

Review Article

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COVID-19 Vaccination Response and Its Practical Application in Patients With Chronic Lymphocytic Leukemia

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ABSTRACT

Patients with chronic lymphocytic leukemia (CLL) typically have innate/adaptive immune system dysregulation, thus the protective effect of coronavirus disease 2019 (COVID-19) vaccination remains uncertain. This prospective review evaluates vaccination response in these patients, including seropositivity rates by CLL treatment status, type of treatment received, and timing of vaccination. Antibody persistence, predictors of poor vaccine response, and severity of COVID-19 infection in vaccinated patients were also analyzed. Practical advice on the clinical management of patients with CLL is provided. Articles reporting COVID-19 vaccination in patients with CLL, published January 1, 2021–May 1, 2022, were included. Patients with CLL displayed the lowest vaccination responses among hematologic malignancies; however, seropositivity increased with each vaccination. One of the most commonly reported independent risk factors for poor vaccine response was active CLL treatment; others included hypogammaglobulinemia and age >65–70 years. Patients who were treatment-naïve, off therapy, in remission, or who had a prior COVID-19 infection displayed the greatest responses. Further data are needed on breakthrough infection rates and a heterologous booster approach in patients with hematologic malignancies. Although vaccine response was poor for patients on active therapy regardless of treatment type, CLL management in the context of COVID-19 should aim to avoid delays in antileukemic treatment, especially with the advent of numerous strategies to mitigate risk of severe COVID-19 such as pre-exposure prophylaxis, and highly effective antivirals and monoclonal antibody therapy upon confirmed infection. Patients with CLL should remain vigilant in retaining standard prevention measures such as masks, social distancing, and hand hygiene.

INTRODUCTION

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, there have been over 500 million cases and over 6 million deaths reported worldwide.¹ Patients with hematologic malignancies and COVID-19 infection have significantly higher

rates of hospitalizations (57.1% versus 37.8%), intensive care unit (ICU) stays (29.8% versus 11.2%), and a 3.88-fold higher mortality rate (13.1% versus 3.7%) than respective patients with solid tumor malignancies.² A meta-analysis consisting of 3377 adult patients with hematologic malignancies conducted earlier in the pandemic showed a 34% risk of death in a predominantly hospitalized population, and a subgroup analysis of patients with chronic lymphocytic leukemia (CLL) estimated a pooled mortality risk of 31%.³ Additionally, in a multicenter international cohort study comprising 198 patients with CLL and COVID-19, hospital admission occurred in 90% of patients, among whom, the case fatality rate was 37%.⁴ In a retrospective, international, multicenter study by the European Research Initiative on CLL (ERIC) and Campus CLL including 190 patients with CLL and confirmed COVID-19, 79% presented with severe COVID-19 (requiring hospitalization and oxygen or ICU admission), with a reported CFR of 36.4%.⁵ In an update to this analysis through March 2021, with an expanded population of 941 patients (887 with CLL) the CFR had decreased (27.3% overall, 38.4% for patients with severe COVID-19).⁶ Similar results were seen in a recent retrospective analysis of 188 patients with CLL and COVID-19, which reported a CFR of 27%.⁷ As COVID-19 infection management improved over time, one retrospective analysis in 374 patients with CLL and COVID-19 evaluated CFR stratified by date; they observed a higher percentage of hospital admissions (85% versus 55%) and required ICU admissions (32% versus 15%), and a higher CFR (35% versus 11%) in the early cohort (February–April 2020)

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compared with the later cohort (May 2020–Feb 2021), respectively, indicating a trend toward lower mortality rates over time for patients with CLL and COVID-19.⁸

Factors affecting COVID-19–related risk of death in patients with CLL have been investigated. In the recently published retrospective analysis mentioned above on outcomes in 188 patients with CLL and COVID-19, the type of CLL-directed therapy did not have any impact on COVID-19–related risk of death.⁷ Advanced age, poor performance status, low platelets, and elevated lactate dehydrogenase levels were associated with increased risk of death due to COVID-19. Similar results have been seen in other large retrospective analyses where treatment type did not appear to impact COVID-19 outcomes.^{9,10} However, most patients in these studies had not been vaccinated.

A key feature of CLL is innate and adaptive immune system dysregulation, which may worsen over the course of the disease. This includes increased mobilization, inhibition, and impairment of T cells, and inhibition and decreased numbers of antibody-producing cells, among other immune deficiencies. Thus, the protective effects of vaccination against a variety of pathogens are variable in patients with CLL.¹¹ Given the added concern regarding the CLL treatment impact on immunity and response to vaccination,^{12–16} the pandemic may influence the decision of whether to treat CLL, and when. Optimal timing of vaccination in relation to treatment has also been unclear, with heterogeneity in recommendations across national and international guidelines. The current consensus supported by the American Society of Hematology (ASH), the European Hematology Association, ERIC, and the National Comprehensive Cancer Network® (NCCN®) is that, while all patients should be assessed on a case-by-case basis, and exceptions apply, generally patients should be vaccinated as soon as possible.^{17–19}

Since the COVID-19 vaccination program initiation, numerous studies have been conducted to evaluate antibody response to COVID-19 vaccination in CLL, including patient populations receiving treatment, and a few studies have evaluated T-cell-mediated response. While many prior reviews have included a broader population of hematologic illnesses,^{20–22} we aim to focus on prospective data in patients with CLL specifically to determine the overall humoral and cellular response, and the impact of CLL treatment and COVID-19 infection on immunity. This article also aims to provide practical thoughts on managing these specific groups of patients in clinical practice.

METHODS

Data search strategy

An electronic search of the PubMed database was performed to gather articles reporting on COVID-19 vaccination in patients with CLL, published between January 1, 2021, and May 1, 2022. Search strings covering the terms CLL, COVID19, vaccine, and vaccination were used (Suppl. Table S1). Abstracts presented at the ASH 2021 Annual Meeting and Exposition were also searched using the terms COVID-19 and CLL. To be eligible for inclusion, studies needed to be conducted in humans, and published in English from January 2021 to May 2022. Prospective clinical trials, observational studies, meta-analyses, systematic reviews, and registry studies were included. Finally, studies were required to include serology results in ≥ 20 patients with CLL; this enabled the inclusion of a sizeable number of studies while still providing an adequate number of patients for analysis of subgroups within the data.

Data screening and extraction

Key outcomes included seropositivity rates post-COVID-19 vaccination, defined in most studies as the presence of antibodies against the SARS-CoV-2 spike receptor-binding domain at or above the cutoff level for positivity, for patients with CLL versus healthy controls or patients with other hematologic

malignancies. Studies that only included neutralizing antibodies as an endpoint were excluded.^{22–24} Rates based on treatment status were considered, as well as type of treatment, and timing of vaccination. Antibody persistence, predictors of poor vaccine response, and severity of COVID-19 breakthrough infection in vaccinated patients were analyzed.

Data summary

A descriptive summary of the findings is presented. For the purpose of this review, a full initial vaccine series is defined as two doses of an mRNA vaccine, or one dose of adenovirus vector vaccine. Unless otherwise stated, vaccine response refers to antibody response. It should be noted that currently there is no standard definition of vaccine response – as such, definition of response varied across studies.

RESULTS

Search and study selection

In total, 27 studies were included in the review (Figure 1 and Suppl. Table S2).

How does vaccine response in CLL compare with other hematologic illnesses?

The data from several studies, including 3 large meta-analyses, provided vaccine response results for multiple hematologic malignancies (Table 1 and Figure 2A). Across all studies, with 3 exceptions,^{25,28,30} the lowest seropositivity rate was seen in the CLL population. The humoral response in patients with CLL after a full initial vaccine series ranged from 40% to 67% across all studies, compared with a range of 44%–100% for other hematologic malignancies. Eight studies also included healthy controls with vaccine responses between 97% and 100%.^{20,21,27,33,34,36,40}

As vaccination programs have accelerated in several countries, many patients with CLL have received a third dose of vaccine. In 6 studies, where patients were offered a third dose, 0%–80% (median 44.7%) achieved a serological response. The broad range of responses seen after the third dose may be due to the differences in response to the initial vaccine series. In the 2 studies, with the lowest responses to the third dose, for example, the patients were seronegative after the initial vaccine series,^{24,42} whereas in the study with the highest response rate, 72% were seronegative after the initial vaccine series.⁴³ One study reported a 55% conversion rate in initially seronegative patients; however, patient numbers were low.⁴¹ Six studies included data on response after a single dose of vaccine in addition to response following the second dose; continued vaccination led to a higher percentage of patients reaching seropositivity (Table 2). Limited data are available on the fourth vaccine dose during the period of interest (January 1, 2021–May 1, 2022).

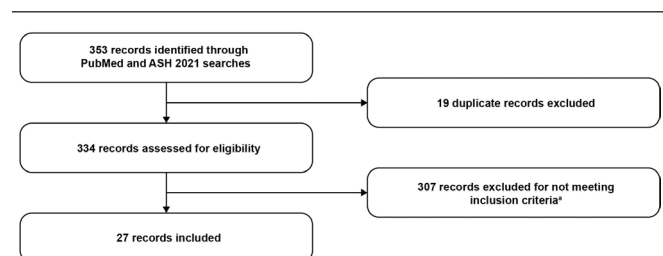


Figure 1. Included studies. *Study not conducted in humans; not published in English between January 21 and May 2022; not one of the following study types: prospective clinical trial, observational study, meta-analysis, systematic review, or registry study; not including serology results in ≥ 20 patients with CLL. CLL = chronic lymphocytic leukemia.

Table 1

Seropositivity Rates Post Initial Vaccine Series Reported for Patients With CLL or Other Hematologic Malignancies

Author	Patients With CLL		Other Hematologic Malignancies	
	N	Response (%)	Disease Type, n	Response (%)
Giuliano et al (2022) ²⁵	23	65.2	HL, 10 AML, 30 MDS, MPN, or MDS/MPN, 49 B-cell NHL, 55 MM, 88	100 100 85.7 58.2 93.2
Teh et al (2021) ²¹	1446	51	Other, <20 patients each ^a AML/MDS, 126 MPN/CML, 281 Myeloma, 1218 Lymphoma, 1296	93 87–88 76–80 52–55
Gagelmann et al (2021) ²⁰	1753	50	HL, 133 MPN, 365 Aggressive NHL, 386 Indolent NHL, 494 Myeloma, 1564	91 83 58 61 76
Gong et al (2022) ²⁶	1709	44	PCD, 2066 Lymphoid malignancies, 1904 MPN, 464 Acute leukemias, 147 MDS, 79	72 52 81 83 63
Šušol et al (2022) ²⁴	53	39.6	HL, 21 aNHL, 32 iNHL, 62 MM, 119 AL/MDS, 33 cMPN, 54 MBL, 21	76.2 37.5 54.8 87.4 84.8 92.6 90.5
Shen et al (2021) ²⁷	160	55	MCL, 27 Smoldering MM, 29	44.4 100
Greenberger et al (2021) ²⁸	650	64.2	AML, 34 CML, 34 MZL, 34 MDS/MPN, 35 NHL NOS, 48 DLBCL, 52 HL, 65 WM, 97 FL, 98 MM, 184	91.2 97.1 61.8 97.1 79.2 78.8 98.5 74.2 77.6 95.1
Herzog Tzarfati et al (2021) ²⁹	34	47	Other, <20 patients each ^a CML, 22 Indolent NHL, 40 Aggressive NHL, 51 MM, 53 MPN, 68 B-cell NHL, 55	91 60 71 76 84 58.2
Dong et al (2021) ³⁰	23	65.2	Other, <20 patients each ^a	
Molica et al (2022) ³¹	2082	52		
Bagacean et al (2022) ³²	506	52		
Molica et al (2022) ³³	70	58.5		
Bergman et al (2021) ³⁴	79	63.3		
Sun et al (2021) ³⁵	58	60.3		

(Continued)

Table 1 (Continued)

Author	Patients With CLL		Other Hematologic Malignancies	
	N	Response (%)	Disease Type, n	Response (%)
Parry et al (2022) ³⁶	500	67		
Benjamini et al (2022) ³⁷	373	43		
Roeker et al (2021) ³⁸	44	52		
Tadmor et al (2021) ³⁹	84	58.3		
Herishanu et al (2021) ⁴⁰	167	39.5		
Ujjani et al (2022) ²³	37	41		
Haydu et al (2022) ⁴¹	36	55.6		

^aResponse rates only reported for hematologic malignancies where the reference cites results for ≥20 patients.

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; CMPN = chronic myeloproliferative neoplasm; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HL = Hodgkin lymphoma; MBL = monoclonal B-lymphocytosis; MDS = myelodysplastic syndromes; MM = multiple myeloma; MPN = myeloproliferative neoplasm; n = number of patients; NHL = non-Hodgkin lymphoma; NK = natural killer.

How does treatment status impact vaccination response?

The majority of studies (17/27) included subgroup analyses on response based on treatment status. The most commonly reported independent factor for poor response was being on active treatment, with responses ranging from 14% to 50% (median 25.3%) after the initial vaccine series, compared with 50% to 94% (median 72%) in those who were treatment-naïve (Table 3). For patients who were off therapy but who had received prior treatment, response rates of 42%–100% (median 61%) were reported,^{27,32,34,35,39,40,42} with 2 outliers of 23% (n = 26)³⁸ and 0% (n = 5).⁴¹ The heterogeneous results seen across studies is reflective of the many variables that can impact vaccine response in patients with CLL, including factors such as age and comorbidities, time since last treatment administration (in particular for anti-CD20 therapy), and study design elements such as the assay used and timing of response evaluation following vaccination. Patients in remission had response rates similar to those who were treatment-naïve (67.5%–87.5%; median 71%),^{27,33,36,40} with 1 outlier of 27.2% (n = 22).³⁹ A similar pattern was observed in patients who were offered a third dose, with higher response in treatment-naïve patients compared with those on active treatment.^{42,44} In 1 study, patients with prior COVID-19 infection had the highest response rate (100%) with just 1 vaccination.³² Another study reported antibody titers in patients with CLL who had a prior COVID-19 infection that were comparable with titers seen in healthy controls.³⁶

How do specific therapies impact vaccination response?

Targeted therapies (inhibitors of Bruton tyrosine kinase [BTKi] and B-cell lymphoma-2 [BCL-2i]), as well as anti-CD20 antibodies, are widely used in CLL. The effect of anti-CLL-targeted therapies on humoral responses is unclear, and may be due to off-target effects on other kinases affecting CD4 T-cell function in the case of BTKi's or reduction in absolute numbers of B cells and T cells, as with BCL2i's¹¹; however, monoclonal anti-CD20 therapy (most commonly with rituximab or obinutuzumab), used in CLL treatment, depletes CD20+ B-cell function, which is vital in forming a serologic response. Seventeen out of 27 studies included subgroup analyses on seroconversion rates for specific therapies (Table 4). Vaccine response for venetoclax monotherapy ranged from 38% to 100% (median 52%).^{32,35–37,40} Response rates in patients on BTKi monotherapy

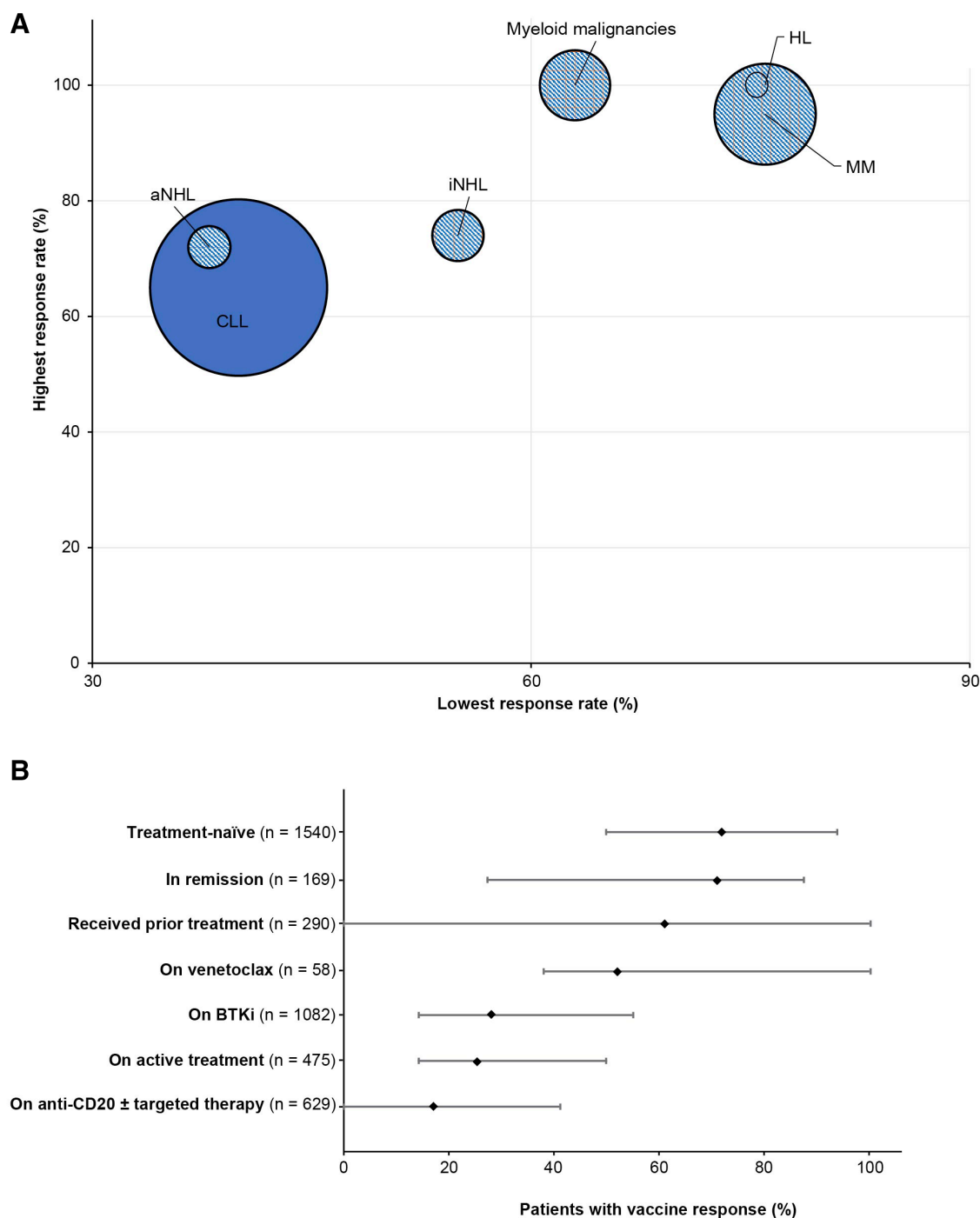


Figure 2. Vaccine antibody responses by disease area (A)^a and treatment status and type (B)^b. ^aThe data for other hematologic malignancies represent only data present in those references that were included for the CLL analysis, and are not a comprehensive evaluation of response rates in those malignancies. The visual shows the range of vaccine responses for each disease area, with the lowest response rate within the range shown on the x-axis and the highest response on the y-axis. The size of the bubbles represent the number of patients within that disease area across all studies; ^bDiamond represents median; bar represents range. Median (range) % responders by treatment status or treatment type: treatment-naïve, 72 (50–94); active treatment, 25.3 (14–50); prior treatment, 61 (0–100); remission, 71 (27.2–87.5); venetoclax, 52 (38–100); BTKi, 28 (14.3–55); anti-CD20, 17 (0–41). AML/MDS = acute myeloid leukemia/myelodysplastic syndromes; BTKi = Bruton tyrosine kinase inhibitor; CLL = chronic lymphocytic leukemia; CR = complete remission; HL = Hodgkin lymphoma; MM = multiple myeloma; MPN = myeloproliferative neoplasm; NHL = non-Hodgkin lymphoma; TN = treatment-naïve; ven = venetoclax.

ranged from 14.3% to 55% (median 28%), with 11 of the 14 studies reporting response rates less than 36% after 2 doses of vaccine, and in those on anti-CD20s from 0% to 41% (median 17%) (Figure 2B). For those on any venetoclax-based regimen, including anti-CD20 or BTKi combinations, response was reduced (0%–39%); it should be noted that the studies included in this range did not provide a breakdown of the

venetoclax-based regimens (ie, mono or combo and specific combination partner).^{28,31,36,37,39,40} The NCCN recommendations do not distinguish between therapies, stating that patients on maintenance therapies for CLL, including anti-CD20 antibodies and BTKi’s, may have an attenuated response to vaccination.¹⁸ Currently, it is unclear if the rates of vaccine response correlate to better outcomes in patients with CLL.

Table 2

Seroconversion Rates in Patients With CLL for First, Second, and Third Dose of Vaccines

Author	N	Response (n Evaluable)		
		First Dose Response	Second Dose Response	Third Dose Response
Bagacean et al (2022) ³²	530	27% (158)	52% (506)	35% (95) ^a
Dong et al (2021) ³⁰	23	21.7% (23)	65.2% (23)	NA
Shen et al (2021) ²⁷	160	20.8% (125)	55.0% (160)	NA
Herishanu et al (2022) ⁴²	172	NA	NA	23.8% (172) ^a
Greenberger et al (2021) ⁴³	25	NA	NA	80% (25) ^b
Del Poeta et al (2021) ⁴⁴	46	NA	NA	54.3% (46) ^c
Haydu et al (2022) ⁴¹	36	NA	NA	55% (11) ^a
Giuliano et al (2022) ²⁵	23	21.7% (23)	65.2% (23)	NA
Šušol et al (2022) ²⁴	53	NA	NA	0% (15) ^a
Teh et al (2021) ^{21,d}	1446	18% (111)	51% (1446)	NA

^aSeronegative after initial vaccine series.

^b72% seronegative after initial vaccination.

^cInitial vaccination response not reported.

^dMeta-analysis, rate after first dose is from 1 study with 111 patients, rate after second dose is pooled across included studies of patients with CLL.

CLL = chronic lymphocytic leukemia; n = number of patients; NA = not available.

How does timing of vaccination post-anti-CD20 anti-CD20 treatment impact vaccine response?

As mentioned previously, patients who had had prior therapy, but were no longer on active treatment had a greater response than those on active treatment.^{32,35-41} However, the optimal time for vaccine administration post-anti-CD20 treatment has yet to be determined. Table 5 summarizes prospective studies that analyzed vaccine response in patients on anti-CD20 therapy, based on the timing of vaccination. Patients who were given their initial vaccine series at least 12 months following end of anti-CD20 therapy had a greater vaccine response (35%–56.2%) compared with a range of 0%–24% for those who were vaccinated less than 12 months after anti-CD20 therapy.^{27,31,36-40} One study reported a response rate of 20% (n = 10) when the vaccine was given as early as within 6 months after treatment with an anti-CD20, so some patients do respond earlier than 12 months post-treatment.²⁴ A similar pattern was seen in the 1 study that measured response based on timing of a third vaccine in relation to anti-CD20 therapy (22.7% of patients not treated with an anti-CD20 in the 12 months before vaccination versus 3.6% of those who were).³⁷ Studies did not report correlations between vaccine timing post-targeted therapy specifically and vaccine response.

What factors were shown to be predictors of poor vaccine response?

The most commonly reported independent risk factors for poor vaccine response were low immunoglobulin (Ig)M, IgG, or IgM and/or IgA^{27,30,32,34,36,39,42,44}; anti-CD20 therapy (active or within the last 12 months)^{23,24,28-30,32,36,40,42,43}; BTKi therapy^{28,29,34-36,40,42,45}; active therapy in general^{30,32,33,39,42,44}; age >65 years^{29,32,38,42}; CLL-directed therapy of any kind in the last 12 months^{27,32,38}; and BCL-2i regimens^{29,42} (+ anti-CD20^{35,40}). Other factors identified in more than one study included the number of prior therapies/lines of therapy^{29,42}; Cumulative Illness Rating Scale score >6⁴⁶ or ≥6³⁷; vaccine type (BNT162b2)^{28,32}; low B-lymphocyte count^{23,30}; and gender (male^{36,44} and female^{28,39}).

How long did patients maintain seropositivity?

Five studies provided results on antibody persistence in patients with CLL. In 4 of these studies, 64%–90% of patients

Table 3

Seropositivity Rates According to Treatment Status

Author	CLL N	Response (n Evaluable)			
		Treatment-naive	Active Treatment	Prior Treatment	In Remission
Second dose					
Sun et al (2021) ³⁵	58	71% (21)	50% (34)	100% (3)	NA
Dong et al (2021) ³⁰	23	81.3% (16)	28.6% (7)	NA	NA
Shen et al (2021) ²⁷	160	63.4% (82)	21.9% (32)	NA	67.5% (40) ^a
Molica et al (2021) ³³	70	87% (23)	41.7% (36)	NA	87.5% (8) ^a
Parry et al (2022) ³⁶	500	78% (284)	43% (200) [on/prior]	73% (11) ^b	71% (75)
Bagacean et al (2022) ³²	506	72% (210)	22% (166)	60% (130)	NA
Benjamini et al (2022) ³⁷	373	61% (158)	14% (113) ^c	42% (55) ^d	NA
Herishanu et al (2021) ⁴⁰	167	55.2% (58)	16% (75)	64.7% (34)	79.2% (24)
Roeker et al (2021) ³⁸	44	94% (18)	NA	23% (26)	NA
Tadmor et al (2021) ³⁹	84	76.2% (16)	28.6% (6)	61.9% (26)	27.2% (22)
Bergman et al (2021) ³⁴	79	84.6% (26)	NA	NA ^e	NA
Ujjani et al (2022) ²³	37	50% (14)	NA	NA	NA
Haydu et al (2022) ⁴¹	36	72% (25)	33% (6)	0% (5)	NA
Molica et al (2022) ³¹	2082	73% (533)	NA	NA	NA
Haggenburg et al (2022) ⁴⁵	94	70% (56)	NA	NA	NA
Third dose (booster results)					
Herishanu et al (2022) ⁴²	172	40% (40)	12% (100)	40.6% (32)	41.7% (24)
Del Poeta et al (2021) ⁴⁴	46	88.2% (17) ^f	34.5% (29)	NA	NA

^aComplete or partial remission.

^bPrior targeted therapy.

^cTargeted therapy.

^dPrior targeted therapy.

^ePrior ibrutinib: 9 (55.6%); prior anti-CD20 (median 13 mo): 18 (88.9%).

^fIncludes prior treatment.

CLL = chronic lymphocytic leukemia; n = number of patients; NA = not available.

remained seropositive over a 3–6-month timeframe following the initial vaccine series.^{36,39,47} In the other study, 100% (n = 14) of patients remained seropositive at 6 months; however, 7 of the patients had also received a third dose.²³ Although patients with CLL may start out with a lower response rate, in 1 study, it was noted that the decay in antibody response over time is similar between patients with CLL and healthy controls aged ≥70 years.³⁹

In terms of whether anti-CD20 therapy post-vaccination impacts antibody persistence, none of the studies captured in the literature search addressed immune response when treatment is initiated postvaccination. However, in a recent study (published January, 2022) evaluating vaccine response in 126 patients with lymphoma, 15 patients received a full initial vaccine series before beginning anti-CD20 therapy.⁴⁸ Ten of these patients

Table 4**Seroconversion Rates Post Initial Vaccination According to Type of Targeted Therapy Received**

Author	CLL N	Response (n Evaluable)				
		Targeted Treatment	Venetoclax Mono	BCL2i ± Combo	BTKi	Anti-CD20 Response ± Targeted
Second dose						
Sun et al (2021) ³⁵	58	NA	100% (1)	NA	55% (29)	20% (5)
Molica et al (2021) ³³	70	43% (35)	NA	NA	NA	10% (10)
Parry et al (2022) ³⁶	500	24% (114)	38% (16)	0% (5) ^a	34% (93) ^b	NA
Bagacean et al (2022) ³²	506	NA	52% (23)	0% (6) ^a	22% (104)	0% (19)
Bergman et al (2021) ³⁴	79	NA	NA	NA	26.9% (26)	NA
Molica et al (2022) ³¹	2082	NA	NA	32% (94)	29% (325)	41% (254)
Benjamini et al (2022) ³⁷	373	14% (113)	62% (13)	6% (34)	18% (79)	14% (49)
Roeker et al (2021) ³⁸	44	NA	NA	NA	21% (14)	10% (21)
Tadmor et al (2021) ³⁹	84	NA	NA	16.7% (6)	36.4% (4)	NA
Herishanu et al (2021) ⁴⁰	167	NA	40% (5)	13.6% (22)	16% (50)	NA
Greenberger et al (2021) ²⁸	650	NA	NA	39.3% (28)	47.5% (282)	36.9% (263)
Shen et al (2022) ²⁷	160	16% (25)	NA ^c	NA	14.3% (21)	NA
Ujjani et al (2022) ²³	37	NA	NA	NA	33% (15)	38% (8) ^d
Haydu et al (2022) ⁴¹	36	NA	NA	NA	33% (6)	NA
Haggenburg (2022) ⁴⁵	94	NA	NA	NA	27% (34)	NA
Third dose^e						
Herishanu et al (2022) ⁴²	172	NA	60% (5)	NA	15.3% (59)	7.7% (39)
Del Poeta et al (2021) ⁴⁴	46	NA	25% (8)	NA	38.1% (21)	NA

^aPatients receiving venetoclax + a BTKi.

^bBTKi monotherapy.

^cFour patients (response 25%) were on venetoclax, but had completed anti-CD20 therapy within the last 12 mo.

^dVenetoclax + anti-CD20 therapy ongoing/within 1 y.

^eHerishanu: seronegative after initial vaccination; Del Poeta: any patient (may include prior treatment).

BCL2i = B-cell lymphoma-2 inhibitor; BTKi = Bruton tyrosine kinase inhibitor; CLL = chronic lymphocytic leukemia; Combo = combination therapy; Mono = monotherapy; n = number of patients; NA = not available.

Table 5**Seroconversion Rates According to Timing of Vaccination Post-anti-CD20 Therapy**

Author	CLL, N	Response (n Evaluable)	
		CD20 <12 mo	CD20 ≥12 mo
Second dose			
Shen et al (2022) ²⁷	160	22.2% (9)	NA
Parry et al (2022) ³⁶	500	24% (17)	56% (136)
Herishanu et al (2021) ⁴⁰	167	0% (22)	45.5% (55)
Molica et al (2022) ³¹	2082	4% (94)	NA
Benjamini et al (2022) ³⁷	373	5% (39)	35% (92)
Roeker et al (2021) ³⁸	44	14.3% (14)	NA
Tadmor et al (2021) ³⁹	84	NA	56.2% (18)
Third dose (booster)			
Herishanu et al 2022 ⁴²	172	3.6% (28)	22.7% (66)

CLL = chronic lymphocytic leukemia; n = number of patients; NA = not available.

generated an antibody response, and rates of persistence in this group were comparable with age-matched healthy controls. This study demonstrates little to no impact on vaccine response when patients are vaccinated before anti-CD20 therapy.

What was the severity of illness for patients who developed an infection postvaccination (breakthrough infection)?

There were only 3 studies that reported breakthrough COVID-19 infection in patients with CLL during the study period. In 1 study, 3 of 400 patients developed a COVID-19 infection following vaccination, one in between the first and second dose of vaccine and 2 after the initial vaccine series was complete (14 and 24 days post-vaccination) – all 3 recovered uneventfully.³⁷

In another study, 1 patient (out of 37) who did not seroconvert upon initial vaccination, and was not assessed after a subsequent booster, developed a COVID-19 infection. The patient received casirivimab/imdevimab and recovered without significant complications.²³ In the third study,⁴² 4 patients, who had received a third dose of an mRNA vaccine after being seronegative with the first 2 doses, developed a COVID-19 infection, 2 with severe disease, and 2 with mild disease. One patient died due to their infection, while the others recovered. Three of the patients were seronegative after the third dose and 1 was seropositive with a low antibody titer. Although patients who were seronegative seemed to have more severe disease in this analysis, given the small number of patients with COVID-19 infection across all studies, further research is needed to characterize outcomes of breakthrough infections postvaccination.

In a retrospective cohort study with 984 fully vaccinated patients with CLL, identified between December 2020 and October 2021, there was a 15.2% risk of breakthrough infection (confidence interval: 13–17.6) versus 4.5% in 508,457 fully vaccinated patients without cancer. In the same study, hospitalization risk and mortality were shown to be significantly higher in patients with versus those without breakthrough infections across all hematologic malignancies (hazard ratios: 34.49 and 10.25, respectively).⁴⁹

How did the type of vaccine impact seropositivity, is there an advantage to mixing vaccines?

Ten studies reported on the use of different vaccine types (eg, mRNA1273 or BNT162b2 or Ad26.COV2.S), though not all specifically in patients with CLL: 4 studies showed no difference in serology and/or titers between the vaccines used^{27,35,36,43}; 6 studies reported a difference in vaccine response depending on the vaccine used, of which 3 identified vaccine type as a predictor of response,^{28,32,41} and 3 did not analyze the difference

observed.^{22,23,38} Overall, for the studies reporting response rates by vaccine type, mRNA1273 had the highest response rates, followed by BNT162b2 (both mRNA-based vaccines), and finally the adenovirus-based vaccine, Ad26.COV2.S. One study reported that this difference was only seen in hematologic patients and not in healthy controls.²⁸ Similarly, in a retrospective analysis of 239 hematologic patients, seroconversion rates were significantly higher for patients who received mRNA1273 (57%) versus BNT162b2 (36%; $P = 0.006$).⁵⁰ This difference has also been seen in immune compromised patients in general.⁵¹

Additional vaccinations (third and fourth doses) currently approved under emergency use authorization (EUA) are restricted to homologous mRNA vaccines.⁵² There have been studies reporting results on heterologous, or mixing of, booster vaccinations. In one phase 1/2 study of 458 individuals, a homologous booster increased antibody titers 4.2–20-fold, whereas heterologous boosters increased titers 6.2–76-fold (pre-print).⁵³ Other studies have shown similar increases in either systemic reactogenicity or immunogenicity with a heterologous booster approach^{45,54,55}; however, these studies are in healthy adults.^{56,57} Only 1 study evaluated heterologous boosters in patients with hematologic malignancies.⁵⁸ Seventeen percent of 18 patients with CLL mounted a response to the Ad26.COV2.S vaccine after being seronegative on the initial full series of BNT162b2 vaccine, yet there was no comparison with a homologous booster. Further data are needed on the use of heterologous vaccines to boost vaccine response in hematologic patients.

Expert opinion on management of patients with CLL and COVID-19: clinical scenarios

The following perspectives on the clinical management of patients with CLL and COVID-19 infection is based on expert opinion and should not be perceived as clinical practice recommendations. Clinical judgement is required to ensure that treatment decisions are appropriate for individual patients. It is important to note that not all opinions here are based on published data; practices are discussed that may go beyond the scope of this review.

Should I vaccinate all of my patients?

Patients who are moderately or severely immunocompromised, such as patients with CLL, should be vaccinated and offered subsequent boosters regardless of treatment status or type of B-cell directed therapy. We agree with the current recommendation of the Center for Disease Control (CDC) for a fifth dose for patients aged 12 and older who are moderately or severely immunocompromised. It is advisable to follow the relevant treatment guidelines for patients receiving hematopoietic stem cell transplantation or chimeric antigen receptor T-cell therapy.

Should I stop or delay treatment to vaccinate?

There is no evidence to support interruption of CLL treatment for vaccination. Where possible, it is preferable to vaccinate before initiating therapy; however, therapy should not be delayed in order to complete the vaccine series.

Should I measure B lymphocytes or other biomarkers for response before vaccination?

B-cell levels and/or antibody levels are not predictive of the quality and quantity of immune protection nor the capacity to develop a response to vaccination. Accordingly, Haggenburg et al⁴⁵ states the following: “effective B-cell depleting therapy precludes generation of antibody responses, although B-cell numbers do not need to be normalized to generate sufficient antibody concentrations.” Currently, there are no validated biomarkers for predicting vaccine response, and decisions regarding vaccination should not be based on such variables.

Should I use antibody titers to assess immunity after COVID-19 vaccination?

Similar to the above, antibody testing is not currently recommended to assess immunity after COVID-19 vaccination (outside of a research study) – this is in line with the NCCN, and Food and Drug Administration (FDA) Safety Communication, and guidance from the CDC, and other international agencies.^{18,59–61}

Should I avoid anti-CD20 therapy?

Vaccine response is poor for patients on any active treatment, not only anti-CD20 therapy. Patients who need treatment should not be limited to certain classes of medications based upon potential vaccine response. The best available therapy should be used for the patient, especially during an endemic state. We now have several strategies available to mitigate risk of severe COVID-19 infection, even among those patients who may have a poor vaccine response, such as pre-exposure prophylaxis with anti-SARS-CoV-2 monoclonal antibodies (tixagevimab/cilgavimab), highly effective antiviral therapies (nirmaltrelvir/ritonavir), and postexposure prophylaxis with monoclonal antibody therapy (bebtelovimab). All patients with CLL on active treatment, including with anti-CD20 therapy, should be offered prophylactic anti-SARS-CoV-2 monoclonal antibody injection to lower the risk of severe infection.

Should I stop treatment if a patient develops a COVID-19 infection?

In cases of severe COVID-19, where there is a need for hospitalization and oxygen, it should be verified whether treatment can be postponed until the patient is cleared of COVID-19 infection (as confirmed by a negative swab). In most cases of mild infection, therapy can continued.^{62–64} The decision to stop treatment can be based on factors such as length of therapy, response, absence of signs of progression, and minimal expected impact of treatment break.

To what extent do T cells contribute to immunity against COVID-19?

Current evidence is unclear and contradictory: most data suggest that a T-cell response may be impaired when antibodies are not produced, while some studies have indicated otherwise (Table 6). The current level of evidence is not adequate to propose any clinical guidance. In addition, routine assessment of a T-cell response is challenging without any commercially available assays, and therefore difficult to implement in regular clinical practice, and is not recommended.

Could T-cell response compensate for lack of seroconversion and provide sufficient protection against COVID-19 infections?

Most studies show a correlation between IgG and T-cell responses; in the absence of an antibody response, a cellular response is less likely to occur. While efforts have been made to assess T-cell response, the data are insufficient and inconsistent.

Table 6

T-cell Response to COVID-19 Vaccination in Patients With CLL

Author	CLL N	T-cell Response (n Evaluable)		
		Seropositive	Seronegative	Correlation
Sun et al (2021) ³⁵	58	52.4% (21) ^a	42.9% (21) ^a	$P = 0.4^b$
Itchaki et al (2021) ⁴⁶	68	32% (68)	68% (68)	$P = 0.048^b$
Haydu et al (2022) ⁴¹	36	NA	78% (9)	NA
Shen et al (2022) ²⁷	160	81% (25) ^c	19% (6) ^d	NA

^aData missing for 1 patient.

^b P value for correlation of T-cell response with antibody response.

^cPatients with a normal response, albeit of variable intensity.

^dPatients with a weak or negative response.

CLL = chronic lymphocytic leukemia; COVID-19 = coronavirus disease 2019; n = number of patients; NA = not available.

Factors such as the evolving state of the pandemic, and differing vaccine statuses/policies and treatment availability across locations have confounded efforts to fully understand this topic.

Should I use a COVID-19 monoclonal antibody for pre-exposure prophylaxis in all my patients with CLL, and is there an optimal time to utilize them?

Tixagevimab/cilgavimab is a combination of long-acting monoclonal antibodies that is indicated for pre-exposure prophylaxis under FDA EUA for immunocompromised individuals who may not mount an adequate response to vaccination. Tixagevimab/cilgavimab is currently recommended in all patients with CLL, particularly those who are on active treatment. However, as with vaccines, it will be important to follow changes over time in circulating variants that may evade protection, thereby limiting the efficacy of tixagevimab/cilgavimab. Active monitoring of symptoms remains critical to start effective antiviral therapy after exposure. Tixagevimab/cilgavimab is indicated for those individuals without active COVID-19 infection or recent exposure and, as of June 2022, the FDA EUA Fact

Sheet indicates that repeat doses can be given every 6 months.⁶⁵ It is not a substitute for vaccination but may provide an additional layer of protection against symptomatic infection. Special attention should be given to drug–drug interactions that can occur with available SARS-CoV-2 antiviral drugs (Table 7), for which a precautionary hold of the antileukemic treatment may be suggested while also considering the short duration of the antiviral therapy (5 days).

Do you recommend your patients who are vaccinated to continue COVID-19 prevention measures?

Despite vaccination, patients with CLL are still at risk of COVID-19 infection and therefore should continue to use standard infection prevention measures such as masks, social distancing, and hand hygiene.

DISCUSSION

The pandemic has been a challenge to navigate for patients living with CLL and their healthcare providers. Since the start of the vaccination program, numerous studies have been conducted to look at serologic response and, less frequently, T-cell-mediated response to COVID-19 vaccination in the CLL population, the data from which can now be analyzed to provide guidance around treatment and vaccination.

Despite having the lowest vaccination response relative to other malignancies in the majority of studies included, seropositivity rates in patients with CLL are shown to increase with each vaccination, and in some cases even when a response had not been mounted prior.^{32,41,42} This may be due to the timing of the third dose post-treatment; however, it indicates that additional vaccinations are warranted regardless of initial response. The CDC recommends an updated COVID-19 vaccine booster to help restore protection that has decreased since the last vaccine administration and that may provide improved protection against newer variants. Updated boosters, also known as bivalent boosters, target the most recent Omicron subvariants, in addition to the original SARS-CoV-2.⁶⁰

One of the most common independent predictors of poor vaccine response was being on active CLL therapy, with response rates as low as 14% across all studies.³⁷ Regarding the impact of specific treatments on vaccine response, the findings of this review indicate that vaccine response is poor regardless of the treatment given, with responses ranging from 14.3% to 55% (median 28%) for BTKi monotherapy^{27,35} (11 of 14 studies with response rate <36%) and 0% to 41% (median 17%) for anti-CD20 therapies given with or without venetoclax.^{31,32,35} The wide range of responses seen may be reflective of the varied time points at which serology was evaluated postvaccination. Greater responses were seen in patients who were vaccinated more than 12 months post-anti-CD20 treatment.^{36,37,40,42} Nevertheless, serological responses have been reported in patients being vaccinated within 12 months of treatment; therefore, patients should still be offered vaccination before the 12-month mark.^{8,25,27,36} In addition, vaccination response was shown to wane over time (eg, 33% loss of vaccine response at 4 months³⁶), which may explain the lower responses observed through continuous BTKi therapy.^{33,39,42} According to emerging data, treatment given post-vaccination, if feasible, does not appear to impact the persistence of vaccine response nor does the rate of decay differ between patients on treatment and healthy controls.

There is a question as to whether cellular response is still present in the absence of antibody response and whether serology to evaluate humoral response is the best measure of viral protection. Cellular response was seen in the absence of antibody response, with 2 studies showing no association with antibody response^{35,41}; however, 1 study did show a correlation,⁴⁶ therefore the data are conflicting. A small retrospective cohort study of patients treated with B-cell-targeting therapies (of whom

Table 7
Regimens/Agents Used in the Management of COVID-19 That Interact With Therapies for CLL

COVID-19 Treatment	Metabolism/Elimination	CLL Treatment With Potential Drug Interaction	CLL Treatment Considerations
Tocilizumab ⁶⁶	Inhibition of IL-6 may lead to increased metabolism of drugs that are CYP450 substrates	Acalabrutinib, duvelisib, ibrutinib, idelalisib, venetoclax, zanubrutinib	Caution should be exercised when coadministering tocilizumab with CYP3A4 substrate drugs where decrease in effectiveness is undesirable. The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy
Remdesivir ⁶⁷	In vitro, remdesivir is a substrate for drug metabolizing enzyme CYP3A4 and P-gp transporters	Acalabrutinib, duvelisib, ibrutinib, idelalisib, venetoclax, zanubrutinib	Because remdesivir is an inhibitor of CYP3A4, coadministration of remdesivir and CLL drugs may increase levels and toxicities of CLL drugs. It is not clear if remdesivir is a strong or moderate CYP3A4 inhibitor. Either interrupt dosing or reduce dose of CLL drug while remdesivir is being used; refer to USPIs of CLL drugs for dose modification recommendations
Nirmatrelvir plus ritonavir ⁶⁸	A strong inhibitor of CYP3A; components are CYP3A substrates	Ibrutinib, venetoclax, acalabrutinib, idelalisib, zanubrutinib	Because nirmatrelvir plus ritonavir is a strong inhibitor of CYP3A, coadministration of nirmatrelvir plus ritonavir and CLL drugs (ibrutinib, venetoclax, acalabrutinib, duvelisib, idelalisib, zanubrutinib) may increase levels and toxicities of CLL drugs. Avoid coadministration or interrupt dosing of CLL drug while nirmatrelvir plus ritonavir is being used

CLL = chronic lymphocytic leukemia; COVID-19 = coronavirus disease 2019; IL = interleukin; IV = intravenous; mAb = monoclonal antibody; MoA = mechanism of action; OATP1B1 = organic anion transporting polypeptides 1B1; P-gp = P-glycoprotein; USPI = United States Prescribing Information.

47% had CLL) compared with healthy participants also found no trends between antibody and cellular responses, and the probability of developing a cell-mediated immune response negatively correlated with disease burden, mainly in patients with CLL.⁶⁹ A more recent cohort study of patients with CLL found that cellular responses after the second and third vaccine doses were comparable with those in healthy participants, but also noted that cellular response was markedly higher in patients who had received a heterologous vaccine series.⁷⁰ Therefore, cellular responses to vaccination may play a role in preventing severe disease but may vary between vaccine types/series.

There are also limited-to-no data on breakthrough infection and survival outcomes in patients who achieve a cellular versus antibody response. Further research is needed in this area. Real-world evidence from the National COVID Cohort Collaborative showed that patients with solid tumors and hematologic malignancies had significantly higher risk for breakthrough infections and severe outcomes compared with non-cancer patients. Compared with solid tumors, hematologic malignancies were associated with an increased risk for breakthrough infections, with the highest observed for lymphoid leukemia. Unexpectedly, however, patients with lymphoid leukemia were at decreased risk of severe COVID outcomes versus those with solid tumors.⁷¹

In addition to being on active CLL therapy, there were other common independent factors identified for poor vaccine response, most notably hypogammaglobulinemia and age >65–70 years.³² These may be additional factors to consider if there is a need to prioritize recipients of COVID-19 prophylaxis, alongside standard infection prevention measures. In contrast, patients who were treatment-naïve, currently off therapy, in remission, or who had a prior COVID-19 infection had the greatest responses, with the latter being similar to that of healthy controls.^{35,69} As many patients are able to achieve remission with B-cell directed therapies, and with the recent availability of COVID-19 monoclonal antibodies for pre-exposure prophylaxis that could be used for patients at risk for poor vaccine response, antileukemic treatment should not be delayed in patients with CLL.

Limitations

Different vaccines were used in the studies eg, BNT162b2 (Pfizer), mRNA-1273 (Moderna), Ad26.COV2.S (J&J), and vaccine type was shown to be a predictor of vaccine response in 3 studies.^{28,32,41} Although in most studies, the time between the 2 doses of vaccination was 3 weeks, in 1 study in particular, the majority of patients were on an extended vaccine series with 10–12 weeks between doses, which the authors implied may enhance seropositivity.³⁶ The studies evaluated serology at various time points post-vaccination, ranging from 14 to 139 days, which may impact results, as antibody responses may wane over time.^{33,36,39,42} Many different testing methods/assays were utilized in the studies, with various thresholds for adequate response depending on the type of test used. There were also varying time points from last treatment to final vaccination dose, which may impact response.

SUMMARY OF FINDINGS

All patients with CLL should be offered vaccination, regardless of treatment type or status. There is no evidence for CLL treatment to be interrupted for vaccination; however, when possible, it is preferable to vaccinate prior to CLL treatment initiation.

Currently, there are no validated biomarkers for predicting vaccine response, and antibody testing is not recommended to assess immunity after COVID-19 vaccination (outside of a research study).

All patients on active therapy are at risk of having a poor response to vaccination regardless of therapy type; the best available CLL therapy should be given to the patient, with anti-SARS-CoV-2 monoclonal antibody pre-exposure prophylaxis administered to reduce the risk of severe COVID-19 infection.

Pre-exposure prophylaxis with SARS-CoV-2 monoclonal antibody injection (tixagevimab/cilgavimab) is recommended in all patients with CLL, particularly those who are on active treatment. It is not a substitute for vaccination or standard infection prevention measures (mask wearing, social distancing, hand washing).

Targeted therapies (eg, BTKi) are not routinely interrupted when a patient presents with mild COVID-19 symptoms. In cases of severe COVID-19, where there is a need for hospitalization and oxygen, it should be evaluated whether treatment can be postponed until after the patient's infection has resolved.

AUTHOR CONTRIBUTIONS

All authors were involved in interpreting the data and writing the manuscript. All authors approved the final version for submission.

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