LYMPHOMA
RESEARCH · FOUNDATION

Proceedings of the COVID-19 and Lymphoma Panel: September 29, 2021

A LYMPHOMA RESEARCH FOUNDATION WHITE PAPER

Introduction

On September 29, 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.

Panel Participants

Ash A. Alizadeh, MD, PhD
Stanford University School of Medicine

Bruce D. Cheson, MD, FACP, FAAAS, FASCO
LRF Scientific Advisory Board
Panel Steering Committee Member

Leo I. Gordon, MD, FACP
Robert H. Lurie Comprehensive Cancer Center of Northwestern University
Panel Steering Committee Member

Thomas M. Habermann, MD
Mayo Clinic, Rochester

Mini Kamboj, MD
Memorial Sloan Kettering Cancer Center
Panel Steering Committee Member

David Knorr, MD, PhD
Memorial Sloan Kettering Cancer Center

Brian K. Link, MD
University of Iowa

Lindsay M. Morton, PhD
National Cancer Institute
Panel Steering Committee Member

Kanti R. Rai, MD
Hofstra Northwell School of Medicine

David W. Scott, PhD, MBChB
George Washington University

Laurie Sehn, MD, MPH
BC Cancer (Vancouver)
Panel Steering Committee Member

Sonali M. Smith, MD
The University of Chicago
Panel Steering Committee Member

John Timmerman, MD
UCLA Oncology Center

Andrew D. Zelenetz, MD, PhD
Memorial Sloan Kettering Cancer Center
Panel Steering Committee Chair

Presentations

Background: Antibody Production

Dr. David Knorr of Memorial Sloan Kettering Cancer Center (MSKCC) opened the meeting by providing an overview of antibody structure and function, and the role of immune cells in antibody production. Antibodies are bifunctional molecules with a bivalent fragment antigen-binding (Fab) domain, which recognize targets of interest, and a conserved fragment crystallizable (Fc) region, which dictates effector functions. Fc-mediated activity is essential for regulation of a variety of innate and adaptive immune processes, including cellular cytotoxicity, phagocytosis, uptake of antibody-coated immune complexes, dendritic cell maturation, and antigen presentation. The goal of vaccination is to develop an immune response in which antigen-specific B cells interact with antigen-specific T follicular helper (TFH) cells, driving an iterative process in which B cells undergo repeated class switching and hypermutation to generate high-affinity, protective antibodies. During this process, post-translational modifications are made to the core Fc structure (ie, an IgG subclass domain and a conserved sugar molecule), which can lead to the generation of inflammatory or anti-inflammatory IgG molecules.

Dr. Knorr presented research from his lab on the dynamics of typical antibody responses in healthy individuals following influenza vaccination.[1] At 1-week post-vaccination, there is a significant increase in sialylated and fucosylated forms of Fc, which correlates with an enhanced plasmablast response. Within the expanding plasmablasts, there is increased expression of ST6Gal1, the enzyme responsible for the post-translational modification of Fc sialylation, during the development of antigen-specific B cells. Changes to the Fc glycan dictate both antibody titer and affinity, and hypersialylated Fc exhibits increased affinity for type 2 receptors, including CD2[3]. This stimulates in the upregulation of Fc receptors and increases the threshold for B cell selection, resulting in the generation of high-affinity IgG. CD2[3] is overexpressed in various types of leukemias and lymphomas, but the impact of this on immune complex signaling in the context of vaccination is unknown.

Antibody responses that occur within germinal centers are critically dependent on interactions between B cells and TFH cells. In oncology, the highest levels of several immune checkpoints are often observed within the germinal center, pathways that are now routinely blocked to exert an anti-tumor effect. Dr. Knorr proposed that vaccination can be used as a model to understand the relationships between these cells and answer questions about what happens in these systems when B cells are depleted. In addition to understanding the effects on vaccine response, the information may be able to be utilized to enhance anti-tumor responses as well.

Immune Modulation and Viral Immunity

Dr. Knorr described ongoing research from his lab, done in collaboration with Dr. Ramin Herati at New York University and John Wherry at UPENN, utilizing influenza vaccination and PD-1 blockade to understand the impact of immune modulation on normal human immunity. In healthy adults, there is a 1- to 1.2-fold expansion in the TFH cell population at 1-week post-vaccination. However, with immune checkpoint (PD-1) blockade, which disrupts interactions between TFH and B cells, this population is enhanced, such that there is a significantly higher amount of TFH cells found in the peripheral blood. A similar trend was observed in the plasmablast population, driven by a rise in cells with a memory B cell phenotype. In addition to the cellular responses, antibody responses to vaccination were examined. High hemagglutination inhibition (HAI) titers, which are indicative of how much virus can be neutralized, were significantly lower at baseline for anti-PD-1-treated individuals compared with untreated, healthy controls. However, by 1-week post-vaccination, these levels were able to be rescued, and remained at normal levels through later time points. Levels of the CXCL13, which is responsible for bringing CXCR5-expressing TFH and germinal center B cells together, also dramatically increased in patients treated with PD-1 blockade, suggesting a robust chemokine response as well.

Collectively, these results suggest that patients that are on PD-1 blockade are not at overt risk for annual infection with influenza and do benefit from vaccination. Although experiments of this nature are ongoing for COVID-19 vaccination, these results may have important implications in this context as well. However, Dr. Knorr noted that an important caveat of this research is that there is significant pre-existing immunity against influenza, whereas SARS-CoV-2 is a truly novel antigen. In a case report examining immune responses to COVID-19, large expansions of plasmablasts and TFH cells are also observed in the early phases of active infection, as was seen in the influenza vaccine model.[2]

Immunity in Patients with Hematologic Malignancies
A variety of drugs used to treat hematologic malignances (eg, rituximab, daratumumab, Bruton's tyrosine kinase [BTK] inhibitors) target the TFH-B cell axis or downstream signaling pathways and may affect responses to SARS-CoV-2 immunity. Some of these immune effects have been known for some time. For example, in patients treated with rituximab, there is a prolonged suboptimal response to vaccination, which lasts for up to 6 to 12 months post-treatment. Dr. Knorr shared that clinically, it has been see that some patients who have received rituximab have been getting COVID-19 over 12 months after ending treatment, even after vaccination or prior COVID-19 exposure. Diminishing effects on immune responses to COVID-19 and other vaccinations, including pneumococcal and influenza, have also been observed in patients treated with BTK inhibitors due to an inability to mount a normal B cell response. The ability to identify a pharmacodynamic biomarker of response to vaccination would be important for these patient populations to help guide vaccination and booster strategies.

Dr. Knorr reiterated that with COVID-19, the lack of pre-existing immunity is an important consideration. Recent research examining vaccination responses against a novel antigen (hepatitis B) vs one with pre-existing immunity (zoster) in patients with chronic lymphocytic leukemia (CLL) found that BTK inhibition significantly diminishes the immune response to a novel antigen compared with untreated controls.[2] Having some pre-existing immunity though, even in the setting of BTK inhibition, meant that patients were able to mount an adequate, albeit somewhat diminished, immune response. These results have important implications for patients with hematologic malignancies who are on therapy when considering COVID-19 vaccination strategies. Inhibition of BTK signaling is not sustained for very long when patients are taken off the drug, indicating that withholding treatment may be a viable therapeutic strategy when considering vaccination. This strategy is potentially supported by evidence of diminished responses to COVID-19 mRNA vaccination in CLL patients on active treatment with either BTK inhibitor or venetoclax ± anti-CD20 therapy compared with either treatment-naïve patients or patients off-therapy in either remission or relapse.[4]

Dr. Knorr concluded the research presentation with a discussion of an ongoing collaborative project at MSKCC across the fields of leukemia, lymphoma, and multiple myeloma, designed with significant input from infectious disease colleagues, to understand COVID-19 mRNA vaccine response in patients with heme malignancies.[4] Compared with healthy controls, patients with hematologic malignancies have diminished anti-spike antibody responses, regardless of disease type. Patients with prior COVID-19 infection tend to have a robust memory B cell response, however some patients with hematologic malignancies still don't mount an adequate immune response after either vaccine dose. Again, hematologic patients who were off treatment were found to mount a stronger response to vaccination at later time points (ie, after the second dose) than those who were on active treatment. Diminished antibody responses were seen across disease states regardless of treatment type; however, in multiple myeloma, current data suggest that treatment with immunomodulatory drugs may help restore or maintain vaccine responses. Dr. Knorr added that the results did not examine combinatorial effects and noted that it was important to consider that there are many patients in trials who are treated with more than one therapeutic agent. The long-term effects of vaccination in these patients are unclear, and these results highlight the need to vaccinate patients prior to initiation of therapy.

Neutralization capacity correlated with antibody levels, and Dr. Knorr noted that although it would be useful to identify an adequate range of antibody titers that is predictive of effective neutralization activity, a strong enough biomarker to dictate vaccine approaches has not yet been identified.

Additional Insights From COVID-19 Immune Responses
Additional trends in COVID-19 vaccination responses were observed among healthy individuals that may have important implications when considering vaccine strategies. For example, female patients had stronger immune responses than male patients, and immune responses decreased with age. Additionally, higher antibody titers were observed at 3 months after the first vaccine dose for the mRNA-1273 (Moderna) vaccine compared with the BNT162b2 (BioNTech-Pfizer) vaccine. This may be related to higher total doses of antigen administered with the mRNA-1273 vaccine, but Dr. Knorr commented that it is interesting to consider how the timing of the second dose may affect responses. A second dose given later after initial vaccination may allow more time for the germinal center response, which may last up to 15 weeks, allowing for a more adequate primary response before boost. This is supported by some experience reported from the United Kingdom, which extended out booster doses during early vaccination efforts.

Results from similar analyses of COVID-19 vaccine humoral responses have also been reported in hematologic transplant patients.[6]

Discussion

Overall, panelists were very intrigued by the data presented and the potential implications for COVID-19 vaccination in patients with hematologic malignancies. Similar analyses using the COVID-19 delta variant are eagerly anticipated.

Managing Patients with Inadequate Immune Responses
Both patients and clinicians are unsure of the benefits of a third COVID-19 vaccine dose in patients without an adequate response to the initial doses of mRNA vaccine. The updated recommendations from the CDC and United States Food and Drug Administration (FDA) helped protect patients by allowing them to receive a third dose, but limited data are available in patients with hematologic malignancies. Based on the available evidence, it remains unclear when a third dose is needed and when it is effective, and gathering the data to answer these questions is challenging now that boosters are easily available without clinical input. In the absence of data showing that it is harmful to give boosters, panel members from MSKCC noted that they favor providing immunocompromised patients such as those with hematologic malignancies a third dose. Additionally, there has been increasing interest outside of the United States in using a heterologous vaccination approach (i.e., boosting with a non-mRNA vaccine) to achieve a more robust immune response.

Panelists noted that it remains clear that there will be some patients who, regardless of vaccination, will be unable to mount an adequate immune response. For these patients, passive antibody therapeutic strategies may be an option, of which two have already received approval. There is also interest in whether this strategy can be employed prophylactically, and a number of trials have been developed across the country to address this question. Some antibody-based therapies are longer lived, and the question remains of whether these can be used as pre-exposure prophylaxis against seasonal infections for people without immunity.

Lenalidomide and Immunomodulatory Drugs
Panelists were interested in learning more about the effects of lenalidomide on immune responses, and how it maintained vaccine immune responses. Preliminary results suggest that immunomodulatory drugs may have a positive impact on TFH and possibly B cell responses. Up until recently, lymphoma patients would have received lenalidomide as a monotherapy, but now many are also on anti-CD20 antibody therapy. Theoretically, these patients should receive the same benefit, as the hypothesized effects are an independent T cell effect, but more data are needed to support this. Additional tools can be leveraged to examine specific T cell responses in these patients, particularly in the absence of B cells. Additionally, if it can be determined how long lenalidomide treatment is needed to augment the vaccine response, panelists envisioned a therapeutic strategy in which lenalidomide was given for some amount of time prior to initiating anti-CD20 therapy to maintain immune responses.

Remaining Questions
Panelists outlined several remaining questions based on the data provided:

❚ Do drug holidays work to help achieve adequate immune responses? If so, how long do they have to be? Do these differ between specific agents?

❚ Is there value in using specific lymphocyte subsets to predict B and T cell responses to vaccination? What cutoffs can be used to decide whether patients will benefit from vaccination?

❚ How can we measure T cell responses? If patients have adequate T cell responses, is passive antibody therapy necessary?

❚ When considering the influenza data, was the observed boost in immune response due not only to previous influenza exposure, but previous exposure to influenza vaccines over the years? Might this provide justification for more frequent vaccinations against COVID-19?

Recommendations

Panelists agreed to circulate the data provided in the first panel, along with a list of key questions, for further review prior to discussion. The implications of the presented B cell data and potentially strategies for how to respond will be discussed at the second meeting (October 19, 2021). At this time, additional data on T cell responses will also be presented if available, with plans to develop recommendations based on these data in subsequent meetings (November 30, 2021 and December 21, 2021). Panelists intend to potentially use the Lymphoma Research Foundation as a central point to help generate additional data needed to answer the remaining questions. Ahead of future meetings, identification of key resources to support these efforts is recommended.

References

1. Wang TT, Maamary J, Tan GS, Bournazos S, Davis CW, Krammer F, Schlesinger SJ, Palese P, Ahmed R, Ravetch JV. Anti-HA Glycoforms Drive B Cell Affinity Selection and Determine Influenza Vaccine Efficacy. *Cell*. 2015 Jul 2;162(1):160-9. doi: 10.1016/j.cell.2015.06.026. PMID: 26140596; PMCID: PMC4594835.

2. Thevarajan I, Nguyen THO, Koutsakos M, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. *Nat Med.* 2020;26(4):453-455.

3. Pleyer C, Ali MA, Cohen JI, et al. Effect of Bruton tyrosine kinase inhibitor on efficacy of adjuvanted recombinant hepatitis B and zoster vaccines. *Blood*. 2021;137(2):185-189.

4. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood*. 2021;137(23):3165-3173.

5. 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.

6. Tamari R, Politikos I, Knorr DA, et al. Predictors of Humoral Response to SARS-CoV-2 Vaccination after Hematopoietic Cell Transplantation and CAR T Cell Therapy. *Blood Cancer Discovery*. 2021:bloodcandisc.0142.2021.

LYMPHOMA

RESEARCH · FOUNDATION

National Headquarters
Wall Street Plaza
88 Pine Street, Suite 2400
New York, NY 10005

LRF Helpline
(800) 500-9976
Helpline@lymphoma.org

lymphoma.org