International Waldenstrom's Macroglobulinemia Foundation's Official Statement Concerning Prioritizing Waldenstrom's Macroglobulinemia Patients When Triaging Care During the COVID-19 Pandemic

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Dear Healthcare Provider,

Thank you for all you are doing. The International Waldenstrom's Macroglobulinemia Foundation recognizes the present COVID-19 pandemic can strain limited healthcare resources and may demand thoughtful and ethical triage of the healthcare team's time and resources. There are mounting data suggesting an increased risk of COVID-19 infection in adults with cancer, and that patients with cancer have an increased risk of severe complications after contracting COVID-19,[1] but it not clear if this is related to the increased age of cancer patients.[2,3] Waldenstrom's macroglobulinemia (WM), a subset of lymphoplasmacytic lymphoma (LPL), is a hematologic malignancy of the B-cells. It has been reported that ~15%-25% of patients with hematologic malignancies fail to make anti-spike (anti-S) antibodies in response to full dosing of SAS-CoV-2 mRNA vaccines.[4,5] Patients with B-cell malignancies are at the highest risk of not making anti-S antibodies. Although the complete immune response in B and T cells is not fully understood, these findings suggest that seronegative patients or those with reduced immune response to vaccination may be vulnerable to breakthrough infections. Patients with B cell malignancies are of particular concern because, in the pre-vaccine period of the pandemic, some patients with blood cancer who contracted COVID-19 had prolonged, severe infections; generated variant strains[6] and demonstrated significantly higher mortality rates compared to the general population.[7,8]
Given that WM is an indolent non-Hodgkin's lymphoma with distinct features and treatment options,[9] the International Workshop on Waldenström Macroglobulinemia has provided consensus recommendations which are listed below.[10] In particular, the immunomodulatory and anti-inflammatory responses of Bruton tyrosine kinase inhibitors (BTKi), and the potential risks of cytokine storm and hyperviscosity caused by BTKi withdrawal in worsening late complications of COVID-19 are highlighted. These international consensus recommendations are made based on current understanding of WM and of COVID-19 infection and must be interpreted and applied in the context of new data, as they become available.

- The median age of presentation of WM is in the sixth and seventh decade of life, and patients are therefore at higher risk of developing severe complications from COVID-19 infections.[1]
- The risk of COVID-19 infection and of morbidity and mortality in WM for various treatment regimens is unknown. There are currently no concrete data that suggests that cancer therapies should be ceased in patients on active treatment. However, treatment decisions require consideration based on patient's clinical status, degree of response, and risk of developing COVID-19 infection.

- Patients receiving BTK inhibitors should be continued on their current therapy due to the possibility that these agents may reduce rates of COVID-19 pulmonary manifestations.[11,12] Cessation of treatment also has a high risk of causing IgM rebound, potentially increasing risk of constitutional symptoms (which can be confused as COVID-19 related) and symptomatic hyperviscosity.[13]

- Trial monitors and/or sponsors should be contacted to seek advice on management of patients who are ~~i~~n clinical trials.

- Serological lab tests for COVID-19 analyze COVID-19 specific IgM and will not be affected by the total IgM or paraprotein levels.

- Patients on rituximab or with hypogammaglobulinemia have been reported to have a severely blunted humoral response to vaccination,[14,15] and the Panel recognized that there is a possibility of a false negative serological test after exposure to the COVID-19 virus in WM patients.

- Testing and management of COVID-19 should be as per existing protocols within each country.

- Treatment of underlying WM will depend on the clinical condition of patient and type of treatment (e.g., continuation of BTK inhibitors treatment is recommended at this stage in patients who are mildly symptomatic, or asymptomatic).

- For more symptomatic patients, the dilemma is between a traditional approach to cease anti-cancer treatment, and of continuing treatment. This is especially pronounced for BTK inhibitors because of the potential immunosuppressive effect reported with ibrutinib.[15,19] This may be of potential danger in mounting a response to COVID-19 but may be of benefit in reducing late and severe immune-mediated complications. There are preliminary data on the anti-inflammatory effects of Ibrutinib in murine lung,[12] including suppression of inflammatory cytokines such as TNF, IL2RA, and CXCL13,[16] and down regulatory effects on T cells and macrophages.[17] A recent paper has shown that use of Ibrutinib in a small number of WM patients is associated with a low rate of COVID-19 related pulmonary complications.[11] There is the additional risk of developing IgM flare and potentially worsening the clinical situation because of a cytokine storm if BTK inhibitors are withheld.[18]

Other recommendations, not included in the International Workshop on Waldenström Macroglobulinemia consensus recommendations

- Dosing of venetoclax, ibrutinib, acalabrutinib, or zanubrutinib should be adjusted or held in patients requiring Paxlovid (nirmatrelvir and ritonavir tablets) for Covid-19 infections due to potential clinically significant drug interactions leading to an increased concentration of the anticancer drugs. After discussion with the patient's hematologist/oncologist, if clinically indicated, the BTK-inhibitor could potentially be held or the dose adjusted to allow for treatment with Paxlovid if necessary.

- Treatment changes may be required for patients receiving steroids as part of the treatment regimen for WM. Steroid dose holds or steroid cessation may be indicated.

- Although no drug interactions have been identified for Lagevrio (molnupiravir), it is critical to consult with the patient's hematologist/oncologist before administration of this nucleoside analogue.

- If the patient is at risk for serious COVID-19 and has tested positive by PCR or been in close contact with someone who has recently tested positive, monoclonal antibody (mAbs) infusion may be indicated.

- Close follow up, multidisciplinary approaches to management and agility in decision making is required.

It is also noteworthy that a 2021 study, funded by the Leukemia & Lymphoma Society (LLS), in a small cohort of 49 patients with B-cell malignancies, including 7 patients with WM, 35% were non-responders, who were seronegative after initial vaccination and demonstrated no change in antibody level after the booster vaccination.[19] Additionally, many patients with WM are on Bruton tyrosine kinase inhibitors (BTKi). The use of BTKi has been shown to correlate with a lack of response to vaccination. Several of the treatment regimens for WM include rituximab alone or in combination. Recovery of B-cells begins 6-9 months after rituximab therapy.[20] The data from LLS data suggests that recent treatment regimens containing the anti-CD20 antibodies may suppress the response to booster vaccination.

Preliminary data (from a presentation at the American Society of Hematology/ASH December 2021) of 141 patients suggest impaired serologic responses following COVID-19 vaccines (Pfizer/BioNTech, Moderna or Johnson & Johnson) in patients with multiple myeloma and WM. Overall, WM patients showed more severe impairment of COVID-19 S antibody responses. Moderna elicited significantly higher spike antibody response rates compared to other vaccines. Age 75+ years was associated with lower rates of spike antibody response. Most previously untreated WM patients achieved S antibody responses, however suboptimal antibody responses were seen in WM patients who received rituximab within 12 months or on active BTK inhibitors.[21] Further understanding of the immunological response to COVID19 vaccination is needed to clarify patients risks, and necessity for booster or alternative protective measures against COVID-19.

Therefore, please consider the immunocompromised status of patients with Waldenstrom's macroglobulinemia and prioritize their assessment and management when they are asking for your help with a potential or established COVID-19 infection. Immunocompromised patients (such as those with WM) are likely to be amongst those who would most benefit from the early use of SARS-CoV-2 directed monoclonal antibodies to prevent serious infection or hospitalization, and who also might benefit from high titer convalescent plasma used early in hospitalization. Thank you for all your care and dedication in these unprecedented times. We are all in this together.

The IWMF thanks Dr. Shayna Sarosiek, Dana-Farber Cancer Institute, for her review of this letter.

Thank you again for all you do for our patients,

Newton Guerin, President & CEO
International Waldenstrom Macroglobulinemia Foundation

References:

1. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol.* 2020;21:335–337.
2. Lian J, Jin X, Hao S, et al. Analysis of Epidemiological and Clinical features in older patients with Corona Virus Disease 2019 (COVID-19) out of Wuhan. *Clin Infect Dis.* 2020; March 25.
3. Wang H, Zhang L. Risk of COVID-19 for patients with cancer. *Lancet Oncol.* 2020;21:e181.
4. Greenberger, L.M., Saltzman, L.A., Senefeld, J.W., Johnson, P.W., DeGennaro, L.J., and Nichols, G.L. (2021). Antibody response to SARS-CoV-2 vaccines in patients with hematologic malignancies. *Cancer Cell* 39, 1031–1033.
5. Griffiths, E.A., and Segal, B.H. (2021). Immune responses to COVID-19 vaccines in patients with cancer: Promising results and a note of caution. *Cancer Cell* 39, 1045–1047.
6. Corey, L., Beyrer, C., Cohen, M.S., Michael, N.L., Bedford, T., and Rolland, M. (2021). SARS-CoV-2 variants in patients with immunosuppression. *N. Engl. J. Med*. 385, 562–566.
7. Bakouny, Z., Hawley, J.E., Choueiri, T.K., Peters, S., Rini, B.I., Warner, J.L., and Painter, C.A. (2020). COVID-19 and cancer: current challenges and perspectives. *Cancer Cell* 38, 629–646.
8. Vijenthira, A., Gong, I.Y., Fox, T.A., Booth, S., Cook, G., Fattizzo, B., Martı´n-Moro, F., Razanamahery, J., Riches, J.C., Zwicker, J., et al. (2020). Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood* 136, 2881–2892.
9. Leblond V, Kastritis E, Advani R, et al. Treatment recommendations from the Eighth International Workshop on Waldenstrom's Macroglobulinemia. *Blood.* 2016;128:1321–1328.
10. Talaulikar, D., Advani, R. H., Branagan, A. R., Buske, C., Dimopoulos, M. A., D'Sa, S., Kersten, M. J., Leblond, V., Minnema, M. C., Owen, R. G., Palomba, M. L., Tedeschi, A., Trotman, J., Varettoni, M., Vos, J. M., Treon, S. P., Kastritis, E., & Castillo, J. J. (2020). Consensus Statement on the Management of Waldenström Macroglobulinemia Patients During the COVID-19 Pandemic. *HemaSphere*, *4*(4), e433.
11. Treon SP, Castillo J, Skarbnik AP, et al. The BTK-inhibitor ibrutinib may protect against pulmonary injury in COVID-19 infected patients. *Blood.* 2020;135:1912–1915.
12. de Porto AP, Liu Z, de Beer R, et al. Btk inhibitor ibrutinib reduces inflammatory myeloid cell responses in the lung during murine pneumococcal pneumonia. *Mol Med.* 2019;25:3.
13. Gustine JN, Meid K, Dubeau T, et al. Ibrutinib discontinuation in Waldenstrom macroglobulinemia: Etiologies, outcomes, and IgM rebound. *Am J Hematol.* 2018;93:511–517.
14. Md Yusof MY, Vital EM, McElvenny DM, et al. Predicting Severe Infection and Effects of Hypogammaglobulinemia During Therapy With Rituximab in Rheumatic and Musculoskeletal Diseases. *Arthritis Rheumatol.* 2019;71:1812–1823.
15. Intongkam S, Samakarnthai P, Pakchotanon R, et al. Efficacy and Safety of Hepatitis B Vaccination in Rheumatoid Arthritis Patients Receiving Disease-Modifying Antirheumatic Drugs and/or Biologics Therapy. *J Clin Rheumatol.* 2019;25:329–334.
16. Niemann CU, Herman SE, Maric I, et al. Disruption of in vivo Chronic Lymphocytic Leukemia Tumor-Microenvironment Interactions by Ibrutinib--Findings from an Investigator-Initiated Phase II Study. *Clin Cancer Res.* 2016;22:1572–1582.
17. Ping L, Ding N, Shi Y, et al. The Bruton's tyrosine kinase inhibitor ibrutinib exerts immunomodulatory effects through regulation of tumor-infiltrating macrophages. *Oncotarget.* 2017;8:39218–39229.

18. Castillo JJ, Gustine JN, Meid K, et al. Ibrutinib withdrawal symptoms in patients with Waldenstrom macroglobulinemia. *Haematologica.* 2018;103:e307–e310.
19. Greenberger et al., Anti-spike antibody response to SARS-CoV-2 booster vaccination in patients with B cell-derived hematologic malignancies, *Cancer Cell* (2021).
20. McLaughlin, P., Grillo-Lo´ pez, A.J., Link, B.K., Levy, R., Czuczman, M.S., Williams, M.E., Heyman, M.R., Bence-Bruckler, I., White, C.A., Cabanillas, F., et al. (1998). Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J. Clin. Oncol*. 16, 2825–2833.
21. Branagan A, Lei, M, Maron JS, Yee AJ, O'Donnell E, Castillo JJ, Raje NS, Treon SP, Flynn CA, Mo CC, Nadeem O, Richardson PG, Panaroni C, Meid K, Bernstein ZS, Lyons RT, Gammon MT, Lively KJ, Packer L, Waterman M, Gallaher R, Juleg B, Alter G, Sarosiek S, Covid-19 vaccine responsiveness in patients with Multiple Myeloma and Waldenstrom Macroglobulinemia, *ASH Annual Meeting & Exposition,* Oral and Poster Abstracts, December 13, 2021, https://ash.confex.com/ash/2021/webprogram/Paper154089.html