



Chronic lymphocytic leukemia

Anti-SARS-CoV-2 antibody response in patients with chronic lymphocytic leukemia

Lindsey E. Roeker¹ · David A. Knorr¹ · Melissa S. Pessin² · Lakshmi V. Ramanathan² · Meghan C. Thompson¹ · Lori A. Leslie³ · Andrew D. Zelenetz⁴ · Anthony R. Mato¹

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To the Editor:

Characterizing antibody (Ab)-mediated immune response to SARS-CoV-2 is fundamental to understanding COVID-19 epidemiology, reinfection potential, and vaccine development, particularly in immunocompromised patients. The first report of SARS-CoV-2 directed Abs demonstrated that 100% of 34 hospitalized patients developed virus-specific IgM and IgG by 3 weeks following symptom onset with rising IgG titers during weeks 4 through 7 (end of study period) [1]. A subsequent series of 285 patients with COVID-19 demonstrated that 100% developed virus-specific IgG 17–19 days after symptom onset [2]. While studies with short follow-up have demonstrated that lower proportions of patients develop anti-SARS-CoV-2 IgG [3, 4], studies with follow-up extending into the period of expected peak IgG levels have confirmed high rates of anti-SARS-CoV-2 IgG development (98–100%; peak ~day 30) [5–7]. Persistence of Ab responses requires further study. Given genomic similarity between SARS-CoV-2 and SARS-CoV, dynamics of SARS-CoV Ab response may be relevant; IgG peaked between months 2 and 4 and declined thereafter, though antigen-specific IgG was persistently detected up to 24 months [8, 9]. Data of this nature are not yet available for SARS-CoV-2. Much remains unknown

about neutralizing capacity of Ab and clinical relevance of Ab responses for immune status.

Notably, most data on serologic response to SARS-CoV-2 have come from immunocompetent adults. In contrast, a small series of ten cancer patients (mixed histology) showed a seroconversion rate of 30% (3/10) at 15 days following documented positive RT-PCR, though data on seroconversion at later timepoints were not available [10]. Notably, of the seven seronegative patients with PCR-based COVID-19 diagnosis, six had received cytotoxic therapy or major surgery in the preceding 4 weeks [10].

Ab responses in patients with chronic lymphocytic leukemia (CLL) are of particular interest given cellular and humoral immunodeficiencies resulting from the disease and CLL-directed therapies [11]. While robust epidemiologic data regarding risk of SARS-CoV-2 infection are not yet available, case fatality rates in series of CLL patients with symptomatic COVID-19 are 30–33% [12, 13]. Furthermore, studies of seroconversion in response to vaccines in patients with CLL have demonstrated suboptimal responses [14]. Thus, patients with CLL are at risk for severe COVID-19 given their underlying immunodeficiency, often advanced age, and potentially suboptimal serologic response to infection or related vaccine.

To characterize immune response to COVID-19 in patients with CLL, we identified all patients who receive care for an antecedent diagnosis of CLL at Memorial Sloan Kettering Cancer Center diagnosed with COVID-19 via PCR for SARS-CoV-2 RNA from a nasopharyngeal swab between March 18 and April 29, 2020. We retrospectively examined patients subsequently tested for anti-SARS-CoV-2 IgG Ab utilizing the Abbott Architect SARS-CoV-2 IgG assay (Abbott Park, IL, USA) to detect serum IgG Abs directed against the nucleocapsid protein of SARS-CoV-2 in routine clinical practice. We examined baseline characteristics, CLL-directed therapy history, and details regarding COVID-19 testing and clinical course. Patients were defined as having severe COVID-19 if they required supplemental oxygen and/

✉ Lindsey E. Roeker
roekerl@mskcc.org

¹ Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

² Department of Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

³ John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ, USA

⁴ Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

or ICU admission. Immunoglobulin levels were examined within 3 months of COVID-19 diagnosis; hypogammaglobulinemia was defined as IgG < 650 mg/dL. As a preliminary, hypothesis generating analysis, we used logistic regression to assess association between hypogammaglobulinemia and CLL-directed therapy (current therapy vs. observation, current BTK inhibitor (BTKi) therapy) and Ab development. Proportions were compared with Fisher's exact test.

We identified 30 consecutive patients at our center with CLL who tested positive for SARS-CoV-2 RNA, either in the setting of symptomatic COVID-19 or through screening at entry to the medical system. Hospital admission was required for 63%, 50% had severe COVID-19, and case fatality rate was 13% in this cohort. Two patients (7%) had been discharged from their COVID-19 hospital course with hospice care; both remain alive at the time of analysis. Baseline characteristics, CLL treatment history, details regarding COVID-19 course are included in Table 1.

Twenty-one patients were subsequently tested for anti-SARS-CoV-2 IgG Abs; the four patients who died due to COVID-19 and/or its complications in this cohort did not have serology testing prior to death, and testing was not performed for an additional five patients following acute infection. For the subset of patients who underwent IgG testing, serology testing occurred at a median of 55 days (range 28–93 days) following PCR diagnosis.

Table 1 Baseline characteristics, lab characterization at time of serology testing, and CLL-directed therapy history.

Characteristic	Proportion, unless otherwise specified (n = 30)
Baseline characteristics	
Age at COVID-19 diagnosis, median (range)	65 (41–82)
Age at CLL diagnosis, median (range)	51 (35–76)
Male	73%
CLL-directed therapy history	
Never treated	47%
Current observation	67%
Current therapy	33%
Current BTKi	20%
Prior anti-CD20 monoclonal Ab	43%
Prior fludarabine or bendamustine	30%
Prior cellular immunotherapy	3%
COVID-19 course	
Required hospital admission	63%
Required ICU admission	36%
Required oxygen	50%
Required intubation	23%
Death	13%

Fourteen of 21 (67%) patients tested positive for anti-SARS-CoV-2 Abs, while 7 of 21 (33%) did not have detectable Abs. Testing occurred at median of 57 (range 28–93) vs. 51 (range 38–62) days for patients with positive vs. negative anti-SARS-CoV-2 IgG. Three of 14 (21%) who tested positive for anti-SARS-CoV-2 IgG were receiving CLL-directed therapy at the time of COVID-19 diagnosis (1 with venetoclax, 1 with ibrutinib, and 1 with bendamustine/obinutuzumab). Four of seven (57%) who did not develop anti-SARS-CoV-2 IgG were receiving CLL-directed therapy (three with ibrutinib, one with venetoclax/obinutuzumab).

Of the patients who had serologic testing, 44% (7/16) had hypogammaglobulinemia, 50% (7/14) had IgM < 50 mg/dL, and 14% (2/14) had IgA < 40 mg/dL. Hypogammaglobulinemia (OR 0.05, 95% CI 0.003–0.7, $p = 0.027$) was negatively associated with development of anti-SARS-CoV-2 IgG. Currently receiving CLL-directed therapy (OR 0.2, 95% CI 0.03–1.5, $p = 0.11$) or BTKi (OR 0.1, 95% CI 0.008–1.3, $p = 0.08$) were not significantly associated with anti-SARS-CoV-2 IgG development. Of patients with severe COVID-19, 78% had positive anti-SARS-CoV-2 IgG while 58% with nonsevere COVID-19 were positive for anti-SARS-CoV-2 IgG ($p = 0.64$).

While published data on anti-SARS-CoV-2 IgG response suggest high (98–100%) rates of positive IgG by 17–19 days after PCR-based diagnosis, this series suggests that CLL patients have a lower rate of anti-SARS-CoV-2 IgG development (67%). Hypogammaglobulinemia was negatively associated with anti-SARS-CoV-2 IgG development. Trends toward lack of anti-SARS-CoV-2 IgG development for those currently receiving CLL-directed therapy or BTKi did not reach statistical significance in this small cohort. There was no significant difference in rates of Ab development between those with severe vs. nonsevere COVID-19. These findings need to be interpreted with caution and explored in larger cohorts. Notably, this study did not include patients who died because of COVID-19. Thus, we cannot draw conclusions about Ab formation in CLL patients with severe COVID-19 resulting in death or how lack of testing in this population affected the proportion of patients with positive anti-SARS-CoV-2 IgG.

These hypothesis generating data have important implications as we aim to understand CLL patients' immune response to infection or potential vaccination. Patients in this series were tested 28–93 days following PCR-based diagnosis. We cannot exclude the possibility that these patients had transient immune responses not captured by the testing window. However, these data suggest that 33% of tested CLL patients did not have a persistent Ab-mediated response, which may have implications for risk of subsequent infection. As patients with CLL appear to have variable humoral immune response to infection, it could be hypothesized that some CLL patients may have an impaired response to

potential vaccines that rely on Ab production to confer immunity [15]. Should these findings be validated, response to candidate vaccines will need to be specifically examined in immunocompromised populations. Further characterization of cell-mediated immune response and effect of CLL-directed therapy on immune response are ongoing.

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Compliance with ethical standards

Conflict of interest ER has received grant funding from American Society of Hematology outside of the submitted work and has minority ownership interest in AbbVie and Abbott Laboratories; LVR has received institutional research funding outside of submitted work from Abbott, IBM, and BioPortal; LAL is a member of speaker's bureau for Seattle Genetics, Celgene/BMS, KitePharma, BeiGene, Pharmacyclics/Janssen, AstraZeneca, Epizyme, Karyopharm, advisory board participant for Bayer, Seattle genetics, ADC therapeutics, Abbvie, Janssen, Pharmacyclics, Kite, AstraZeneca, TG Therapeutics; ADZ has received research grants from Abbvie, Adaptive Biotechnologies, BMS, BeiGene, Genentech/Roche, MEI Pharma, consulting fees from Amgen, AstraZeneca, BeiGene, Genentech/Roche, Janssen, JUNO/Celgene/BMS, Kite/Gilead, MEI Pharma, Pfizer, Pharmacyclics, Sandoz/Novartis, and serves on the scientific advisory board of Adaptive Biotechnologies, Lymphoma Research Foundation; ARM has received grants, personal fees and other from TG Therapeutics, grants and personal fees from Pharmacyclics, grants and personal fees from Janssen, grants and other from Celgene, grants and personal fees from Genentech, grants and personal fees from Abbvie, grants and personal fees from Adaptive, grants from Loxo, grants from Sunesis, grants from Regeneron, grants from DTRM, personal fees from BeiGene, grants and personal fees from AstraZeneca.

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