blood advances

TO THE EDITOR:

Activity of mRNA COVID-19 vaccines in patients with lymphoid malignancies

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Patients with lymphoid malignancies are at increased risk of developing COVID-19 and are at high risk of poor outcomes.[1-5] There is a need for protective strategies in this vulnerable population. Although there have been 2 prior phase 3 trials investigating nanoparticle-encapsulated messenger RNA (mRNA)-based vaccines, BNT162b2 (Pfizer, Inc) and mRNA-1273 (ModernaTX, Inc), that encode the prefusion stabilized full-length spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), immunocompromised patients were excluded.[6,7] In the research by Perry et al, humoral responses following administration of BNT162b2 were evaluated in patients with non-Hodgkin lymphoma. Strikingly, patients who had received anti-CD20 antibody therapy within 6 months of vaccination were unlikely to mount a humoral response, a finding that has similarly been described in patients with chronic lymphocytic leukemia (CLL).[8,9] Perry et al also showed that patients with treatment-naive disease were more likely to develop a humoral response, although with lower rates and titer levels as compared with healthy controls. We similarly performed a prospective study to evaluate serologic response following vaccination with BNT162b2 or mRNA-1273 in a cohort of patients with key lymphoid malignancies (including CLL) in various phases of treatment. Our data support the findings by Perry et al. In addition, we report quantitative antibody titers at 3 time points pre- and postvaccination and describe the humoral response following a range of treatment strategies.

Patients were eligible for enrollment if they had a diagnosis of a lymphoid malignancy and were planning to receive either the BNT162b2 or mRNA-1273 vaccine. Patients who had received chimeric antigen receptor therapy (CAR-T) or autologous stem cell transplant were vaccinated at least 3 months after cellular therapy, and all other patients were vaccinated per patient and provider preference. Healthy volunteers were included as controls who were health care workers >18 years old at Brigham and Women's Hospital and had no prior history of COVID-19 infection. This study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board and the Brigham and Women's Hospital Institutional Review Board, and all participants provided written informed consent. Blood was drawn at baseline prior to the first vaccine dose, at the time of the second vaccine dose, and ~28 days later. Using the multiplexed, single-molecule array assay, quantitative detection of immunoglobulin G (IgG) antibodies (in a unit of normalized average enzymes per bead) against the S protein and nucleocapsid (N) proteins was assessed in serological samples.[10,11] Antibody values for healthy adults prepandemic (January to December 2019) sera were used to determine an internal threshold of positivity for anti-S IgG. The Mann-Whitney *U* test was used to compare the anti-S IgG magnitudes for the healthy cohort and lymphoid malignancy cohort. Statistical significance was considered at a level $\alpha = 0.05$ using GraphPad Prism software (Version 9.1.1; La Jolla, CA).

Twenty-three patients have completed the 2-dose vaccine series, and 21 of these patients have had follow-up at all 3 time points. Baseline characteristics are shown in Table 1. The median age at the time of vaccination was 69 years (range, 30-82 years). Sixteen (70%) patients received BNT162b2, and the remainder received mRNA-1273. Fourteen (61%) had CLL, and 9 (39%) had lymphoma, including 3 (13%) with diffuse large B-cell lymphoma (DLBCL), 3 (13%) with mantle cell lymphoma (MCL), and 1 (4%) each with

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Table 1. Patient demographics

	Lymphoma/CLL cohort N = 23 (%)	Healthy cohort N = 23 (%)
Age, y		
Median (range)	69 (30-82)	24 (22-56)
Sex		
Male	10 (43)	10 (43)
Female	13 (57)	13 (57)
Vaccine type		
mRNA-1273	7 (30)	14 (61)
BNT162b2	16 (70)	9 (39)
Disease type		
CLL	14 (61)	
DLBCL	3 (13)	
MCL	3 (13)	
Follicular lymphoma	1 (4)	
MZL	1 (4)	
HL	1 (4)	
No. of prior lines of therapy		
Median (range)	1 (0 - 3)	
Treatment status		
Treatment naive	6 (26)	
Prior treatment	6 (26)	
Current treatment	11 (48)	
Prior CD20 Ab therapy		
Yes	15 (65)	
No	8 (35)	
CD20 Ab within 12 mo		
Yes		
Within 12 mo	6 (26)	
Beyond 12 mo	9 (39)	
No	8 (35)	

follicular lymphoma, marginal zone lymphoma (MZL), and Hodgkin lymphoma (HL). Seventeen (74%) had received any prior anti–lymphoma treatment, with a median of 1 prior therapy (range, 1-3); 15 (65%) had received prior anti-CD20 antibody therapy, 6 (26%) within the past 12 months, including 3 patients with MCL on maintenance therapy; 3 patients had received prior CAR-T within 12 months; and 1 patient had received an autologous stem cell transplant within 6 months.

No patients had detectable anti-N IgG (Figure 1A) at baseline, implying no serologic evidence of prior natural infection with SARS-CoV-2. Baseline anti-S IgG titers were similar among patients in our cohort and healthy volunteers (n = 23) ($P = .66$) (Figure 1B). As compared with the healthy controls, the magnitude of anti-S IgG titers was significantly lower at the time of dose 2 ($P = .0001$) and ~28 days postvaccine ($P = .001$) among patients with any lymphoid malignancy (Figure 1B).

We hypothesized that response could be differentiated by prior therapy. None of the patients (n = 6) who had received anti-CD20 antibody therapy within the past 12 months had an antibody response after the vaccine series (Figure 1C). Of note, 2 patients who received anti-CD19–directed CAR-T within 12 months developed anti-S IgG titers above our predetermined threshold; both of those patients had also received anti-CD20 antibody therapy >12 months from the time of vaccination. The other patient who had received CAR-T and anti-CD20 antibody therapy within the past 12 months did not develop anti-S IgG titers. One patient who had completed therapy with brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine for HL 2 months prior developed IgG S antibodies. All patients who were treatment-naive, including 5 patients with CLL and 1 patient with MZL, developed anti-S IgG titers by day 28 postvaccine series (Figure 1D). Interestingly, as compared with the healthy cohort, there was a significant difference at the time of dose 2, with the treatment-naive cohort having a lower magnitude of response ($P = .017$), suggesting that at least 2 doses are needed to achieve a humoral response. Among CLL patients on Bruton tyrosine kinase inhibitors (n = 6), 3 had a serologic response. There was 1 CLL patient on venetoclax, without prior CD20 antibody within the last 12 months, who did not develop anti-S IgG antibodies.

One patient with DLBCL who was 3 months post–CAR-T developed COVID-19, with persistent fever requiring hospitalization, 1 week after the first dose of vaccination and subsequently withdrew from the study and was not included. The patient has since made a full recovery. No other patients in our cohort developed COVID-19 following vaccination.

Our data are limited by the small sample size and the heterogeneous nature of our cohort. Healthy controls were also generally younger than those patients with a lymphoid malignancy. The threshold titer that confers protection against the SARS-CoV-2 has also yet to be established, and clinical efficacy cannot be determined. Furthermore, the role of T-cell immunity in the protection against COVID-19 remains unknown. However, as it has been shown by Perry et al, our study demonstrates impairment in humoral response in select patients with lymphoid malignancies, most notably those who have received recent anti-CD20 antibody therapy. Our data and those presented by Perry et al have implications for the use and timing of vaccination (and potentially booster immunizations) in this patient population. Importantly, not only is the timing of vaccination from CD20 therapy important but also the underlying disease state as demonstrated by Figure 3B from Perry et al, suggesting that nuanced recommendations for patients by both disease state and therapies are needed. By following humoral responses after both the first and the second dose, we also demonstrate that 2 doses are necessary even for treatment-naive patients to achieve the same humoral response as compared with healthy controls. In sum, patients with lymphoid malignancies should not be assumed to be protected from vaccination and should remain maximally prudent to avoid infection. Conversely, our findings suggest that humoral response can be seen following cytotoxic chemotherapy, in patients receiving anti-CD19–directed cellular therapy, and among patients who have not received prior therapy, even with CLL.

In conclusion, our study provides further data to support that patients with lymphoid malignancies, and most dramatically those with recent anti-CD20 monoclonal antibody treatment, have reduced humoral responses to mRNA COVID-19 vaccines as compared with healthy controls. Larger studies are needed to further assess humoral response to vaccination within specific malignancy and treatment subgroups, clinical efficacy, and durability of protection in this population.

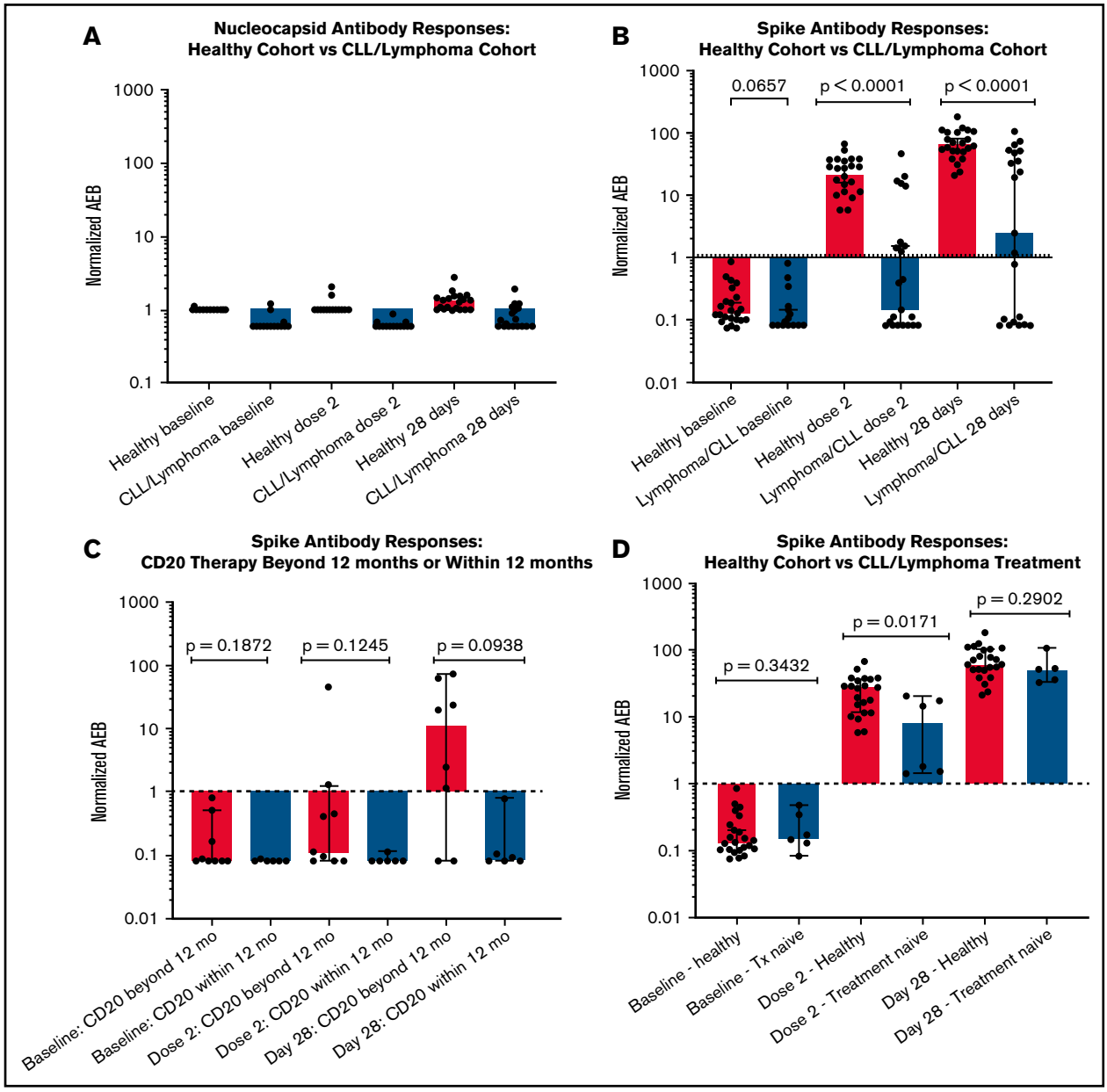

Figure 1. COVID-19 antibody responses in patients with CLL/lymphoma and healthy controls. (A) The IgG N antibody responses at baseline, time of dose 2, and 28 days after vaccination for the healthy cohort (red) and CLL/lymphoma cohort (blue). Low magnitudes at all time points demonstrate no prior history of natural infection or infection with COVID-19 during the study. (B) IgG S antibody titers in healthy cohort (red) (n = 23), as compared with the CLL/lymphoma cohort (blue) (n = 23). (C) The magnitude of IgG S antibody for patients who received CD20 therapy in the last 12 months (blue) (n = 6), as compared with those who received CD20 beyond 12 months (red) (n = 9). (D) IgG S antibody responses for the healthy cohort (red) (n = 23), as compared with patients with CLL/lymphoma who were treatment-naive (blue) (n = 5). The dotted horizontal line in panels B-D at 1.07 is an internally validated threshold that marks a positive or negative antibody response. The black error bars denote median with a 95% confidence interval AEB, average enzymes per bead.

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Authorship

Contribution: J.L.C., A.C.S., L.R.B., and N. Issa designed research, performed research, analyzed data, and wrote the paper; and C.-A.C., C.E.R., R.Z., M.D., P.B., M.M., N. Izaguirre, B.B., J.K., T.G., Y.S., D.R.W., M.S.D., J.R.B., and P.A. performed research, analyzed the data, and provided critical review of the manuscript.

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