



## PRIORITIZING WALDENSTROM'S MACROGLOBULINEMIA PATIENTS DURING THE COVID-19 PANDEMIC

*International Waldenstrom's Macroglobulinemia Foundation Official Statement: February 2022*

***The International Waldenstrom's Macroglobulinemia Foundation (IWMF) is asking healthcare providers to 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.***

**Background:** 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 SARS-CoV-2 mRNA vaccines.<sup>1,2</sup> 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<sup>3</sup> and demonstrated significantly higher mortality rates compared to the general population.<sup>4,5</sup>

**Treatment recommendations:** Given that WM is an indolent non-Hodgkin's lymphoma with distinct features and treatment options,<sup>6</sup> the International Workshop on Waldenström Macroglobulinemia (IWWM) has provided consensus recommendations which are listed below.<sup>7</sup> 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.<sup>8</sup>
- 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 on rituximab or with hypogammaglobulinemia have been reported to have a severely blunted humoral response to vaccination,<sup>9,10</sup> 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.

- Serological lab tests for COVID-19 analyze COVID-19 specific IgM and will not be affected by the total IgM or paraprotein levels.
- 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.<sup>11,12</sup> 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.<sup>13</sup>
- 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.<sup>10,14</sup> 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,<sup>12</sup> including suppression of inflammatory cytokines such as TNF, IL2RA, and CXCL13,<sup>15</sup> and down regulatory effects on T cells and macrophages.<sup>16</sup> 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.<sup>11</sup> 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.<sup>17</sup>

- Trial monitors and/or sponsors should be contacted to seek advice on management of patients who are in clinical trials.
- Testing and management of COVID-19 should be as per existing protocols within each country.

**Other recommendations (not included in IWWM consensus):**

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

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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. Thank you for all you do for our patients. We are in this together.

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