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On the end of COVID Restrictions: the CLL patient's dilemma

Raymond Vles, CLL Canada Board Chair

1) Introduction

With the steady progress of COVID vaccination, restrictions are being lifted and rules are being eased; gradually in some places, more rapidly in others. This new situation poses a particular problem for us as CLL patients, who, we are told, continue to be at risk from COVID even if we are vaccinated. How do we deal with this return to the nearly normal?

In a peculiar way, life was easier during lockdown. Social distancing and mask wearing were rules that everyone followed, at least in most places. We only had to do what everyone else was doing, perhaps with more rigour, but nothing that would make us stand out.

Now that restrictions are being lifted, we have opportunities to see friends and family, to eat in restaurants, to shop in stores, to go to see a show. Do we turn down these invitations and social occasions, justifying our absence by the risk of COVID and the reduced effectiveness of vaccines in CLL patients? Can we keep asking our spouses and children to reduce their social contacts so we can stay safe? Staying hunkered down has its own costs in terms of mental health and reduced social life, on us but also on the people we care about.

Faced with these issues, I began to ask myself some questions. What exactly is meant by the statement "CLL patients are at higher risk from COVID and are less protected by vaccines"? What kind of risk? The chance of catching the illness or the chance of hospitalization or even death? How much bigger is the risk, compared to those who do not have CLL?

How vulnerable are we? If vaccines provide us with less protection than the general population, how much less?

Is the effectiveness of COVID vaccines sufficiently weak and the consequences of falling ill sufficiently dire to justify continuing the social isolation of the lockdown period?

In an attempt to answer these questions, I read a number of studies, most of them specifically dealing with CLL patients. As we will see, these provide useful information, but no definitive answers.

This led me to reflect on how we can use what information we have to make decisions that make the best of the situation.

What follows are the fruits of my research and reflection. It is not medical advice. It does not pretend to be a comprehensive survey of the scientific literature. Our knowledge evolves as new studies continue to be released every week. Last but not least, the new variants of the virus can change the facts on the ground, as we are seeing at this writing with the Delta variant.

What follows is simply an attempt by one CLL patient to figure out how to make better decisions about balancing the benefits of resuming cherished activities with the protection offered by measures to prevent being infected by COVID.

2) Summary of key points

What follows in this section is a summary of the key points explored in each section of this article.

What are the consequences of catching COVID for CLL patients?

While the chance of CLL patients catching COVID and dying from it is higher than that of the general population, it is only a minority who get infected and of those, a smaller number that are hospitalized and an even smaller number who do not survive.

How much protection should we expect to receive from vaccines?

Some but not all CLL patients are likely to produce antibodies in response to two doses of the vaccine. Table 1, below, summarizes the proportion of CLL patients who produce antibodies, according to their treatment or disease status.

CLL patients who produce antibodies usually produce them in a smaller quantity than does the general population. However, we do not know the level of antibodies necessary to provide immunity, so a smaller quantity may be sufficient to assure protection, or it may not.

How do we manage the unknown?

In the same way as we develop rules of thumb to deal with a 30% or 60% or 80% probability of rain in a weather forecast, some guidelines are proposed to help CLL patients make decisions about which activities to undertake and which to avoid.

Living with uncertainty

We live with risk daily, whether it is in the form of a traffic accident, Lyme disease or any day to day accident. We have learnt to manage these risks by being careful and taking precautions, but not by avoiding activity altogether. In the final analysis, it is this same approach we need to develop as we come out of lockdown and life returns to what it was before the pandemic, or at least, something resembling life as it used to be.

3) What are the consequences of catching COVID for CLL patients

How much more susceptible are CLL patients to being infected by COVID, compared to the general population?

A review of the literature on CLL patients and COVID[1] concluded that

- "a summary of the findings of the selected studies reflects the fact that first the overall prevalence of COVID-19 in CLL patients ranged from 0.5% to 0.7% which is partially higher than the general population, except in epidemic areas".

How do CLL patients fare if they fall ill from COVID 19? I consulted a number of studies:

- Two international studies[2] compiled data on the experience of 609 patients who were hospitalized for COVID. In the three groups of patients examined (one study had 2 groups), the proportion of hospitalized patients in each group who did not survive was 30%, 34% and 37%, about 3 in 10. About two-thirds of hospitalized patients survived, about 6 in 10.

[1] Concurrent chronic lymphocytic leukemia and COVID-19: A comprehensive review of epidemiological, diagnostic, and therapeutic challenges, March 2021
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7962997/

[2] Outcomes of COVID-19 in patients with CLL: a multicenter international experience, September 2020
https://ashpublications.org/blood/article/136/10/1134/461426/Outcomes-of-COVID-19-in-patients-with-CLL-a
Worldwide Examination of Patients with CLL Hospitalized for COVID-19 November 2020
https://ashpublications.org/blood/article/136/Supplement%201/45/471342/Worldwide-Examination-of-Patients-with-CLL

- One of the 2 international studies included 20 CLL patients who were not admitted to hospital. They were younger on average and had less comorbidity (other illnesses) than the hospitalized CLL patients. Only 5% of these patients passed away, 1 in 20.
- Treatment of COVID has improved over time, which has reduced the mortality of CLL patients. In a recent analysis[3] of CLL patients diagnosed with COVID and requiring hospitalization in the period from May 2020 to February 2021, only 20 % did not survive, 1 in 5. Note that a number of other factors could have contributed to the reduced mortality rate, such as younger patients and less severe COVID illness.
- The factors that increase the chance of mortality from COVID are the same for CLL patients as for the general population, namely age (over 75[3]) and comorbidities. Note that CLL patients, as a group, tend to be older and have other illnesses, which may partially account for the higher mortality rate.

To put these numbers in context,

- An analysis[4] of 26 studies in the period of April to December 2020 with a total of 10,769 hospitalized COVID patients from the general population found the mortality rate to be 11.5%, a bit more than 1 person in 10.
- As of July 12, 2021, there were 1,420,531 declared cases of COVID in Canada, representing 3.7% of the population of 38 million people.

It is not the actual numbers in these studies that are significant; rather it is the broad picture they provide: while the chance of CLL patients catching COVID and dying from it is higher than that of the general population, it is only a minority who get infected and of that group, a smaller number that are hospitalized and an even smaller number who do not survive.

The situation we face was succinctly summarized in one article as follows[5]:

> "These data support the notion that some patients (emphasis added) with CLL are at increased risk to develop severe/critical COVID-19. However, this

[3] COVID-19 in patients with CLL: improved survival outcomes and update on management Strategies, July 2021, https://ashpublications.org/blood/article/doi/10.1182/blood.2021011841/476453/COVID-19-in-patients-with-CLL-improved-survival

[4] COVID-19 fatality rates in hospitalized patients: systematic review and meta-analysis May 2021 https://pubmed.ncbi.nlm.nih.gov/33662494/

[5] When CLL meets COVID-19, September 2020 https://ashpublications.org/blood/article/136/10/1115/463533/When-CLL-meets-COVID-19

should not be interpreted as the destiny of CLL patients is to contract severe, deadly COVID-19."

4) How much protection should we expect to receive from vaccines?

The effectiveness of anti-COVID vaccines in the general population was clearly demonstrated in clinical trials and subsequently confirmed by real world experience. However, CLL patients and other patients with compromised immune systems did not participate in these trials, therefore they provide us no guidance on the degree of protection that we can expect from the vaccine.

Furthermore, we hear that vaccinated CLL patients produce few antibodies or none at all. This has led some people to conclude that that vaccines offer little or no protection to CLL patients.

Is the situation really that bad?

The major conclusions can be drawn from the studies I consulted:

- Some but not all CLL patients are likely to produce antibodies in response to two doses of the vaccine. Table 1, below, summarizes the proportion of CLL patients who produce antibodies, according to their treatment or disease status.
- CLL patients who produce antibodies usually produce them in a smaller quantity than does the general population. However, we do not know what levels of antibodies are necessary to provide immunity, so a smaller quantity may be sufficient to assure protection, or it may not.

Table 1: Percent of CLL patients with an antibody response after 2 doses of COVID vaccines

Treatment type or status	% of patients with antibody response per study			
	UK Study[6]	Israeli Study #1[7]	LLS Study[8] (treatment is within past 2 years)	Israeli Study #2[9]
Number of patients in the study	67 (2 doses)	167	650	373
All CLL patients	75%	40%	64%	43%
Less than 65 or 70 years old		52% (<65)		48% (<70)
65 or 70 years or older		34%(>65)		37% (>70)
No treatment yet	83%	55%	83%	61%
On therapy		16%		13%
Off therapy in remission		79%		
Off therapy in relapse		30%		
Previously treated				51%
Multi-drug therapy, including chemotherapy			29%	
Ibrutinib/Acalabrutinib (BTK Inhibitors)	Less likely to make antibodies	16%		18% ongoing 37% past
Venetoclax with or without anti CD20 (rituximab, etc.)		4%		6% ongoing 46% past
Anti-CD 20 (rituximab, obinutuzumab, etc.)		0% Within 12 month 45% More than 12 months		5% Within 12 month 35% More than 12 months

[6] COVID-19 vaccine and CLL patients: An analysis of the first published results, updated 16th June 2021 https://www.leukaemiacare.org.uk/support-and-information/latest-from-leukaemia-care/blog/covid-19-and-cll-patients-an-analysis-of-the-first-published-results/

[7] Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia June 10, 2021 https://ashpublications.org/blood/article/137/23/3165/475742/Efficacy-of-the-BNT162b2-mRNA-COVID-19-vaccine-in

[8] Study from The Leukemia & Lymphoma Society Shows COVID-19 Vaccine Is Safe But 25% Of Blood Cancer Patients Do Not Produce Detectable Antibodies, July 2021, https://lls.org/news/study-leukemia-lymphoma-society-shows-covid-19-vaccine-safe-25-blood-cancer-patients-do-not

[9] Safety and efficacy of BNT162b mRNA Covid19 Vaccine in patients with chronic lymphocytic leukemia, July 2021, PDF file downloaded from https://haematologica.org/article/view/haematol.2021.279196

Treatment type or status	% of patients with antibody response per study			
	UK Study[6]	Israeli Study #1[7]	LLS Study[8] (treatment is within past 2 years)	Israeli Study #2[9]
IgA at normal levels	10-fold increase in the probability of generating antibodies			

The data in Table 1 should be interpreted in the light of the following factors.

There is a lot we do not know about the human immune system. The vaccines may stimulate other mechanisms besides antibodies that provide immunity, such as T cells, which seek out and destroy cells that are already infected with the virus. These are not measured by antibody tests.

Indeed Israeli Study #2 is encouraging in this regard:

- "During the course of the study and 3 months observation period post second vaccination dose we had only 3 (CLL) patients out of 400 (CLL) patients who developed COVID-19 infection following vaccine. One patient acquired the infection between the first dose and the second dose (3 weeks) and two patients after 14 days and 24 days after the second dose, all three of them recovered uneventfully"

Antibodies happen to be an easy parameter to measure, even though we don't know the relationship between the level of antibodies and the degree of protection. Nonetheless, antibody levels are commonly used as surrogate measures of vaccine efficacy and the only studies that have been done are on antibody response.

There are a number of studies ongoing in Canada and elsewhere on the vaccine response of immune compromised patients, including a Canadian study which CLL patients can join by going to their website here. There are also discussions underway regarding the safety and efficacy of providing a third dose of vaccines to immune compromised patients[10].

[10] See CLL Support Health Unlocked forum post "CDC advisory panel discussed third COVID-19 shot for immunocompromised" https://healthunlocked.com/cllsupport/posts/private/146541989/cdc-advisory-panel-discussed-third-covid-19-shot-for-immunocompromised

It should be noted that even in the general population, the vaccines do not provide complete protection. A recent Israeli study[11] concluded that

- "A small minority of fully-vaccinated BNT162b2 recipients might still develop severe SARS-CoV-2 infection despite the vaccine's high effectiveness, with need for in-patient care. This representative cohort of hospitalized patients is characterized by older age, high rate of comorbidities predisposing for progression to severe COVID-19, and a high rate of immunosuppression."

Based on these data, we can conclude vaccines offer some protection from COVID to some CLL patients. Nonetheless, vaccination is recommended for all CLL patients (and their families), since a little protection is better than none at all and some of us will be well protected. The main problem is that we don't know our individual level of protection.

How then can we strike the right balance between our desire for safety and the benefits of taking up activities which we have missed doing for over a year?

5) How do we manage the unknown?

We have seen that, compared to the general population, CLL patients have a somewhat greater chance of catching COVID and if they do, have a somewhat greater chance of hospitalization and death. Being infected and suffering severe consequences is not inevitable, just more likely.

However, all the data we have seen are presented as a proportion of patients in a group. They do not tell us specifically about our own individual vulnerability and level of protection when vaccinated. Thus it is very difficult for an individual patient to use this information to decide whether or not to partake in different activities.

There is a parallel here to weather forecasts. The typical forecast does not say it will rain, nor does it say it will not rain. It will say there is a probability of rain, which it expresses as a percentage 20%, 40%, 80% etc.

How do we as individuals interpret these percentages? Most of use rules of thumb, for example: 30% or less means in won't rain, 40% to 70% means take the umbrella just in case, 80% or above means it will rain.

[11] BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully-vaccinated hospitalized COVID-19 patients in Israel, July 2021, https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00367-0/fulltext

Faced with a probability of rain, we can also adjust our plans. We might postpone an activity to another day or we might have an alternative plan for the activity if it does rain, or perhaps we will take the chance of getting wet.

Of course, the stakes are much higher with COVID and we don't have years of experience like we do with the weather. But the thought process is the same. We need to develop rules of thumb that will help us make decisions about the activities we can undertake and those we should avoid.

Different people will have different rules for different situations, taking into account:

- The benefits of the activity, or put differently, the penalty paid by not doing the activity in terms of mental and physical health, social relations or simply from forfeiting a good time.
- What are our own risk factors, aside from our CLL, such as age, comorbidities[12] (see footnote for more information) and whether we are under treatment?
- What is the likelihood that we will produce antibodies, according to the studies in Table 1 above?
- Is there another way of doing the activity or gaining the benefit we are seeking, one that would result in less exposure to people who might be carrying the virus?
- How prevalent is the COVID virus in the community environment? There are few infections in some regions, while in others they are increasing, in particular due to the Delta variant. More cases mean more potential for exposure to a virus carrier.
- Have the people we will be seeing received two doses of the vaccine? What are the vaccination rates in our area? It is important that family members, loved ones and caregivers get vaccinated.
- Whether the activity is held indoors or outdoors, the latter being safer than the former, because COVID is primarily transmitted by air. In outdoor settings, the wind blows away the virus.

[12] For more information on which health conditions increase the risk of COVID, see the US CDC website article, People with Certain Medical Conditions https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
Statistics Canada has done an analysis of the impact of various comorbidities: COVID-19 death comorbidities in Canada https://www150.statcan.gc.ca/n1/pub/45-28-0001/2020001/article/00087-eng.htm

- Are there ways to minimize exposure to potential virus carriers? These are the measures we have been taking all along: masking, social distancing, etc.
- Can we go out in public at times when fewer people are around? Can we shop when stores are less crowded?
- What is your personal tolerance for risk? Some of us are glass half full optimists, who will be more willing to take some chances in order to enjoy certain activities. Others will prefer to play it safe. There is no one right answer; there is only the answer that is right for each one of us and the people we care about.
- Should we get tested for antibodies? The medical answer to this question is no, because we don't know enough to establish how much protection is provided by a given level of antibodies. A positive result in antibody test could give patients a false assurance that they are protected. However, if as a patient you feel that knowing whether or not you have antibodies will help you make better decisions about which activities you can undertake and which to avoid, there is nothing stopping you from being tested. Make sure it is the spike antibody test.

6) Living with uncertainty

Living with the risk of COVID may seem new, different and dangerous, but every day we live with risk being infected, injured or dying, without thinking too much about it. Accidents do happen: whether we drive, cycle or walk, however we get around there is a chance of being injured. We can injure ourselves while exercising; we can catch Lyme disease by going for a walk in the woods; the list is endless. As CLL patients, we are used to being vulnerable to infections of all kinds.

We have learnt to manage these risks by being careful and taking precautions, but not by avoiding activities and contact with people altogether.

In the final analysis, it is this same approach we need to develop as we come out of lockdown and life returns to what it was before the pandemic, or at least, something resembling life as it used to be.

For more information on CLL, visit cllcanada.org