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LETTER

Chronic Lymphocytic Leukemia

COVID-19 vaccine efficacy in patients with chronic lymphocytic leukemia

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To the Editor:

While randomized controlled trials demonstrated 94–95% efficacy of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike messenger RNA (mRNA) vaccines [1, 2], efficacy in immunocompromised patients has not been established. We aimed to understand serologic response to mRNA vaccination in patients with chronic lymphocytic leukemia (CLL), a population of interest given the immunocompromised state associated with this malignancy and disease-directed therapies, as well as incomplete immune responses following other vaccinations [3–10].

Methods

We examined 44 consecutive patients with CLL who received two doses of mRNA vaccine (BNT162b2 or mRNA-1273) between 1/2/21 and 3/12/21 and were tested for anti-SARS-CoV-2 S1/S2 antibodies. Serology testing was performed in routine clinical practice with the Liaison® SARS-CoV-2 S1/S2 IgG assay (DiaSorin; Saluggia, Italy) with ≥15 AU/mL constituting a positive result. Baseline demographics, treatment history and laboratory parameters prior to first dose of COVID-19 vaccine were collected. Logistic regression was used to examine relationship between baseline characteristics and positive serology testing; all other statistics are descriptive. Analyses were performed using Stata 16 [11]. This retrospective study was institutional review board approved.

Results

Median age at time of vaccination was 71 years (range 37–89) and 23/44 (52%) were male. Twenty-six patients (59%) received at least one prior CLL-directed therapy. Eighteen (41%) were actively treated at the time of vaccination (14 (32%) with Bruton Tyrosine Kinase (BTK) inhibitor, 7 (16%) with venetoclax, 14 (32%) with anti-CD20 monoclonal antibody (mAb) within 1 year). CLL-directed therapy was not held or modified at the time of vaccination. BNT162b2 was administered to 25/44 (57%) and mRNA-1273 to 19/44 (43%). Serology was tested a median of 21 days (range 14–48) following second vaccine dose. Twenty-three patients in this cohort of 44 (52%) tested positive for anti-SARS-CoV-2 S1/S2 antibodies.

We found that treatment naïve patients (OR 56.7, 95% CI 6.2–518) and those under age 70 years (OR 12.0, 95% CI 2.9–50.5) were more likely to produce anti-SARS-CoV-2 S1/S2 antibodies (Table 1). Production of antibodies was significantly less common in patients receiving BTK inhibitors at time of vaccination or in patients who received anti-CD20 mAb within 12 months. Anti-SARS-CoV-2 S1/S2 antibodies were detected in 17/18 (94%) of never treated patients vs. 6/26 (23%) of treated patients. Additionally, 3/14 (21%) of those receiving BTK inhibitors, 2/14 (14%) of those who had received anti-CD20 mAb within 12 months, and 0/7 (0%) of those receiving venetoclax with anti-CD20 mAb within 12 months tested positive for anti-SARS-CoV-2 S1/S2 antibodies.

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Table 1 Baseline characteristics and association between baseline characteristics and positive anti-SARS-CoV-2 S1/S2 IgG result at least 14 days following 2nd dose of BNT162b2 or mRNA-1273 vaccine.

Characteristic	Proportion, unless otherwise specified	
Baseline characteristics		
Age at vaccination, median (range)	71 years (37–89)	
Male	23/44 (52%)	
CLL treatment history		
Never treated	18/44 (41%)	
Prior CLL-directed therapy	26/44 (59%)	
Current CLL-directed therapy	18/44 (41%)	
BTK inhibitor	14/44 (32%)	
Venetoclax	7/44 (16%)	
Anti-CD20 monoclonal antibody within 1 year	14/44 (32%)	
Lab parameters prior to vaccination		
IgG, median (range)	776 mg/dL (294–1483)	
ALC, median (range)	5.6 cells/μL (0.4–151.2)	
ANC, median (range)	3.4 cells/μL (0.9–8.3)	
Anti-SARS-CoV-2 S1/S2 antibody		
Positive	23/44 (52%)	
Negative	21/44 (48%)	
Predictors of positive antibody response	Odds ratio	95% confidence interval, p value
Age <70 vs. ≥ 70	12.0	2.9–50.5, $p = 0.001$
Never treated vs. prior-CLL directed therapy	56.7	6.2–518, $p < 0.001$
Active observation vs. current therapy	16.7	3.6–77.7, $p < 0.001$
BTKi at time of vaccination	0.14	0.031–0.60, $p = 0.009$
Anti-CD20 monoclonal antibody within 1 year	0.071	0.013–0.39, $p = 0.002$

Discussion

Given that immunocompromised patients were excluded from clinical trials testing SARS-CoV-2 spike mRNA vaccines [1, 2], understanding efficacy in this population is crucial. Patients with hematologic malignancy [12–20], particularly those with CLL [21–23], are of interest given prior reports suggesting poor outcomes following diagnosis of COVID-19. Furthermore, patients with CLL experience suboptimal vaccine efficacy, especially those receiving CLL-directed therapy [3–10]. For example, a recent report by Pleyer, *et al*. demonstrated a 4% response rate to the recombinant hepatitis B vaccine in patients treated with BTK inhibitors versus a 28% response rate in treatment-naïve patients. In that same report, 42% of BTK inhibitor treated patients and 59% of treatment-naïve patients mounted a response to the recombinant herpes zoster vaccine. Collectively, these data suggest that BTK inhibitors profoundly impact response to vaccines for pathogens in which pre-existing immunity is not present.

In this study, we found that only half of vaccinated patients with CLL develop detectable anti-SARS-CoV-2 S1/S2 antibodies. Furthermore, we found a significant difference between rates of detectable anti-SARS-CoV-2 S1/S2 antibodies between treatment-naïve patients (17/18, 94%) and those who had received CLL directed therapy (6/26, 23%). These striking findings suggest that vaccination in patients with CLL may not confer the efficacy that we expect in the general population, particularly in patients receiving CLL-directed therapy. These findings have further implications for a broader population as BTK inhibitors, venetoclax, and anti-CD20 mAb are commonly used for other diseases. These data support conducting prospective clinical studies of vaccine efficacy in patients with CLL and other immunocompromising conditions. While we await establishment of herd immunity, specific guidance for patients with CLL are warranted as the current Center for Disease Control and Prevention recommendations regarding relaxed personal protective equipment use when around other vaccinated people may not apply to this population [24]. Without consistent antibody responses, patients with CLL should continue to exercise extreme caution following vaccination until further data on clinical efficacy are available.

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Compliance with ethical standards

Conflict of interest LER has served as a consultant for AbbVie, AstraZeneca, Pharmacyclics, Vaniam group, and Verastem, holds minority ownership interest in Abbott Laboratories, and has received research funding (paid to the institution) from Pfizer and Aptose Biosciences outside of the submitted work. DAK receives research support on COVID-19 from Pfizer. MCT has received honoraria from MJH Life Sciences, VJ Heme Onc, Curio Science. KB has consulted for AbbVie and Janssen. ARM has served as a consultant and received research funding from Curio Science, TG Therapeutics, Celgene, Janssen; AbbVie, Adaptive, Loxo, Nurix, Genmab, Genentech, Pfizer, Octopharma, Pharmacyclics, AstraZeneca, Sunesis, DTRM, Gilead, and Johnson & Johnson. He served as DSMB member at TG Therapeutics. All other authors declare no competing interest.

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