Humoral serologic response to the BNT162b2 vaccine is abrogated in lymphoma patients within the first 12 months following treatment with anti-CD20 antibodies

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An Original Article

Humoral serologic response to the BNT162b2 vaccine is abrogated in lymphoma patients within the first 12 months following treatment with anti-CD2O antibodies

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Running title: Response to BNT162b2 vaccine in lymphoma patients

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Conflict of Interest Statement

The authors declare no potential conflicts of interest.

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All the procedures involved in this study were in accordance with the ethical standards of the 
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The data that support the findings of this study are available from the corresponding author upon 
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Author Contribution Statement
R.G.: designed and performed research, interpreted the data, wrote the paper, approved the final 
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U.R.: designed research, analyzed the data, wrote the paper, approved the final version of the paper
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Abstract
Patients with lymphoma, especially those treated with anti-CD20 monoclonal antibodies (MoAb), suffer high COVID-19-associated morbidity and mortality. The goal of this study was to assess the ability of lymphoma patients to generate a sufficient humoral response after two injections of BNT162b2 Pfizer vaccine and to identify factors impacting the response.

Antibody titers were measured with the SARS-CoV-2 IgG II Quant (Abbott®) assay in blood samples drawn from lymphoma patients 4±2 weeks after the 2nd vaccine dose. The cutoff for a positive response was set at 50AU/ml.

Positive serological responses were observed in 51% of the 162 patients enrolled in this cross-sectional study. In a multivariate analysis, an interval of <12 months between the last anti-CD20 MoAb dose and the second vaccine dose [OR 31.3 (8.4-116.9), p<0.001] and presence of active lymphoma [OR 4.2 (2.1-8.2), p=0.006] were identified as negative response predictors. The rate of seropositivity increased from 3% in patients vaccinated within 45 days from the last MoAb administration to 80% in patients vaccinated >1 year after this therapy. The latter percentage was equal to that of patients never exposed to MoAbs.

Lymphoma patients, especially those recently treated with anti-CD20 MoAbs, fail to develop sufficient humoral response to BNT162b2 vaccine. While a serologic response is not the only predictor of immunity, its low level could make this population more vulnerable to COVID-19, which implies the urge for a different vaccination schedule for such patients.

Keywords: Lymphoma, anti-CD20 monoclonal antibodies, COVID-19, BNT162b2 vaccine, serological response
Introduction:
The global pandemic of coronavirus disease (COVID-19) has resulted in about 3.85 million deaths world-wide as of June 2021, with the estimated fatality rate among infected patients between 1.5-2.1%. Emerging data demonstrate higher mortality rates among certain high-risk populations with significant co-morbidities, such as organ transplant recipients and cancer patients. Evidence shows that patients with hematological malignancies are the most vulnerable cancer population, with a higher risk for hospitalization and mortality following exposure to the virus. Estimated odds ratios (ORs) for mortality are reported to vary between 2.09 and 12.16, depending on the type of malignancy and whether the disease has been actively treated within the months preceding the infection. Both non-Hodgkin lymphoma (NHL) per se and prior chemotherapy with or without anti-CD20 monoclonal antibodies (MoAbs) have been suggested to contribute to patient reduced survival and prolonged hospitalization following infection with SARS-Cov-2.

The damage the pandemic inflicted on multiple healthcare systems which collapsed as a result of the high incidence of respiratory illness and intensive care demand, mostly due to the severity of COVID-19, led to an accelerated FDA approval of several anti-SARS-Cov-2 vaccines, following the successful completion of phase 3 studies. Among them was the BNT162b2 mRNA vaccine, that demonstrated the efficacy of 95% in disease prevention in the pivotal phase 3 study. While the trial included approximately 40000 volunteers, patients with active cancer were not enrolled into the study. Promptly after the FDA approval, this vaccine was approved by the Israel Ministry of Health (December 2020), and vaccination was initiated at a high scale nation-wide level, with around 70% of the population aged 16 years and above having been fully vaccinated by April 2021. In addition, vaccination of potentially immunocompromised populations was started, including hematological patients, despite the lack of good quality efficacy data for these patients, but in accordance with recommendations by hematological and infectious disease agencies around the world. The rationale for this action has been the emerging data regarding the high infection-related morbidity and mortality among these patients, especially during the periods of peak virus spread, along with the probable low risk of vaccine-induced complications. However, at the physiological level, it is unclear whether patients with lymphoma will be able to generate good quality immune responses to this vaccine, since the response to any vaccine requires interaction between various compartments of the immune system, many of which are compromised by the lymphoproliferative disease itself, but even more so, by the chemo-immunotherapy regimens used for the treatment of these diseases. The
lower prevalence and slower evolution of a humoral response to COVID-19 infection observed in this patient population\textsuperscript{20,21} insinuate that this might be the case with humoral responses to the vaccine as well\textsuperscript{22}.

The objectives of this study have been to evaluate the rates of anti-spike (anti-S) antibody responses to the BNT162b2 vaccine among lymphoma patients and to identify patient- and treatment-related factors impacting the antibody responses.

**Methods:**

This is a non-interventional cross-sectional study conducted at two medical centers in Israel (Rambam Health Care Campus, Haifa, and Rabin Medical Center, Petach Tikva). The study protocol was approved by institutional ethical committees. All patients signed the informed consent form. The inclusion criteria were: age \( \geq 18 \) years, the diagnosis of a lymphoproliferative disease, including Hodgkin and NHL according to the WHO 2016 classification\textsuperscript{23} and no known history of COVID-19 infection. Study participants were divided into the following two groups: 1. Patients who received treatment, including chemotherapy or immunochemotherapy, i.e., MoAbs, tyrosine kinase inhibitors (TKI) or immunomodulatory imide drugs (IMIDs), within 12 months prior to anti-COVID-19 vaccination; 2. Patients with indolent lymphoma who were under "watch-and-wait" management before anti-COVID-19 vaccination.

All patients were vaccinated with two doses of BNT162b2 vaccine, 21 days apart, and were followed at hematology clinics. Blood samples were drawn 4±2 weeks after the second vaccine dose and were evaluated for anti-S SARS-CoV-2 antibodies. The SARS-CoV-2 IgG II Quant (Abbott©) assay was performed as per manufacturer’s instructions for quantitative measurement of IgG antibodies against the spike protein of SARS-CoV-2. The test result was considered positive if the IgG level was \( \geq 50 \) AU/ml. Baseline patient characteristics, collected from institutional electronic medical records, included patient's demographics, comorbidities, lymphoma characteristics, duration, type and the first and last dates of anti-cancer treatment as well as disease activity before vaccination. Lab evaluations such as complete blood count and serum protein electrophoresis before vaccination were also documented. The primary outcome was the rate of seropositivity for anti-spike antibodies.

*Statistical consideration:*
We analyzed patient characteristics using frequencies (percentages) for categorical variables and median (range) for continuous variables. A logistic regression model with the exp(β) was applied as an estimator of an OR and the 95% confidence interval (CI) around it to define the baseline variables that predict negativity of a serologic response to SARS-COV-2 vaccine. We used the likelihood ratio of the receiver operator characteristics (ROC) curves and area under the curve to define the optimal cutoff for continuous variables. Univariate and multivariate logistic regression analyses were performed to evaluate potential predictors of seronegativity. To predict anti-spike IgG levels, we fitted a multiple-variable linear regression model based on: age, gender, lymphoma type, absolute lymphocyte count (ALC) and time from the last anti-CD20 MoAb treatment to vaccination. Stepping method criteria for entry and removal were 0.05 and 0.2, respectively. The Kruskal-Wallis test was used to compare medians of antibody titers. To generate 95% CI around proportions, we used the binomial approximation of the normal distribution. Statistical analyses were performed using SPSS software (version 27, SPSS inc. Chicago, IL) and GraphPad Prism version 6.0 software (GraphPad Software, San Diego, CA).

Results:

Patient characteristics:

A total of 162 lymphoma patients who received two doses of the BNT162b2 vaccine between February and April, 2021 were included in the study. The median age of participants was 65 years (interquartile range, IQR: 52-73), 55% were males, 142 (88%) had NHL, including indolent and aggressive disease and the remaining 20 (12%) had Hodgkin disease. Reported comorbidities included diabetes mellitus (19%), ischemic heart disease (10%), and other malignancies (17%). Most (55%) of the patients received first-line anti-lymphoma therapy, while about 17% were under "watch-and-wait" management. The most common treatment protocols included CHOP (cyclophosphamide, vincristine, adriamycin and prednisone) or bendamustine with or without antiCD20 MoAbs, either rituximab or obinutuzumab. Few patients received other therapies, such as Bruton's tyrosine kinase (BTK) inhibitors, lenalidomide or antiPD1 antibodies. Patient characteristics are presented in table 1.

Serologic response to vaccination:

Eighty-three patients (51%) were seropositive (IgG levels ≥50 AU/ml) and 49% had negative serology. In univariate analysis (UVA), the following variables were found to be significantly associated with a
lack of serological response: age above 80 years (OR=4.3, 95% CI 1.1-1.6), ALC below 1.2 G/L (OR=2.3, 95% CI 1.1-4.4), IgG levels below 630 g/L (OR=15.8, 95% CI 1.9-129.9), active disease (defined as being under treatment for remission induction or by a positive PET/CT result) at vaccination (OR=4.2, 95% CI 2.1-8.2), a time period of less than 12 months between the last anti-CD20 treatment and vaccination (OR=31.3, 95% CI 8.4-116.9), the use of obinutuzumab vs. rituximab (OR>4.54), aggressive NHL vs. Hodgkin lymphoma (OR=15.4, 95% CI 3.1-76.6) (table 2). The lack of seroconversion was most frequent among patients suffering from aggressive lymphoma (63%) followed by those with indolent lymphoma (54%) and was lowest in Hodgkin disease patients (10%). With the negative response rate in the latter group used as a reference, the OR of this variable for patients with indolent disease was 1.5 (not statistically significant), while it was as high as 15 for patients with aggressive lymphoma (statistically significant, p<0.01). The rates of negative serologic responses in patients receiving CHOP relative to those treated with bendamustine, with or without anti-CD20 MoAbs, equated to 63% and 84%, respectively (p=0.056). In multivariate analysis (MVA), two variables remained significant: a time period of less than 12 months between the last anti-CD20 treatment and the second vaccine dose, and presence of active lymphoma (table 3).

The effect of anti-CD20 treatment on vaccination results:
Among 98 patients who received anti-CD20 MoAbs, as the time period between the last dose of this treatment and vaccination was getting longer, the likelihood of seropositivity was increasing. Patients vaccinated at least 12 months after anti-CD20 MoAb administration demonstrated an 80% seropositivity, while this rate was only 3% in patients vaccinated within 45 days from anti-CD20 therapy (table 4). It is noteworthy that the seropositivity rate in the former group was similar to that observed in lymphoma patients who had not received this treatment (i.e., were treated with chemotherapy only or were under “watch-and-wait”).

None of the 28 patients treated with obinutuzumab developed a serologic response in comparison to 62% seronegativity demonstrated in patients treated with rituximab within the same time frame.

Levels of SARS-CoV-2 IgG:
In a linear regression model, a shorter time period between anti-CD20 therapy and vaccination predicted lower levels of anti-spike IgG and explained the 18% variance in antibody titers, while all other evaluable variables, such as age, gender, lymphoma type and ALC had no predictive power. A
correlation was revealed between the levels of circulating anti-S IgG antibodies and the time between the last anti-CD20 treatment and vaccination. Significant difference was found between the patients never exposed to anti-CD20 therapy (median of 1161 AU/ml, range 0-15,567) or those receiving these agents more than 12 months prior to vaccination (median of 661 AU/ml, range 0-15,220), relative to patients treated with these drugs within 12 months pre-vaccination: 0-45 days (median of 0 AU/ml, range 0-225); 46-120 days (median of 0.7 AU/ml, range 0-1575); 121-180 days (median of 0.5 AU/ml, range 0-234); 181-365 days (median of 0 AU/ml, range 0-373 AU/ml) (figure 1). In a model taking into account age, gender, ALC, activity of disease and the time from the last anti-CD20 treatment to vaccination, only the latter variable was statistically significant and predicted the titers of IgG antibodies.

Discussion
The current study, evaluating the antibody-mediated response in lymphoma patients who received two doses of BNT162b2 vaccine, showed that only 51% of these individuals developed seropositivity. These findings were in line with results of the studies assessing the efficacy of other anti-viral vaccines in the lymphoma setting. Indeed, studies assessing the efficacy of the influenza vaccine demonstrated insufficient humoral immunity and higher rates of overt clinical disease in patients treated with chemotherapy, with only 10% of patients developing a sufficient antibody titer to at least one of the influenza A antigens, as compared to 45% in the control group. Moreover, lymphoma patients vaccinated within a randomized trial of the recombinant zoster vaccine administered during or after a maximum of 6 months post anti-lymphoma therapy, also showed low levels of seropositivity, varying between 20 and 50.

Currently available data point to the vital importance of COVID-19 prevention in cancer patients in general and in those with hematological malignancies in particular. Evidence-based prophylactic approaches such as vaccination, become the top priority measures significantly contributing to infection control. Yet, the pivotal study, demonstrating 95%-efficacy of the BNT162b2 vaccine in COVID-19 prevention, did not include patients with lymphoma. In a single-center Israeli study, examining antibody-mediated response rates with the Elecsys anti-SARS-CoV-2 S assay in patients with chronic lymphocytic leukemia (CLL), positive humoral responses were observed in 52% of patients, compared to 100% in an age- and sex-matched control cohort. Notably, the assay used in the latter study differed from the one employed in our analysis.
In the current study, treatment with anti-CD20 MoAbs as well as an active disease at time of vaccination emerged as significant predictors of a negative serologic response to BNT162b2. Likewise, the impact of anti-CD20 therapy was evident in the observed titers of anti-spike IgG antibodies, which were increasing as the time period between the last anti-CD20 administration and vaccination was getting longer. With a cutoff of 12 months, our findings demonstrated significant difference in the antibody titers between patients vaccinated less than or more than 12 months after anti-CD20 therapy, while the impact of exposure to this therapy became negligible after this time point. Actually, the titers became similar to those found in naïve (untreated) lymphoma patients. A plausible explanation could be that rituximab and other anti-CD20 MoAbs commonly used for the treatment of B-cell lymphoma lead to prolonged B-cell depletion and subsequent hypogammaglobulinemia. Consistent with our results, several studies reported the data suggesting lower likelihood of developing a serologic response following anti-CD20 treatment in immunocompromised patients. For instance, patients with rheumatoid arthritis (RA) were reported to demonstrate lower titers of anti-influenza antibodies upon treatment with rituximab compared to RA patients not receiving such therapy\cite{27}. In another study, none of the 67 lymphoma patients vaccinated against influenza A (H1N1) within six months of receiving rituximab-containing regimens, developed antibody-mediated response compared to 82% in the control group\cite{28}. Finally, in the recently published study including a small cohort of anti-CD20 treated CLL patients, none of those treated with rituximab within a year prior to vaccination developed anti-spike antibodies against COVID-19\cite{26}.

Remarkably, in our study, patients receiving rituximab demonstrated attenuated serologic response to the vaccine, whereas patients treated with obinutuzumab failed to generate any anti-spike antibodies during the study period. This could be attributed to differences in pharmacodynamic properties between these two agents, as observed in in vitro studies, showing enhanced direct cell death and antibody-dependent cellular cytotoxicity for obinutuzumab compared to rituximab\cite{29}.

In the present study, active disease emerged as an additional factor negatively affecting the humoral response to vaccine. While this could reflect the time-wise proximity to anti-CD20 treatment in these patients, it could also be associated with the effect of chemotherapeutic agents and corticosteroids commonly used during induction therapy in this clinical setting. Since humoral immunity requires functional T-cells for the development of memory B-cells and plasma cells\cite{30,31}, agents such as bendamustine and high-dose steroids, applied in lymphoma, might impede the serologic response.
This study has several limitations, the lack of a control group being one of them. Yet, Grupper et al., utilizing the same assay as in our study, showed that all healthy individuals included in the control group developed serologic response to the BNT162b2 vaccine\textsuperscript{32}. In addition, nucleocapsid antibody assessment was not part of the current analysis, since only patients with no documented febrile or respiratory events within months prior to vaccination were included in the study. Hence, the generation of anti-spike antibodies in response to subclinical COVID-19, while being possible, was unlikely in this patient population.

A potential relationship between a weak serologic response and the true protection from clinical COVID-19 disease will only become evident with longer follow-up. However, these data might never mature, as presently the pandemic has significantly subsided in Israel. Moreover, there are several newly validated assays capable of examining cellular immune responses to the vaccine, which will be implicated in future studies aimed at better understanding the true extent of protective immunity achieved with this vaccine.

In conclusion, the current study has shown that this heterogeneous group of lymphoma patients has developed an attenuated serologic response to the BNT621b2 vaccine. Patients recently treated with anti-CD20 MoAbs (time since the last anti-CD20 treatment <12 months) are less likely to develop serologic response to this vaccine.
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Table 1. Lymphoma Patient Characteristics

| Characteristics                                                                 | N (%)            |
|---------------------------------------------------------------------------------|------------------|
| Age (years), median (interquartile range, IQR)                                  | 65 (52-73)       |
| Males                                                                           | 89 (55%)         |
| **Comorbidities**                                                               |                  |
| Diabetes mellitus                                                               | 30 (19%)         |
| Ischemic heart disease                                                          | 17 (11%)         |
| Hypertension                                                                    | 54 (34%)         |
| Chronic renal failure                                                           | 12 (7.5%)        |
| Chronic obstructive pulmonary disease                                           | 7 (4%)           |
| Other malignancy                                                                 | 27 (17%)         |
| **Type of lymphoma**                                                            |                  |
| DLBCL                                                                           | 32               |
| FL                                                                              | 64               |
| MZL                                                                             | 24               |
| HL                                                                              | 20               |
| PTCL                                                                            | 8                |
| Other lymphomas                                                                 | 14               |
| **Line of treatment**                                                           |                  |
| Watch & wait                                                                     | 30               |
| 1<sup>st</sup> line treatment                                                   | 89               |
| 2<sup>nd</sup> line treatment                                                   | 20               |
| 3<sup>rd</sup> line treatment and above                                          | 23               |
| **Type of Treatment**                                                           |                  |
| **Non-chemotherapy**                                                            |                  |
| Anti-CD20 monoclonal antibodies                                                 |                  |
| Rituximab                                                                       | 68               |
| Obinutuzumab                                                                    | 30               |
| Anti-PD1 monoclonal antibodies                                                  | 5 (3.5%)         |
| Treatment                      | Count (%) |
|--------------------------------|-----------|
| BTK inhibitors                 | 4 (3%)    |
| Lenalidomide                   | 6 (4%)    |
| **Chemotherapy**               |           |
| CHOP                           | 36 (25%)  |
| Bendamustine                   | 32 (22%)  |
| ABVD/BEACOPP                   | 10 (7%)   |
| COP                            | 9 (6%)    |
| **Other treatments**           | 19 (13%)  |

Abbreviations: DLBCL=diffuse large cell lymphoma; FL=follicular lymphoma; MZL=marginal zone lymphoma; HL=Hodgkin lymphoma; PTCL=peripheral T cell lymphoma; Other lymphomas: Waldenstrom macroglobulinemia, mantle cell lymphoma, primary mediastinal B-cell lymphoma

CHOP=cyclophosphamide+ adriamycin+ vincristine+ prednisone; ABVD=adriamycin+ bleomycin+ vinblastine+ dacarbazine; BEACOPP=bleomycin+ adriamycin + vinblastine + procarbazine+ prednisone; COP=cyclophosphamide+ vincristine+ prednisone; BTK=Bruton kinase inhibitors; Other treatments: platinum-based chemotherapy, gemcitabine, brentuximab vedotin, polatuzumab vedotin, pralatrexate, romidepsin, phosphoinositide 3-kinase (PI3K) inhibitors
Table 2. Univariate Analysis of Factors Associated with a Lack of Serologic Response

| Variable                                      | Reference                  | Odds ratio (95% CI) | P-value |
|-----------------------------------------------|----------------------------|---------------------|---------|
| Age ≥80                                       | Age < 80                   | 4.3 (1.1-1.6)       | 0.031   |
| Gender - Female                               | Male                       | 0.8 (0.42-1.5)      | 0.9     |
| ALC ≤1.2 G/L                                  | ALC >1.2 G/L               | 2.3 (1.1-4.4)       | 0.02    |
| IgG ≤630 g/L                                  | IgG >630 g/L               | 15.8 (1.9-129.9)    | 0.001   |
| Active disease                                | Disease in remission       | 4.2 (2.1-8.2)       | <0.001  |
| Time between the last anti-CD20 treatment and vaccination <12 months | >12 months or non-exposure to anti-CD20 | 31.3 (8.4-116.9) | <0.001 |
| Type of anti-CD20 MoAb – obinutuzumab         | Rituximab                 | >4.54 (NA)          | 0.04    |
| Type of lymphoma – indolent lymphoma          | Hodgkin lymphoma          | 1.46 (0.67-3.1)     | 0.34    |
| Aggressive lymphoma                           | Hodgkin lymphoma          | 15.4 (3.1-76.6)     | <0.01   |
| Time between the last chemotherapy administration and vaccination <19 days | >19 days                  | 1.75 (0.32-9.4)     | 0.515   |

Abbreviations: ALC = absolute lymphocyte count; NA = not applicable; CI = confidence interval; aggressive lymphoma included DLBCL, PMBCL, PTCL; Indolent lymphoma included follicular lymphoma, marginal zone lymphoma, mantle cell lymphoma, Waldenstrom macroglobulinemia
Table 3. Multivariate Analysis of Factors Associated with Lack of Serologic Response

| Variable | P-value | Odds Ratio (95% CI) |
|----------|---------|---------------------|
| Age ≥80  | 0.5     | 2.8 (0.13-61.9)     |
| ALC ≤1.2 | 0.4     | 2.1 (0.4-10.4)      |
| Active disease | 0.006 | 11.8 (2-67.6) |
| Time between the last anti-CD20 treatment and vaccination <12 months | <0.001 | 93 (12.3-704.4) |
| Type of lymphoma | 0.8 | 1.2 (0.25-6.1) |

Abbreviations: ALC=absolute lymphocyte count; CI=confidence interval

- IgG variable was removed due to missing data
Table 4. Serologic Response in Patients Treated with Anti-CD20 MoAbs Compared to Those Who Did Not Receive This Treatment

| Time from anti-CD20 therapy to vaccination (days) | N   | No. of patients with positive serology | % of patients with positive serology (CI) | % of patients with negative serology (CI) |
|--------------------------------------------------|-----|--------------------------------------|------------------------------------------|------------------------------------------|
| 0-45                                             | 34  | 1                                    | 3 (1-15)                                 | 97 (85-99)                               |
| 46-120                                           | 21  | 5                                    | 24 (8-47)                                | 76 (53-92)                               |
| 121-180                                          | 4   | 1                                    | 25 (1-81)                                | 75 (19-99)                               |
| 181-365                                          | 7   | 1                                    | 14 (1-58)                                | 86 (42-99)                               |
| ≥366                                             | 21  | 17                                   | 81 (58-95)                               | 19 (5-42)                                |
| No anti-CD20 therapy                             | 56  | 45                                   | 80 (68-90)                               | 20 (10-32)                               |

Abbreviations: No.=Number; CI=confidence interval
Figure Legend:

Figure 1. Correlation between the levels of circulating anti-S IgG antibodies and the time from the last anti-CD20 treatment to vaccination

Dots represent antibody titer values; red lines represent medians. ***=P<0.0001; **=P<0.001; *=P<0.01; NS=non-significant
Anti-Spike IgG (AU/ml)

Time since last anti-CD20 Treatment to vaccination