

Proceedings of the
COVID-19 and Lymphoma Panel:
November 30, 2021

A LYMPHOMA RESEARCH FOUNDATION WHITE PAPER

Introduction

On November 30, 2021, the Lymphoma Research Foundation convened an expert panel of medical and scientific advisors as part of a monthly meeting series, to discuss the current state of research regarding the COVID-19 vaccine and people with lymphoma. The panel discussed recommendations for oncologists caring for people with these cancers, as well as related scientific research and education programming.

This white paper reflects the panel discussion and the state of research as of the date of the above. Oncologists and other healthcare providers are encouraged to consult the most recent guidance from the Centers for Disease Control and Prevention (CDC) and other federal healthcare agencies when making treatment recommendations. Patients should consult with their own healthcare providers when making treatment decisions.

For additional information, members of the lymphoma community are also encouraged to visit the Lymphoma Research Foundation's COVID-19 Learning Center at lymphoma.org/covid19 and/or contact the LRF Helpline at 800-500-9976 or helpline@lymphoma.org.

The Foundation is grateful to the friends and family of Dr. Robert Schroeder whose support made this program possible.

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Presentations

Introduction and Updates

Panel Chair Dr. Andrew Zelenetz, Memorial Sloan Kettering Cancer Center (MSKCC), opened the meeting by providing updates on discussion topics from the previous two Lymphoma Research Foundation (LRF) COVID-19 panel meetings. Data on T cell responses in lymphoma patients are still pending but are expected by the December meeting.

Likewise, emergency use authorization (EUA) of the AstraZeneca monoclonal antibody (mAb) cocktail, AZD7442, is still pending, although authorization is expected shortly based on the results of the phase III PROVENT trial.¹ While the results of this trial were promising, only a small percentage (about 3%) represented truly immunosuppressed patients representative of the populations panelists are interested in. In the meantime, lymphoma patients and their clinicians are likely to be interested in the role of this emerging therapy in COVID-19 prevention, and a consensus on recommendations for its use in these populations is needed. Following authorization, access to the AstraZeneca antibody therapy is expected to be severely limited, with individual institutions receiving less than 5 doses per week. It is unclear how long this will last or how production will be scaled up following authorization, but it is not anticipated that the AZD7442 will be a go-to treatment option for most lymphoma patients right away. Allocation and prioritization are expected to be determined at the state level, though, and a recommendation statement from the panel may help to influence state policy makers.

Lymphoma Research Foundation Patient Programming and Services

Sarah Quinlan, Senior Director of Programs and Strategy, provided an overview of patient programs and support services offered by LRF. Over 50,000 individuals have accessed LRF COVID-specific resources during the COVID-19 pandemic, the most accessible of which is the COVID-19 webinar series. This series began with an overview of COVID-19 and how to protect patients and has since evolved to cover COVID-19 vaccines, third doses, and telehealth. There is also a robust learning center with a variety of resources for diverse types of learners that has been well utilized throughout the pandemic. The learning center can be easily updated with emerging information and to reflect the most common concerns of patients that LRF hears through their helpline service and patient programming. Other services include hosting of a plenary session on COVID-19 during the North American Educational Forum on Lymphoma in October, expansion of financial assistance, and a peer support network.

As vaccines have become available, patients are increasingly interested in understanding what COVID-19 vaccines mean for them, if they are protected, and whether they should pursue antibody testing with their doctor. Most recently, patients have been requesting more guidance on vaccine boosters if they had already received a third dose. Many patients have been asking both LRF and their clinicians whether a fourth dose is right for them. The CDC does provide guidance on a fourth dose for immunocompromised individuals, and while no patients should be ready for a fourth dose at this time (considering authorization of third dose and booster intervals), some patients report that they are hearing about this practice online and in the literature. "Mix and match" vaccination may have also been occurring before it was authorized to try to boost antibody responses. Diminished vaccine responses in lymphoma patients are both poorly recognized and poorly understood, and people are trying many different things in an attempt to protect themselves and their patients.

Other common questions that lymphoma patients have about COVID-19 and vaccination:

- The safety and efficacy of the influenza vaccine in combination with COVID-19 vaccines, boosters, and third doses
- How vaccination should be sequenced after various lymphoma treatments
- Navigating children returning to school and possibly exposing at-risk family members

Across LRF patient services, there has been an uptick in the number of patients treated in community settings rather than academic settings. This is likely due to the virtual format, and as LRF moves forward, expansion of virtual programming is expected to increase accessibility.

Discussion

Omicron and COVID-19 Preventatives

It is expected that moving forward, LRF can anticipate more questions about the emerging Omicron variant and what it means for lymphoma patients, COVID-19 vaccines, and future booster shots. Dr. Mini Kamboj of MSKCC emphasized that any inferences about the impact of mutations in the Omicron variant on the efficacy of COVID-19 preventatives is purely speculation at this point. At this time, the efficacy of all preventatives (mAbs and vaccines) is expected to be impacted. This effect is expected to be strongest for antibody therapies, which target only one or two epitopes. Vaccines, in contrast, elicit polyclonal antibody responses, and are expected to retain higher efficacy. However, whereas mutations in the Delta variant only affected one key neutralizing antibody (nAb)-binding site, all three key binding sites are affected in the Omicron variant. Dr. Kamboj again emphasized that all of this information is speculative and it remains to be seen how this plays out in the real world, but noted that all therapies are expected to continue to provide protection against severe disease.

Identifying Immunocompromised Patients for Pre-Exposure Prophylaxis

As EUA approaches for pre-exposure mAb prophylaxis, there is a need for guidance or recommendations on its use in immunocompromised patients. While the PROVENT trial demonstrated that mAb therapy reduced the risk for COVID-19 and likely severe disease, the patient population representative of truly immunocompromised patients was underrepresented, and panelists emphasized that data in a more at-risk population would be highly valuable. In the interim, it is expected that LRF will be inundated with questions about the use of pre-exposure prophylaxis in lymphoma patients, and that organization needs to be prepared for what should be said. Recommendations from the CDC are that anyone who is profoundly immunosuppressed should receive mAb prophylaxis, regardless of vaccination status. However, from a practice standpoint, there is no clear definition of what constitutes “profound” immunosuppression. When the third vaccine dose was authorized, many people were labeled immunocompromised who maybe should not have been because there was a lack of quality guidance.

Any guidance on the identification of immunocompromised patients for pre-exposure prophylaxis should be both practical and scientifically founded. However, the lack of evidence available in lymphoma patients on T cell responses to vaccination and universal B and T cell thresholds that confer protection. Previous work is available in transplant patients that, while not directly applicable, may be used to infer scientifically reasonable B cell thresholds needed for the production of an immune response. Additionally, approximately half of solid organ transplant recipients who received an mRNA COVID-19 vaccine developed a productive T cell response in the absence of any detectable B cell response.² If protective thresholds for B and T cell populations could be established, a more precise definition of immunosuppression could be made, with the potential to even tease apart different levels of immunosuppression (mild, moderate, severe). However, as is, there is no robust and universally available method of measuring these responses, and protective thresholds remain to be established.

Rather than attempting to quantify individual responses, panelists agreed that a simpler, more standardized recommendation for the use of pre-exposure prophylaxis in lymphoma patients was more appropriate at this time. For example, for patients who have received active systemic chemotherapy within the last 6 months, it can be assumed that they are unprotected and that mAb prophylaxis should be initiated. Many patients have not reconstituted their B cell populations by 6 months, though, and may remain unprotected up to 2 years following discontinuation of anti-CD20 therapy.³ For these patients, testing of spike Ab levels may be considered as a recommendation. While it may be unclear what constitutes a “positive” B cell response, it is clear that patients are unprotected in the absence of a response, and commercially available anti-spike Ab assays are readily available.

Blocking and Neutralization Assays

Seroconversion status can be obtained rather quickly (within hours to a couple of days). However, blocking or neutralization assays take longer to complete (4 to 5 days), which can be stressful for patients to “wait and see”. Research from Dr. David Knorr’s lab suggests that antibody titers tend to correlate with the presence of neutralizing antibodies,⁴ but this is not always the case. Additionally, these studies were done using the original SARS-CoV-2 strain, and although anecdotally similar trends have been observed with the Delta variant, it is unclear how well these measures correlate across new and emerging strains. Neutralization and blocking can also be clinically challenging to measure, and without clear actionable recommendations based on results, many have been reluctant to complete these assays in the clinic.

Engaging the Centers for Disease Control and Prevention (CDC)

Several panelists noted that they have attempted to engage officers at the CDC throughout the COVID-19 pandemic. While these officers likely understand that more nuanced recommendations are needed for truly immunosuppressed patients, lymphoma patients represent a small minority of the population, and there may be a fear of diluting “big picture” messaging surrounding the importance of vaccination. While it may be difficult to coordinate, panelists feel that there would be value in engaging a CDC public health officer to participate in an upcoming or special meeting of the LRF COVID-19 and Lymphoma Panel.

Recommendations

As pre-exposure prophylaxis therapy nears authorization, LRF can expect to receive an increasing volume of inquiries related to its use in lymphoma patients. Clear guidance on what is known, what is not known, and current recommendations for its use in immunosuppressed patients is needed. It is recommended that LRF develop a first draft of these recommendations based on the conversations from this and last month's meetings, which can then be circulated for review and approval. Once these recommendations are finalized, they should be added to LRF's patient-facing resources for easy access. When drafting these recommendations, it is important to keep in mind that guidance should be simple, scientific, and practical, and that early intervention should be emphasized for best outcomes. A lack of clear, clinically actionable recommendations may result in the underutilization of an effective prophylactic option for many high-risk patients.

Although individual panelists have struggled to connect with public health officers at the CDC, they agreed that LRF may have better luck engaging key decision makers at the organization. Ahead of next month's meeting, it is recommended that LRF attempt to invite CDC public health officers to participate in the next meeting (December 21, 2021) or in a special meeting dedicated to discussion and review of COVID-19 vaccination and prophylaxis protocols for immunocompromised individuals. Such efforts may be difficult, but panelists would be grateful to include these officials as part of ongoing discussions.

In addition, the 63rd American Society of Hematology (ASH) Annual Meeting is scheduled for December 11-14, 2021 and will be hosted in a hybrid format including both in-person and virtual participating options.⁵ Panelists expect that there will be several meaningful presentations regarding COVID-19 in patients with hematologic malignancies. Dr. Zelenetz noted that he plans to try to attend and will attempt to bring back key references to discuss, but LRF may consider having another representative participate who can summarize relevant research that may support ongoing and future discussions for the panel.

References

1. AstraZeneca COVID-19 and RSV presentations at IDWeek 2021 will showcase scientific progress in infectious diseases [press release]. September 27, 2021 2021.
2. Hall VG, Ferreira VH, Ierullo M, et al. Humoral and cellular immune response and safety of two-dose SARS-CoV-2 mRNA-1273 vaccine in solid organ transplant recipients. *Am J Transplant*. 2021.
3. Shee T, Shankar V, Czerwinski DK, et al. Abstract 2064: Time Since Last Anti-CD20 Treatment Is a Major Determinant of Sars-Cov-2 Vaccine Response in a Large Cohort of Patients with B-Cell Lymphoma. ASH 2021.
4. Chung DJ, Shah GL, Devlin SM, et al. Disease and therapy-specific impact on humoral immune responses to COVID-19 vaccination in hematologic malignancies. *Blood Cancer Discovery*. 2021:bloodcandisc.0139.2021.
5. American Society for Hematology. ASH Annual Meeting & Exposition. <https://www.hematology.org/meetings/annual-meeting>. Accessed December 8, 2021.



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