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INVITED REVIEW

Current perspectives regarding SARS-CoV-2 vaccination in chronic lymphocytic leukemia

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Abstract

In immunocompetent people, the mRNA vaccines BNT162b2 and mRNA-1273 have been shown to be safe and effective against coronavirus disease of 2019 (COVID-19). However, results of cohort studies and meta-analyses have indicated that the degree of humoral response to SARS-CoV-2 vaccines in patients with chronic lymphocytic leukemia (CLL) appears to be lower than that observed in the general population. These inadequate responses are mainly related to the disease itself and to the immunosuppressive effect of therapies administered. In the specific context of CLL, enrolling patients with sub-optimal vaccine-response in pivotal vaccine trials could be considered as an appropriate approach to improve response to the COVID-19 vaccine. These clinical trials should also address the issues of regularity and timing of vaccine booster doses or re-vaccinations, especially in patients undergoing therapy with pathway-targeting agents and anti-CD20 monoclonal antibodies. However, since hypogammaglobulinemia is a serious consequence of CLL, patients who do not have a detectable antibody response should be natural candidates for preventive antibody therapy.

KEYWORDS
chronic lymphocytic leukemia, CLL, immunological response, SARS-CoV-2 vaccination, vaccine booster dose

1 | INTRODUCTION

The coronavirus disease of 2019 (COVID-19) has challenged health-care systems worldwide and threatened people's general health[1] and until now, the rapid diffusion of the virus has resulted in over five million deaths worldwide.[2] In this respect, age and comorbidities represent the main risk factors for severe respiratory infection leading to death.[3] Since these conditions frequently recur in patients with hematological malignancies, clinical management of these cases deserves special consideration.[4,5] A recent meta-analysis assessed the risk of death in patients with hematological malignancies and COVID-19.[4] This study involved a sample of 3240 mostly hospitalized patients from three continents and reported a 34% death rate.[4] In another cohort of 740 patients with hematological malignancies from Turkey, the case fatality rate (CFR) was considerably higher than that observed in controls matched for age, sex, and comorbidities (13.8% vs. 6.8%).[6]

In chronic lymphocytic leukemia (CLL), defects in the innate and adaptive immune responses are evident in almost all patients at an early stage of their disease and may account for the relatively high (31%–33%) CFR related to COVID-19 infection.[7-11] In addition, the transition from exclusively relying on chemo-immunotherapy to the more frequent use of treatment with novel molecular-targeted agents may impact the existing immunodeficiency of CLL in a different way than chemotherapy.[8]

The rapid development of anti-SARS-CoV-2 vaccines offers the general population a chance of clinical protection from SARS-CoV-2 infection,[12] although there are some concerns regarding vaccine efficacy in CLL patients.[13-16] The current situation presents a challenge

for hematologists to improve the efficacy of vaccination coverage for patients with CLL.

Here, we review current results and potential strategies to improve anti-SARS-CoV-2 vaccination in patients with CLL, taking into consideration the urgent need to develop adjustments in CLL treatment programs and provide novel approaches to vaccine administration.

2 | IMPACT OF THE CORONAVIRUS DISEASE OF 2019 PANDEMIC ON CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS

In earlier pandemic reports, it was apparent that patients with CLL were more susceptible to SARS-CoV-2 infection and had a higher CFR than the general population.[9-11] The Campus CLL group (identified on its homepage as an "interactive network of Italian specialists active in the field of CLL") reported a 30.4% CFR in a CLL-specific Italian cohort of 46 COVID-19–infected patients.[9] In a joint survey by Campus CLL and the European Research Initiative on CLL (ERIC), involving 190 patients with CLL and COVID-19, the CFR was 32.5%.[10] The study identified advanced age as a factor related to poor clinical outcome of COVID-19 infection, but the impact of comorbidities and hypogammaglobulinemia was only marginal.[10] They also reported the potential benefit of therapy with Bruton kinase (BTK) inhibitors, which was based on the lower rate of hospitalization observed among patients on therapy with ibrutinib.[10] Another study from the USA, involving 198 patients with COVID-19 and CLL, reported a similar CFR (33%); however, therapy with BTK inhibitors did not affect the severity of COVID-19 infection.[11] Finally, a recent retrospective international analysis of 941 CLL patients diagnosed with COVID-19 from the start of the pandemic to 16 March 2021, reported a CFR of 38.4%. The risk of death was higher for older patients and for those with cardiac failure, while untreated CLL patients had a better chance of survival than those recently treated or on current treatment.[17]

An important issue is whether the improvements in clinical outcomes of COVID-19 infection observed in the general population during the second pandemic wave are also evident in patients with CLL.[18] A United States multicenter study analyzed clinical presentation and outcome changes at the different periods of the COVID-19 pandemic by extending the follow-up of previously reported CLL cases and also added patients who were more recently diagnosed.[19] The CFR declined from 35% in the preceding observation period (until December 2020) to 11% in the subsequent observation period.[19] In another study of 60 consecutive patients from a well-defined area in Sweden, outcomes were analyzed during 13 months of the COVID-19 pandemic; in months 1–6 versus months 7–13 of the pandemic, fatalities decreased from 32% to 18%.[20]

In the updated Italian CLL Campus study, the CFR remained stable at 25% throughout the different pandemic phases.[21] These results were confirmed in the expanded retrospective international multicenter study of ERIC and Campus CLL, showing no difference in the CFR during the first and second COVID-19 pandemic waves.[17]

Overall, these studies that captured mostly hospitalized symptomatic CLL patients without accounting for asymptomatic COVID-19 infections basically overestimated patient CFRs by systematically underestimating the total COVID-19 prevalence in patients with CLL. Other potential biases include patient heterogeneity, mostly relating to differences in treatment status, and disparities in the existing healthcare systems of the countries in which patients were encountered.[9-11,19,20]

3 | RESPONSE TO mRNA SARS-CoV-2 VACCINES IN CHRONIC LYMPHOCYTIC LEUKEMIA

Earlier studies have revealed that patients with CLL who developed SARS-CoV-2 infection have inadequate antibody responses, anticipating what was later observed for these patients after COVID-19 vaccination.[19,22] Greenberg and co-workers assessed the extent of antibody response to SARS-CoV-2 vaccines in over 1400 patients with hematological malignancies recruited in a prospective cohort registry in the United States[16]; among the 650 patients with CLL included in this study, only 64.2% developed a positive antibody response after two doses of mRNA SARS-CoV-2 vaccination. It is interesting to note that 28% of the patients who failed to produce a spike antibody response had received no prior therapy in the preceding two years.[16] Two studies conducted in Israel assessed the efficacy of SARS-CoV-2 mRNA vaccines in patients with CLL.[13,14] In the first study, conducted within the ERIC framework and including 167 CLL patients, the antibody response rate was 52.2% in treatment-naïve patients and 16.0% in patients on active treatment.[13] In the second study which enrolled 373 CLL patients from nine Israeli medical centers response rate to the BNT162b mRNA COVID-19 vaccine was 61% in treatment-naïve patients and between 23% and 24% in those treated with BTK and BCL-2 inhibitor agents (BTKi and BCL-2i) respectively.[14] These findings are similar to those observed in a smaller single center series of patients with CLL vaccinated with the BNT162b2 and mRNA-1273 vaccines at the Memorial Sloan Kettering Cancer Center in New York, USA.[15] Investigators in the United Kingdom evaluated spike-specific antibody responses in 299 CLL patients following the first and second COVID-19 vaccination doses (154 with BNT162b2 mRNA and 145 with the ChAdOx1 vaccine).[23] After the first vaccination dose, 34% of patients had spike-specific antibody responses, compared to 94% in healthy recipients. In patients with CLL, however, antibody responses increased to 75% after the second dose compared to 100% in healthy recipients.[23]

In two large trials, lower immunoglobulin concentrations were found to be negative predictors of response to the BNT162b2 mRNA COVID-19 vaccine in patients with CLL, confirming what had previously been reported with the influenza virus vaccine.[13,14,24]

Furthermore, according to the results of three reports presented at the 2021 American Society Hematology meeting, the rate of seroconversion in CLL patients ranged from 52% to 61%.[25-27]

Overall, the rates of seroconversion after COVID19 vaccination indicate a sub-optimal response to SARS-CoV-2 mRNA vaccines in CLL patients.[13-6,22-28] However, as shown in Figure 1 results are heterogeneous. A potential confounder with the results of these studies is the inclusion of CLL patient cohorts which are also heterogeneous in terms of treatment status at the time of COVID-19 vaccination (Table 1). According to the results of a recent meta-analysis, the rate of seroconversion was 73% in treatment-naïve patients but only 29%–32% in patients on therapy with BTKi or BCL2i.[29] These results confirm the detrimental effect of BTKi on the antibody response to de novo antigens, as previously observed with the hepatitis B and influenza vaccine in patients receiving ibrutinib.[30,31] A practical implication is that COVID-19 vaccination should be administered before initiating therapy with a BTKi. Finally, the rate of seroconversion was only 4% in vaccinated patients within 12 months of their last anti-CD20 antibody infusion.[29] Overall, these results suggest that SARS-CoV-2 vaccination should be offered before starting anti-CD20 therapies. Furthermore, when feasible, physicians should delay administering anti-CD20 monoclonal antibodies to prevent vaccination inefficacy.[32]

Another unaddressed issue concerns the relative effectiveness of the SARS-CoV-2 mRNA vaccines in patients with hematological neoplasms compared to matched controls. In a cohort of 32,516 vaccinated patients with hematological neoplasms, which did not include patients with CLL, increased risks of documented COVID-19 infections, COVID-19-related hospitalization, and COVID-19-related deaths were seen when compared to age-, sex-, and comorbidity-matched vaccinated controls.[33] This study indicates that vaccinated patients with hematological neoplasms, particularly those who are on treatment, have worse COVID-19 outcomes than vaccinated individuals with an intact immune system.

4 | HOW TO IMPROVE THE EFFICACY OF SARS-CoV-2 VACCINATION IN CHRONIC LYMPHOCYTIC LEUKEMIA

Since immunocompromised individuals (including CLL patients) exhibit a suboptimal serologic response after two doses of the mRNA SARS-CoV-2 vaccine, they were deemed eligible for a third dose as early as September 2021 in a number of countries. The results of pivotal studies conducted in the setting of patients with oncological and hematological disorders lended support for this approach.[27,34,35] In a small interventional phase one trial involving patients with solid tumors undergoing active anti-cancer therapy, an increase in antibody responses with a median 3-fold increase in virus-neutralizing titers, was observed after the third dose of SARS CoV-2 vaccine.[34] In this regard, the French Innovative Leukemia Organization (FILO) reported that administration of the third dose of the SARS-CoV-2 vaccine achieved effective seroconversion in 13 of 33 (42%) patients considered poor responders after the second dose of vaccine.[27] Furthermore, Kohn et al.[33] analyzed data from 100 patients with Non-Hodgkin Lymphoma and CLL who had received a third dose of the mRNA SARS-CoV-2 vaccine in the context of an observational study and recorded that 50% of the patients failed to show a serologic response to vaccination. Factors associated with poor responses included lower B cell counts and reduced IgG concentrations. It is also of interest to note that an anti-CD20 infusion received within a year prior to the first vaccine injection prevented effective seroconversion in 74% of patients receiving the third dose.[33] In a recently published study, Herishanu et al.[35] evaluated the antibody response

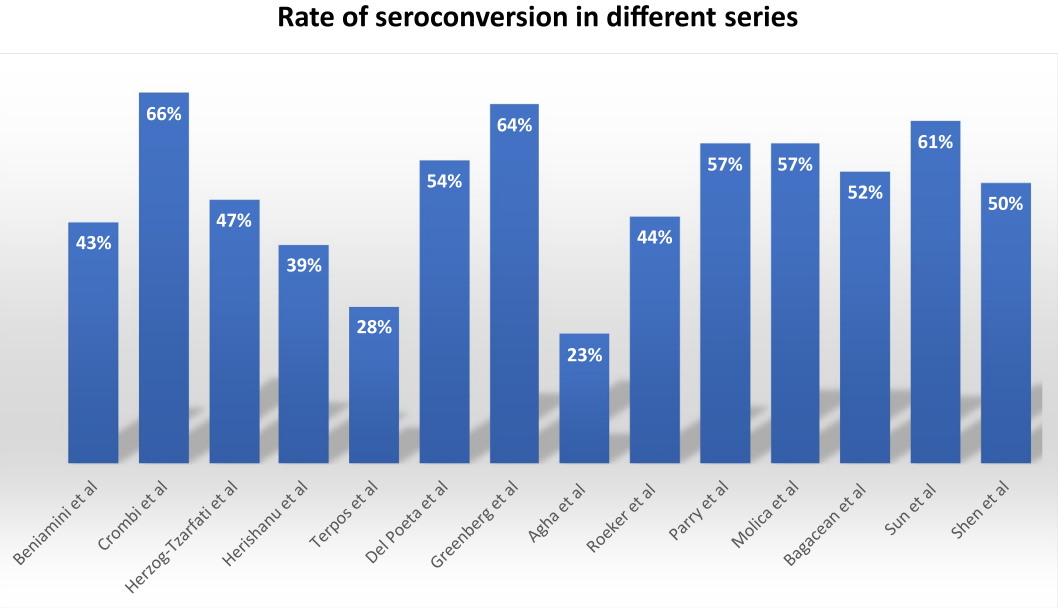

FIGURE 1 Rate of seroconversion in different cohorts of chronic lymphocytic leukemia (CLL) patients who received SARS CoV2 vaccines

TABLE 1 Rate of seroconversion in chronic lymphocytic leukemia (CLL) patients after the second dose of mRNA SARS-Cov2 vaccine stratified according to treatment status

	Rate of seroconversion (%) in CLL pts. After the second dose of mRNA SARS-Cov2 vaccine				
Author	*General population*	*Treatment naive*	*Pts. On tx with ibrutinib single agent*	*Pts. On tx with venetoclax single agent*	*Pts.who received Rituximab < 12 months*
Benjamini et al.	43%	61%	23%	24%	0%
Crombi et al.	67%	100%	50%	0%	0%
Herzog Tzarfati et al.	47%	55%	NA	NA	NA
Herishanu et al.	40%	50%	16%	40%	0%
Terpos et al.	28%	NA	NA	NA	NA
Del Poeta et al.	54%	NA	NA	NA	NA
Greenberg et al.	64%	NA	NA	NA	NA
Agha et al.	23%	NA	NA	NA	NA
Roeker et al.	52%	94%	21%	0%	14%
Parry et al.	75%	73%	NA	NA	NA
Molica et al.	59%	87%	41%	63%	20%
Bagacean et al.	52%	72%	22%	52″	0%
Sun et al.	61%	71%	57%	NA	0%

to a third BNT162b2 mRNA vaccine in 172 patients with CLL who had failed to achieve a humoral response after a standard two-dose vaccination regimen. The antibody response rate was 23.8% and was lower in actively treated patients (12.0%) than in treatment-naïve patients (40.0%) or those not being treated for CLL (40.6%). Of note, only one of the 28 patients (3.6%) treated with anti-CD20 antibodies <12 months before vaccination responded to the BNT162b2 mRNA vaccine.[35]

The incremental benefit of a third vaccine dose in improving the activity of neutralizing antibody responses against the B.1.1.7 (alpha), B.1.351 (beta), and B.1.617.2 (delta) COVID19 variants gave further support for using the fourth dose in patients with blood malignancies.[36] As a result, in several countries, these patients were eligible for a fourth booster dose as early as February 2022.

In theory, the vaccine mixing strategy (a first mRNA vaccine dose and a second non-replicating adenovirus vector dose or vice versa) could be another potential approach to improve vaccine immunogenicity. The Oxford-led Phase II Com-COV trial investigated immune responses in patients who had been given heterologous prime-boost vaccine schedules using AstraZeneca's Vaxzevria (ChAdOx1 nCov-19) and Pfizer's Comirnaty (BNT162b2) COVID-19 vaccines[37]; unfortunately, patients who were immunocompromised or undergoing cancer therapy were not included in this study.

A possible third approach could be to provide CLL patients with a double dose of the mRNA vaccine. In this respect, it is noteworthy that in patients with multiple myeloma, an anti-influenza vaccination strategy at higher dosages leads to greater serologic hemagglutinin inhibition responses and to more durable influenza-specific immunity.[38]

5 | THE MANAGEMENT OF PATIENTS WITH MOLECULAR VARIANTS: BEYOND THE VACCINES

In immunocompromised individuals, the appearance of SARS-CoV-2 strains with immunological escape ability, like the Delta variant (B.1.617.2), is a source of concern.[39] Currently, the extent to which the variant evades vaccine-induced immunity in immunocompromised individuals is still unclear. In a study of 21 healthy controls and 64 patients receiving different immunosuppressive drugs such as rituximab or methotrexate, two doses of BNT162b2 produced a neutralizing response against Alpha and Delta strain of SARS-CoV-2 in 100% of controls. In contrast, only 5% of patients receiving therapy with rituximab developed neutralizing antibodies against the original strain of SARS-CoV-2 and none against the variants.[40]

Recent data suggest that humoral protection against the delta variant is indeed markedly impaired in CLL patients.[41] Overall these results suggest that the BNT162b2 vaccine determines an ineffective humoral response in patients with CLL or in those receiving immunosuppressive therapies, indicating the need for optimizing immune protection in these patient subsets.[40,41]

Results obtained with monoclonal antibodies indicate that complementary approaches to protect immunocompromised patients from SARS-CoV-2 infection more effectively are available.[42] A single subcutaneous dose of casirivimab and imdevimab (REGEN-COV), a combination of the monoclonal antibodies casirivimab and imdevimab, was shown to prevent symptomatic infection throughout a 28-day period.[42] Thus, REGEN-COV could potentially be used for long-term prophylaxis in individuals at risk for SARS-CoV-2 infection who only have limited benefit from vaccination, including patients with CLL. This

combination therapy retains neutralization potency against circulating SARS-CoV-2 variants of concern, including B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta), B.1.429 (Epsilon), and *p*.1 (Gamma), both in vitro and in vivo, and may well protect against a selection of resistant variants.[42,43] However, this monoclonal antibody is not currently an option for many patients due to the striking prevalence *l* of the Omicron variant worldwide. REGEN-COV is indeed inactive against Omicron variants and should only be used in patients with proven infection with other strains of the virus (e.g., Delta variant).[44] Because Omicron has many mutations in the spike protein, only some of the Food and Drug Administration (FDA)-authorized monoclonal antibodies retain the ability to block the virus' potential to infect human cells.[45] In this regard, Evusheld (tixagevimab co-packaged with cilgavimab and administered together) is FDA authorized to prevent COVID-19 in immunocompromised patients (such as blood cancer patients) who are unable to mount an adequate vaccination response.[46] Unfortunately, recent studies indicate that Evusheld (Tixagevimab/Cilgavimab), which induces significant titers against Omicron BA variant (BA).1, apparently failed to neutralize BA.2 spike protein-pseudotyped virus.[47] These data illustrate how difficult it is to produce a pan-neutralizing monoclonal antibody against SARS-CoV-2.

6 | DO CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS WHO RESPOND TO SARS-CoV-2 VACCINE MAINTAIN IMMUNOLOGICAL RESPONSE?

Recent studies on SARS-CoV-2 vaccination in CLL have evaluated the persistence of SARS-CoV-2 antibodies after vaccination.[48,49] Tadmor and co-workers.[48] found that the decline of SARS-CoV-2 antibody levels in CLL patients, assessed after a median time of 100 days after vaccination was no different from that of elderly healthy controls. This observation implies that, despite having lower antibody production, 73% of patients with CLL who respond to the vaccine are able to maintain a potential immunological response. In an extended analysis of the ERIC study, investigators evaluated the decline in SARS-CoV-2 antibody levels six months after the second vaccine dose and demonstrated that serum SARS-CoV-2 antibodies were still detectable in 90.2% of patients with CLL compared to 100% of the controls. However, antibody titers declined dramatically with time, and active therapy was linked to a loss of response.[49]

However, the results of these trials should be interpreted with caution, as the FDA and other organizations advise against using seroconversion levels to assess the efficiency of SARS-Cov2 vaccine or altering preventive measures.[50]

7 | T CELL RESPONSE AFTER SARS-CoV-2 VACCINATION IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS

T cell responses in patients who undergo SARS-CoV-2 vaccination have not been sufficiently studied as yet. In healthy controls, a dynamic and integrated emergence of a spike-specific adaptive immune response has been observed, which is characterized by a T cell response sometimes evident before the development of high levels of anti-RBD antibodies.[51] In this regard, a recent study showed that patients with CLL had a lower T cell response to COVID-19 vaccinations than healthy controls, and only three of 21 (14.3%) CLL patients had both a humoral and a T cellular response.[52] In a report addressing the cellular immunogenicity of COVID-19 vaccinations in patients with CLL, spike-specific T cells were detected in two of 4 patients with anti-spike antibodies and in two of three patients without seroconversion.[25] These results suggest that a cellular response may be observed even in the absence of a humoral response. It is of interest that in another study, CLL patients with a serological response experienced a concomitant increase in CD16/CD56 positive cells ($p = 0.02$).[28] Finally, because most CLL patients have inconsistent immunological responses, humoral responses should not be used as a solitary surrogate sign of protection against the virus in patients with CLL.

8 | CONCLUSIONS

The complex interplay between disease-, patient-, and treatment-related factors makes individuals with CLL particularly susceptible to SARS-CoV-2 infection and sparsely responsive to vaccination. Results of cohort studies and meta-analyses indicate that the degree of humoral response to SARS-CoV-2 vaccines in patients with CLL appears to be lower than that observed in the general population.[13-16,23,25-30] Because of the potential immunosuppressive properties of different agents used to treat CLL, every effort should be made to vaccinate patients who intend to receive a SARS-CoV-2 vaccine (mRNA, replication-deficient, or inactivated) before initiating treatment, unless a delay in initiation of therapy is clinically unacceptable. More data from larger cohorts of CLL patients are sorely needed, and information about various vaccines (both mRNA-based and vector-based) is still required. Future efforts should focus on the frequency of anti–SARS-CoV-2 antibody assessment and the regularity and timing of vaccine booster doses or re-vaccinations, especially in patients undergoing therapy with pathway agents and anti-CD20 monoclonal antibodies.[32] However, since hypogammaglobulinemia is a serious frequent consequence of CLL, patients who do not have a detectable antibody response should be immediate candidates for preventive antibody therapy. However, a recent observation by Merison and Goldman suggests that results relating to *v* the use of the combination of casirivimab and imdevimab (REGEN-COV) in symptomatic individuals should be better supported by the demonstration of absolute risk reduction of developing symptomatic Covid-19.[53]

Finally, despite controversial data, there is no contraindication to the use of complementary measures for infectious prophylaxis in CLL which may include subcutaneous Ig administration.[54] In a small

published series including 10 CLL patients, no patient experienced infectious events nor Covid-19 mediated interstitial pneumonia while on subcutaneous Ig therapy.[54]

Providing close recommendations on how the clinical management of CLL should be modified as a consequence of COVI19 pandemic is beyond the scope of the present review. We remand to specific position papers and guidelines already published, keeping in mind that clinical expertise and medical judgment are still of the utmost importance and should not be replaced.[55,56]

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CONFLICTS OF INTEREST

Authors do not declare any conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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