 (13%)	8
Include anti-CD20		6 (27%)	55
Status of disease a D1			
Active disease		22 (100%)	15 (27%)
In remission		0	40 (73%)
Time since last treatment			
<12 months			22 (40%)
12–24 months			16 (29%)
>24 months			17 (31%)
Baseline immune profile pre-vaccination Mean			
WBC ($x10^3$/ml)	7.29	7.61	**6.00 (p = 0.033)**
Lymph ($x10^3$/ml)	1.91	3.38	**1.19 (p < 0.001)**
Mono ($x10^3$/ml)	0.60	0.53	0.72
CD19 (cells/μl)	199.92	**93.11 (p = 0.016)**	**120.4 (0.032)**
CD4 (cells/μl)	924.35	774.58	**412.5 (p < 0.001)**
CD8 (cells/μl)	439.95	972.70	337.9
NK (cells/μl)	226.7	338.1 (p = 0.052)	221.7
Vaccine type			
BNT162b2 (Pfizer)	19 (100%)	18	47
mRNA-1273 (Moderna)		3	6
Other		1	2
Time between 2 doses (days)	93	77 (p = 0.02)	
		70	73
Time from second dose vaccine to serology assay (mean days)	33	27	
		24	29
Antibody prior to first dose			
Seropositivity	1/15 (7%)	2/15 (13%)	8/51 (16%)
Mean IgG in RLU	3.5	4.7	6.4
Antibody response after dose 1			
Seropositivity	13/15 (87%)	**7/15 (47%) (p = 0.050)**	**14/39 (53%) (p = 0.002)**
Mean IgG in RLU	90,6	**32,9 (p = 0.027)**	65.6
Antibody response after dose 2			
Seropositivity	13/13 (100%)	**12/26 (46%) (p = 0.005)**	**24/49 (49%) (p < 0.001)**
Mean IgG in RLU	303.3	237.45	232.3

Abbreviations: DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; LPL, lymphoplasmacytic lymphoma; CLL, chronic lymphocytic lymphoma; RCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; BR, bendamustine and rituximab; WBC, total white blood cell count; RUL, relative light units
* Only significant p values of ≤ 0.05 are shown.

patients in both cohorts achieving seropositivity compared to 100% of controls. Seven patients had very high antibody levels after their vaccines (> 3x the mean of controls), which could be explained by having prior COVID exposure in 4/7 patients, as previously reported [15–17]. Of note, these "super-responders" had no rituximab exposure within 2 years of their first vaccine dose. Variables associated with vaccine responses in other studies were also observed in our cohorts. Advanced age, active disease and a shorter time between vaccine doses correlated with poor vaccine responses (Supplemental Table 1). Focusing on cohort 2, the timing of exposure to B-cell-depleting therapy was highly predictive of antibody levels. Vaccination within a year of rituximab exposure was associated with a poor humoral response. Only 5% (1/22) of patients achieved sero-positive conversion or increased their pre-existing levels compared to 56% (9/16) and 88% (15/17) of patients who were vaccinated in year 2 and beyond 2 years, respectively (Pearson chi square 28.1, p < 0.0001). All four patients who had rituximab < 1 year and baseline SARS-CoV-2 antibodies failed to increase antibody levels after their two doses of vaccine. This data suggests that additional vaccine "booster" doses within this timeframe may not be effective. Low anti- SARS-CoV-2 antibody levels were also seen in non-treated patients on observation, suggesting that other non-therapy related factors play a role in generating anti-COVID immunity.

Severe B-cell cytopenia (< 50 B cells/μl) was also significantly associated with a poor serological response to the SARS-CoV-2 vaccine. Among those with previous rituximab therapy, 86% (12/14) of patients with > 50 B cells/μl achieved a serologic response compared to 28% (5/18) of those with < 50 B cells/μl. This is a clinically useful threshold that was not observed in any of our controls and was observed in half of the patients. As predicted, there was a significant correlation between antibody levels and the number of circulating B cells as well as the time to the anti-B-cell-therapy (Fig. 1). The patient treated with anti-CD19 CAR-T 4 years prior had no detectable circulating B cells or SARS-CoV-2 antibodies. Importantly, the odds ratios of recent rituximab exposure and B cell cytopenia were both independent factors of response to vaccines even after controlling for age, disease status and time between vaccine doses (Table 2). CD4 and CD8 T cell levels were not correlated with antibody responses, though we can't exclude their contribution given their known role in initiating B cell activation and having direct anti-viral cytotoxic functions.

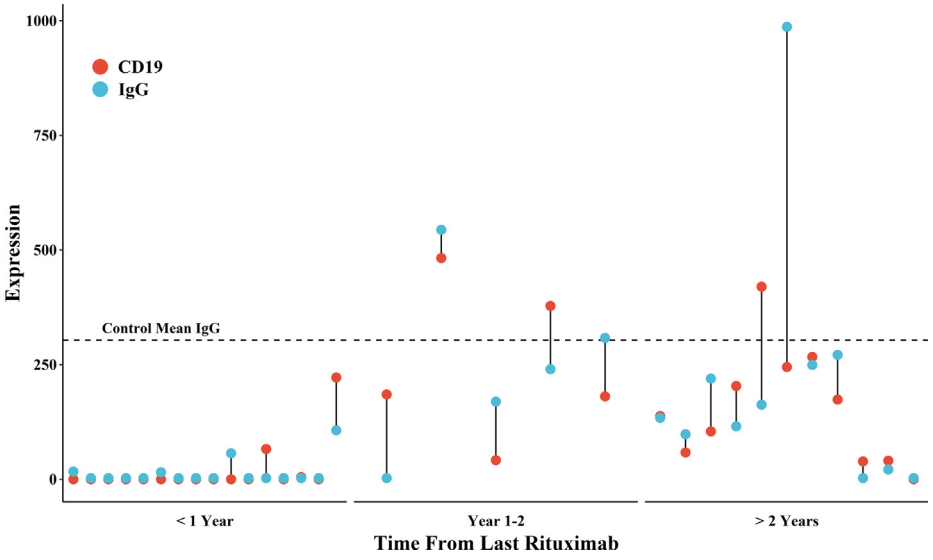

Fig. 1. Blunted anti-SARS-CoV-2 IgG response in non-Hodgkin lymphoma patients with prior rituximab exposure and B cell cytopenia. Dumbbell plot demonstrating relationship between absolute number of B cells/μl (CD19) in the peripheral blood and levels of IgG measured in relative light units, both displayed as expression on the y axis, for each patient. Patient on the x axis are ordered based on time from last Rituximab treatment. Dashed line denotes control group's mean IgG serological expression level (303). * Colors should be used in print.

Table 2
Unadjusted and adjusted associations between timing of past rituximab therapy or CD19 levels and vaccine response.

Group	Group size	Total with a vaccine response	Response rate	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
2 + years post-rituximab	17	15	88%	Ref.	Ref.
<= 1 year post-rituximab	22	1	5%	0.009 (<0.001, 0.094)	0.011 (<0.001, 0.108)
1–2 years post-rituximab	16	9	56%	0.181 (0.015, 1.234)	0.135 (0.003, 1.349)
CD19 levels >= 50	14	12	86%	Ref.	Ref.
CD19 levels < 50	18	5	28%	0.034 (0.002, 0.248)	0.059 (0.002, 0.346)

*Adjusted for age (linear term), current disease status, and time between vaccine doses (linear term) for rituximab timing and age (linear term) and time between vaccine doses (linear term) for low CD19 levels.
Patients with missing variables were not included in this analysis.
**Exact unadjusted p-value for rituximab timing: <0.0001.
***Exact adjusted p-value for rituximab timing: <0.0001.
****Exact unadjusted p-value for low CD19 levels: <0.0001.
*****Exact adjusted p-value for low CD19 levels: 0.0005.

4. Discussion

Overall, these results have broad important clinical implications for patients with lymphoma and possibly for others treated with B-cell-depleting therapy. We identify B-cell cytopenia as an independent risk factor for poor antibody responses to COVID mRNA-based vaccines. In our study, patients were mainly vaccinated with the BNT162b2 (Pfizer) and mRNA-1273 (Moderna) vaccines, yet our results could potentially apply to other vaccines.

In accordance with previous studies, our NHL patients generate poor antibody responses upon COVID vaccine administration, with a more pronounced deficiency detected after exposure to rituximab [18–22]. Our data demonstrates that poor seroconversion rates occur concomitantly with severe B-cell cytopenia, which is most severe within the first year post rituximab. We therefore predict that additional vaccine doses won't be very effective at raising antibody levels within this time frame or before B cell recovery, which occurs in the second- and third-year post treatment. Even in these later timeframes, the average antibody levels were lower than in controls (Fig. 1). Poor antibody production in response to COVID vaccines has been previously observed in B-cell-targeted CAR-T-cell recipients [23,24]. One patient included in our study was vaccinated 4 years after CAR-T cell therapy and demonstrated longstanding severe B-cell depletion with absent antibody production to the vaccine. Again, additional vaccines doses may not be an effective strategy to increase antibody levels in that population at risk of very poor outcomes if infected with SAR-CoV-2 [25]. Baseline B-cell cytopenia can also occur in lymphoma and CLL patients prior to initiating therapy and likely partially explains why untreated patients have been reported to have poor responses to COVID vaccines.

While we focused on antibody levels, other aspects of immunity, including host characteristics (e.g. co-morbidities, medications, germline polymorphisms and more specific immune profiling) were not measured in this study and likely influence anti-COVID-19 immunity. We acknowledge that the specific T-cell response to the vaccine was not measured in this study, but likely plays a role in the development of COVID-19 immunity [26]. Our data confirms the importance of appropriate counselling in these high-risk lymphoma patients that are vaccinated, but not adequately protected against SARS-CoV-2 infection. Social distancing, avoiding high-risk exposures and masking are measures that may protect them and avoid potential outbreaks in non-vaccinated people. Furthermore, the treatment landscape for COVID is continuously evolving and patients with severe B-cell cytopenia should be considered a priority group for anti-viral drugs and monoclonal antibodies.

CRediT authorship contribution statement

Mégane Tanguay: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Marianne Boutin:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Annemarie Laumaea:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Matthew Salaciak:** Data curation. **Alma Mendoza:** Formal analysis. **Chantal Cassis:** Resources. **Lissa Ajjamada:** Resources. **Sarit Assouline:** Resources. **François Patenaude:** Resources. **Michael Webster Clark:** Formal analysis, Data curation. **Andrés Finzi:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Nathalie A. Johnson:** Conceptualization, Methodology, Formal analysis, Resources, Data curation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Nathalie A. Johnson reports financial support was provided by Jewish General Hospital Foundation (Le Week-end pour combattre le cancer event). Dr. Nathalie A. Johnson reports financial support was provided by Quebec Ministry of the Economy and Innovation. Dr. Andres Finzi reports financial support was provided by Fondation du CHUM. Dr. Andres Finzi reports financial support was provided by Canadian Institutes of Health Research grant 352417. Dr. Andres Finzi reports financial support was provided by Canadian Institutes of Health Research grant 465175. Dr. Andres Finzi reports financial support was provided by Canadian foundation for Innovation grant 41027. Dr. Andres Finzi reports financial support was provided by Canada Research Chair on Retroviral Entry no. RCHS0235 950-232424. Annemarie Laumaea reports financial support was provided by MITACS Accélération postdoctoral fellowship. Michael Webster Clark reports was provided by Canadian Institutes of Health Research grant DSE-111845. Dr. Nathalie A. Johnson reports a relationship with Roche that includes: consulting. Dr. Nathalie A. Johnson reports a relationship with Abbvie that includes: consulting. Dr. Nathalie A. Johnson reports a relationship with Merck that includes: consulting. Dr. Nathalie A. Johnson reports a relationship with Beigene that includes: consulting. Dr. Nathalie A. Johnson reports a relationship with BMS that includes: consulting. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.01.040.

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