



Report of consensus panel 5 from the 11th international workshop on Waldenstrom's macroglobulinemia on COVID-19 prophylaxis and management

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ABSTRACT

Consensus Panel 5 (CP5) of the 11th International Workshop on Waldenstrom's Macroglobulinemia (IWWM-11; held in October 2022) was tasked with reviewing the current data on the coronavirus disease-2019 (COVID-19) prophylaxis and management in patients with Waldenstrom's Macroglobulinemia (WM). The key recommendations from IWWM-11 CP5 included the following: Booster vaccines for SARS-CoV-2 should be recommended to all patients with WM. Variant-specific booster vaccines, such as the bivalent vaccine for the ancestral Wuhan strain and the Omicron BA.4.5 strain, are important as novel mutants emerge and become dominant in the community. A temporary interruption in Bruton's Tyrosine Kinase-inhibitor (BTKi) or chemoimmunotherapy before vaccination might be considered. Patients under treatment with rituximab or BTK-inhibitors have lower antibody responses against SARS-CoV-2; thus, they should continue to follow preventive measures, including mask wearing and avoiding crowded places. Patients with WM are candidates for preexposure prophylaxis, if available and relevant to the dominant SARS-CoV-2 strains in a specific area. Oral antivirals should be offered to all symptomatic WM patients with mild to moderate COVID-19 regardless of vaccination, disease status or treatment, as soon as possible after the positive test and within 5 days of COVID-19-related symptom onset. Coadministration of ibrutinib or venetoclax with ritonavir should be avoided. In these patients, remdesivir offers an effective alternative. Patients with asymptomatic or oligosymptomatic COVID-19 should not interrupt treatment with a BTK inhibitor. Infection prophylaxis is essential in patients with WM and include general preventive measures, prophylaxis with antivirals and vaccination against common pathogens including SARS-CoV-2, influenza, and *S. pneumoniae*.

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Introduction

Consensus Panel 5 (CP5) of the 11th International Workshop on Waldenstrom's Macroglobulinemia (IWWM-11) was tasked with reviewing the current data on the coronavirus disease 2019 (COVID-19) prophylaxis and management in patients with Waldenstrom's Macroglobulinemia (WM). The initial consensus statement of the IWWM panel on the management of patients with WM during the COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was published in 2020 [1], when the ancestral Wuhan strain was prevalent worldwide. Since then, new variants have emerged with variable potential for transmission and COVID-19 severity. Vaccines targeting the spike protein of SARS-CoV-2 have been developed and implemented. Despite their use, there is high number of breakthrough infections in WM patients, especially when they are under therapy [2]. The better understanding of COVID-19 pathophysiology has optimized our approach for preventing and treating COVID-19 [3].

Methodology

In October 2022, during IWWM-11 a panel of experts on WM and COVID-19 convened to develop updated consensus on the management of COVID-19 in WM patients based on specific questions of IWWM-11 participants. After a comprehensive review of the recent literature from January 2020 to February 2023, a preliminary draft of the manuscript was distributed to all members of the group who were invited to comment on the proposed items and make suggestions. After the first draft development, further rounds of review and amendments, a final version was produced and approved by all authors.

Consensus report

Should boosters including those for Omicron variant of COVID-19 be recommended to all patients with WM and at what time interval from last dose?

Vaccination against SARS-CoV-2, particularly with anamnestic doses, is an important approach to avoiding severe COVID-19 outcomes, including mortality, in cancer patients [4]. Booster vaccines for SARS-CoV-2 should be recommended to all patients with WM. In a recent report on the effects of booster dose in patients with B-cell malignancies, which included 90 WM patients, one third of patients with suboptimal responses postsecond dose, elicited a protective neutralizing antibody titers after the booster dose [5]. Variant-specific booster vaccines, such as the bivalent vaccine for the ancestral Wuhan strain and the Omicron BA.4.5 strain, are important as novel strains emerge and become dominant in the community. A bivalent vaccine with a booster should be used, if available, otherwise the standard mRNA vaccines should be administered [6].

Following any vaccine-specific primary series, boosters should be administered at least 3 months from the last vaccine dose or documented COVID-19 infection. If a patient is severely immunosuppressed (immunoparesis, frequent infections), then a time interval of 3 months is appropriate. For the other patients, a 6-month interval may be suitable. Data on healthy population suggest that the bivalent vaccination after 8 to 10 months post the initial vaccine against the Wuhan strain can induce potent, durable and broad antibody responses against multiple variants, providing a new tool in response to emerging variants [7,8]; however, humoral immune responses against XBB.1.5 was lower compared to BA.5 and BQ.1.1 strains [9]. These recommendations are in accordance with EMA and other national recommendations that suggest one booster bivalent vaccine per year (together with the flu

vaccine) plus one supplementary booster dose 6 months before in case of high-risk comorbidities (<https://www.ema.europa.eu/en/events/ema-regular-press-briefing-public-health-emergencies-1>).

Patients under treatment with anti-CD20 monoclonal antibodies (or who had received such treatment since less than 1 year) or under treatment with Bruton-kinase (BTK) inhibitors have lower neutralizing antibody responses against SARS-CoV-2 [5,6], and therefore they should continue to follow preventive measures, including mask wearing and avoiding crowded places.

Is a temporary interruption in BTK-inhibitor or chemoimmunotherapy recommended before vaccination or boosters for COVID-19 and for how long?

BTK-inhibitor-based therapy and chemoimmunotherapy based on anti-CD20 monoclonal antibodies have been shown to attenuate humoral responses post COVID-19 vaccination in several studies [5,6,10–12], while it seems that the antigen-specific T-cell responses are preserved [10]. In this context, a temporary interruption for up to 3 months for anti-CD20 rituximab and 3 days for BTKi might be considered, depending on the disease response status and patient symptoms due to WM, and taking into consideration the half-life of each drug and the risk for IgM rebound upon BTKi interruption [13]. Preliminary results from the TRIBECA (TReatment Interruption of BTKi to Enhance COVID-19 Antibody response) trial, which sought to determine if a superior immune response could be gained by pause of BTKi therapy, prior to and up to 4 weeks after third vaccine dose, showed that there may be a higher increment in antibodies against SARS-CoV-2 when BTKi therapy is paused around the time of vaccination [14].

However, even this interruption may not be effective for several WM patients, since there are variations in the pharmacokinetics of the drug, the control of the disease and type of immunosuppression. Reinstitution of a BTKi may also be impactful on vaccination response and is worthy of further study.

Should pre-exposure prophylaxis be recommended for all WM patients or just those undergoing BTK-inhibitor/chemoimmunotherapy or those with suboptimal COVID-19 vaccine response?

Both patients with symptomatic and asymptomatic WM show impaired humoral responses to COVID-19 vaccination [5,6,10–12,15–17]. There is no established and universally accepted method for determining response to COVID-19 vaccines, especially against SARS-CoV-2 variants of concern (vast majority of commercially available methods evaluate humoral responses against Wuhan strain). Therefore, all patients with symptomatic WM who receive active treatment are eligible for pre-exposure prophylaxis [18].

However, given the limited availability in some countries, WM patients who receive treatment with anti-CD20 monoclonal antibodies and/or BTK inhibitors should be prioritized. It should be noted that the combination of monoclonal antibodies tixagevimab/cilgavimab (Evusheld) is no more active against the widely prevalent Omicron subvariants BQ.1, BQ.1.1, and BA.4.6., XBB.1.5 [19–21]. Evidence is therefore lacking that Evusheld can effectively protect vulnerable adults against the current and anticipated variants over the next 6 months of SARS-CoV-2 and is therefore not recommended for prophylaxis. Future novel pre-exposure prophylactic agents should be evaluated on a case-by-case basis.

Is there any role for IVIG/subcutaneous IG as COVID-19 prophylaxis?

Immunoglobulin administration, either as IVIG or as subcutaneous IG, is not a SARS-CoV-2-specific treatment. Therefore, there is no specific indication for COVID-19 infection or prophylaxis

against SARS-CoV-2. It could be considered in patients with multiple episodes of recurrent/persistent infections and remarkably low IgG levels less than 400 mg/mL [22].

For patients already receiving prophylaxis with IVIG/subcutaneous IG, high SARS-CoV-2 antispikes may be detected [23]. Randomized clinical trials are needed in order to determine the exact role of preventive immunoglobulin administration against COVID-19.

Should the antiviral combination nirmatrelvir and ritonavir (paxlovid) be offered to all WM patients who become infected with COVID-19, regardless of disease or vaccination status?

Patients with symptomatic WM, even if they are vaccinated, are at increased risk for severe COVID-19 due to immune dysregulation compared to healthy individuals [2]. Therefore, nirmatrelvir/ritonavir (Paxlovid) should be offered to all symptomatic WM patients with mild to moderate COVID-19 regardless of vaccination, disease status, or treatment, as soon as possible after the positive test and within 5 days of COVID-19-related symptom onset [24]. Paxlovid remains fully active on all circulating SARS-CoV-2 variants (which are mutated in the spike but not in their protease gene).

Paxlovid is administered orally twice daily for 5 days. Based on anecdotal data, a 10-day course has been suggested for immunosuppressed patients or those with symptoms of COVID-19 rebound and may be available in some countries. Clinical trials are ongoing comparing 5 days vs 10 days in immunosuppressed patients.

Patients with asymptomatic WM who are at high-risk for progression to symptomatic disease and are diagnosed with mild to moderate COVID-19 should be systematically offered Paxlovid due to their underlying immune status resembling symptomatic WM. Paxlovid can be also considered for patients with asymptomatic WM who are at lower-risk for progression, if they have other comorbidities that increase the risk for severe COVID-19.

However, it is known that almost 15% of patients cannot receive Paxlovid due to concomitant medication they receive. Serum concentrations of ibrutinib may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk for toxicity including risk of tumor lysis syndrome [13,24]. Coadministration of ibrutinib and ritonavir should be avoided. If treatment with nirmatrelvir/ritonavir is necessary, pausing ibrutinib treatment and starting nirmatrelvir/ritonavir 12 hours after the last ibrutinib dose should be considered. Ibrutinib should restart 3 days after completing nirmatrelvir/ritonavir treatment given that CYP3A4 inhibition takes several days to resolve. Alternatively, a reduction to ibrutinib dose at 140 mg/d could be considered, with close patient monitoring for toxicity. Similarly, the dose of Zanubrutinib can be reduced to 80 mg/d to maintain therapeutic BTKi levels while minimizing excessive levels and toxicity while on Paxlovid. In each case, a tailored consideration of the risk/benefit ratio of interrupting ibrutinib to administer paxlovid vs the risk of IgM flare or coadministering ibrutinib with paxlovid vs ibrutinib toxicity is necessary.

Serum concentrations of venetoclax may also be increased due to CYP3A inhibition by ritonavir, resulting in increased risk of tumor lysis syndrome at the dose initiation and during the ramp-up phase [24]. If a patient with WM is on venetoclax and has to receive Paxlovid, then the dose of venetoclax should be reduced to 25% of the full dose and close monitoring is essential.

For patients who cannot receive Paxlovid, the use of remdesivir is recommended. Remdesivir can be administered in patients with WM and COVID-19 either in the outpatient setting for 3 consecutive days starting within 7 days of symptoms onset or in the inpatient setting, even under common O₂ supply, for 5 consecutive days [25,26]. However, Remdesivir usage is limited in patients with severe chronic kidney failure.

Molnupiravir (Lagevrio) is another antiviral that may be an option for patients with WM in some countries. It is administered orally twice daily for 5 days and within 5 days of the onset of COVID-19-related symptoms. No interaction is expected with the coadministration of molnupiravir with ibrutinib or venetoclax [27]. However, molnupiravir should be given as a third choice as it is less effective than both paxlovid and remdesivir at indirect evidence (only 34% reduction risk for respiratory interventions vs placebo) [28].

Sotrovimab (Xevudy) is active on circulating BQ1, BQ1.1 and XBB.1 variants and could be an option in immunosuppressed patients who cannot receive Paxlovid and Remdesivir [29]. Sotrovimab is currently not authorized in any US region, due to the prevalence of SARS-CoV-2 Omicron BA.2 subvariant, until further notice by the FDA [30].

Should BTK-inhibitor or chemoimmunotherapy be interrupted in patients who become infected with COVID-19 while on therapy? Criteria based on WM response / COVID severity?

Taking into consideration that most symptomatic COVID-19 episodes last for less than 10 days, chemoimmunotherapy can be postponed for 7 to 10 days after COVID-19 diagnosis, similar to our approach for other infections. Severe and complicated COVID-19 infections may necessitate longer treatment interruptions. The use of anti-CD20 monoclonal antibodies leads to a long-lasting B-cell immunosuppression.

Interrupting treatment with a BTK inhibitor is more complicated, due to the risk of IgM rebound [31]. For this reason, patients with asymptomatic or oligosymptomatic COVID-19 should not interrupt BTK inhibitor.

BTK plays an essential role in the activation of B cells and without its activation, these cells would not be able to play an appropriate role in immune reactions, but BTK also plays a role in macrophage function [32]. In COVID-19, the overactivation of immune cells causes the overproduction of cytokines, resulting in cytokine storms. This phenomenon increases the severity of the disease and can lead to acute respiratory distress syndrome. The use of BTKis may help patients experience less severe responses to the SARS-CoV-2 virus and overcome the disease by inhibiting this process [33]. Well-designed studies, especially multicentered double-blind clinical trials, are needed to evaluate the effectiveness of BTKis in the management of COVID-19. Currently, we must wait for the results of ongoing clinical trials before making any firm recommendation.

If treatment with a BTKi or chemoimmunotherapy has been interrupted due to COVID-19 infection, it should be restarted upon resolution of fever and improvement in COVID-19 symptoms after at least 7 days from COVID-19 diagnosis. If patient remains PCR positive for SARS-CoV-2 after 7 days post diagnosis, the decision to restart BTKi is based on a patient basis, especially in the presence of low respiratory tract symptoms in the absence of fever.

Symptoms related to BTK-inhibitor withdrawal may include fever, body aches, chills, night sweats, headache, fatigue, arthralgia, and weakness. This constellation of symptoms shows remarkable overlap with COVID-19 symptoms. Typically, BTK-inhibitor withdrawal symptoms develop within 5 days of BTK inhibitor interruption and resolve rapidly with BTK reinitiation.

What is the role of plasma infusions?

COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies is authorized for the treatment of COVID-19 in patients with immunosuppressive disease, such as WM, or in patients who receive immunosuppressive treatment, such as chemoimmunotherapy or BTKi, based on results in immunocompromised patients [34,35]. Convalescent plasma is administered in inpatient or outpatient settings [36]. This may be an option for

Table
Summary of the key recommendations from the consensus panel on COVID-19 prophylaxis and management in patients with WM (2022)

Vaccination
• Booster vaccines for SARS-CoV-2 are recommended to all patients with WM. • Variant-specific booster vaccines, such as the bivalent vaccine for the ancestral Wuhan strain and the Omicron BA.4.5 strain, are important as novel strains emerge and prevail. • A temporary interruption in BTK-inhibitor or chemoimmunotherapy before vaccination might be considered. • Patients under treatment with anti-CD20 monoclonal antibodies or Bruton-kinase (BTK) inhibitors have lower neutralizing antibody responses against SARS-CoV-2 and therefore they should continue to follow preventive measures, including mask wearing and avoiding crowded places
Pre-exposure prophylaxis
• Patients with WM are candidates for pre-exposure prophylaxis, if indicated, depending on the dominant SARS-CoV-2 variants in the community.
Oral antivirals
• Oral antivirals should be offered to all symptomatic WM patients with mild to moderate COVID-19 regardless vaccination, disease status or treatment. • Oral antivirals should be offered as soon as possible after the positive test and within 5 days of COVID-19-related symptom onset. • Co-administration of ibrutinib or venetoclax with ritonavir should be avoided.
Treatment interruption
• Patients with asymptomatic or oligosymptomatic COVID-19 should not interrupt treatment with a BTK inhibitor. • Severe and complicated COVID-19 cases may necessitate treatment interruptions.
General recommendations
• Infection prophylaxis is essential in patients with WM. • Infection prophylaxis includes general preventive measures, prophylaxis with antivirals and vaccination against common pathogens including SARS-CoV-2, influenza, and <i>S. pneumoniae</i>.

persisting COVID-19 that presents in 3% to 4% of patients who receive anti-CD20 therapy, particularly after Paxlovid treatment if virus production is not abrogated. Available studies have shown an impact of convalescent plasma on improving patient survival in patients with hematological malignancies and COVID-19[37]. But the data on WM patients are very limited. However, the immune escape caused by the current variants considerably limit the efficacy of such infusions.

To ensure the efficacy of convalescent plasma against current SARS-CoV-2 strains, the plasma should be collected from convalescent individuals who have been previously infected by SARS-CoV-2 strains that are currently dominant in the community [38].

Taking into consideration its limited availability and its marginal benefit, convalescent plasma may be considered in selected cases in case of failure of other approved treatments.

Are there financial and access issues for prevention and management of COVID-19?

Oral antivirals (Paxlovid, Molnupiravir) and Evusheld are usually administered through early access programs following application in the regulatory authority of each country.

Intravenous remdesivir for COVID-19 is approved and reimbursed in most countries.

COVID-19 vaccines are reimbursed, and they are also provided by the local authorities free of charge.

Accessibility to oral antivirals and booster vaccine doses may be restricted due to prioritization of specific group of patients who are at particularly high risk for severe infection. Patients with WM under current treatment usually are eligible for these medications and vaccines.

What additional key precautions are recommended for patients with WM?

Flu vaccination: Tandem high-dose influenza vaccination separated by 30 days leads to higher serologic hemagglutinin inhibition titer responses and more durable influenza-specific immunity in patients with plasma cell dyscrasias compared to single-dose standard-of-care vaccination [39].

Therefore, the first flu vaccine shot should be given as early as possible once it becomes available. The second (booster) shot

should be given at least 1 month apart, but after 2 or 3 months may be better to extend protection throughout the flu season.

The influenza vaccine can be administrated at the same time with a booster vaccine for SARS-CoV-2. A recent meta-analysis of the cochrane database of systematic reviews suggests that only vaccines and garlic capsules had advantages in preventing influenza in healthy individuals, and that vitamin C is not effective [40]. Although oseltamivir has been used for influenza prophylaxis in pandemic areas, especially in immunocompromised patients, and the meta-analysis showed that it is probably beneficial, it did not reduce the hospitalization rate [40].

Conclusion

The key recommendations from IWWM-11 CP5 are summarized as follows (Table): Booster vaccines for SARS-CoV-2 should be recommended to all patients with WM. Variant-specific booster vaccines, such as the bivalent vaccine for the ancestral Wuhan strain and the Omicron BA.4.5 strain, are important as novel strains emerge and become dominant in the community. A temporary interruption in BTK-inhibitor or chemoimmunotherapy before vaccination might be considered. Patients with WM are candidates for pre-exposure prophylaxis, if available. Oral antivirals should be offered to all symptomatic WM patients with mild to moderate COVID-19 regardless vaccination, disease status or treatment, as soon as possible after the positive test and within 5 days of COVID-19-related symptom onset. Coadministration of ibrutinib or venetoclax with ritonavir should be avoided. Patients with asymptomatic or oligosymptomatic COVID-19 should not interrupt treatment with a BTK inhibitor. In general, infection prophylaxis is essential in patients with WM and include general preventive measures, prophylaxis with antivirals and vaccination against common pathogens including SARS-CoV-2, influenza, and pneumococcus.

Author contributions

ET, ARB, VL, RGS, JSM, MD, and SPT prepared, reviewed and submitted key questions for consensus panel 4 (CP5). Questions were reviewed in an open general assembly by attendants of IWWM-11, and additional questions for CP5 deliberations were formulated and submitted. ET wrote the first draft of CP5 responses, and draft

was reviewed and modified by ARB, VL, RGS, JSM, MD, and SPT. Final draft was submitted to CP5 general panel for review and commentary. CP5 general panel was composed of individuals with experience in the care of WM patients who attended IWWM-11 and volunteered to be on CP5 panel.

Conflicts of interests

ET received honoraria from Amgen, Astra/Zeneca, Bristol Myers Squibb, Eusa Pharma, GSK, Integrus Pharma, Janssen, Pfizer, Sanofi, and Takeda; research grants from Amgen, GSK, Janssen, Sanofi and Takeda and travel grants from Amgen, Eusa Pharma and Takeda.

ARB reports being and advisory board member for Adaptive, Beigene, CSL Behring, Genzyme, Karyopharm, Pharmacyclics, and Sanofi.

RGS declares honoraria from Amgen, Takeda, Janssen, Incyte, Astellas, BeiGene, AstraZeneca, Pfizer; and research funding from Novartis, Gilead, Astellas, Janssen; and participation in advisory boards for Amgen, Pharmacyclics, Takeda.

JT receives research funds for her institution from Beigene, Pharmacyclics, Janssen, Roche, Cellectar, Takeda and BMS.

LMG has no disclosures.

DMS received research funds for clinical trials from Acerta Pharma, Gilead Sciences, Karyopharm Therapeutics, Mingsight, Arque, Novartis, Verastem, Juno Therapeutics. She has received consulting fees from Pharmacyclics/Janssen, Karyopharm Therapeutics, Beigene, Innate, AstraZeneca, Abbvie, CSL Behring, Cellegene, TG Therapeutics, and Innate Pharma.

PM reports honoraria from Janssen, Astra Zeneca and Incyte; consultancy or advisory role for Janssen and Beigene; and travel support from Abbvie.

EK declares honoraria from Amgen, Janssen, GSK, Pfizer and research funding from Amgen, Janssen, GSK, and Pfizer.

AMF participated in advisory boards and received honoraria from Janssen, Beigene, Abbvie and AstraZeneca

EH received honoraria from Janssen Cilag, Abbvie, and AstraZeneca

JSM declares participation on advisory boards and consulting services, on behalf of my Institution, for Abbvie, Amgen, BMS, Celgene, GSK, Haemalogix, Janssen-Cilag, Karyopharm, MSD, Novartis, Pfizer, Takeda, Regeneron, Roche, Sanofi, and SecuraBio.

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