BC COVID THERAPEUTICS COMMITTEE (CTC)

Clinical Practice Guide for the Use of Sotrovimab in Patients with COVID-19

RECOMMENDATION

Sotrovimab can be CONSIDERED for adults and children 12 years or older (≥ 40kgs) who are **mildly ill** from confirmed COVID-19 (see #1), AND:

- Who are outpatients OR inpatients within a nosocomial outbreak, AND
- Who can receive Sotrovimab **within 7 days of symptom onset** (see #2), AND
- Who have **at least 1 risk factor*** for disease progression such as (see #3):
    - age 55 years or older
    - diabetes mellitus treated with medication
    - obesity (BMI >30 kg/m^2)
    - chronic kidney disease (eGFR, <60 mL/min)
    - congestive heart failure (NYHA class II, III, or IV)
    - chronic respiratory conditions such as COPD or moderate to severe asthma

    *These risk factors comprise trial inclusion criteria. Other significant risk factors or comorbidities may also be used at the discretion of the clinician (e.g. immunocompromise, auto-immune diseases etc.), AND
- Who are **inadequately vaccinated** against COVID-19 (see #4), i.e.:
    - **Unvaccinated or partially unvaccinated** (received 0 or 1 of 2 COVID-19 vaccine doses) with no prior history of COVID-19 infection, OR
    - **Unlikely to adequately respond to vaccination** despite two** COVID-19 vaccine doses due to:
        - Active treatment for solid tumor or hematological malignancies, OR
        - Having received a solid organ transplant and treated with immunosuppression, OR
        - Receiving CAR-T cell therapy or hematopoietic stem cell transplant in the last 2 yrs, OR
        - Having a moderate to severe primary immunodeficiency, OR
        - Having advanced untreated HIV or AIDS, OR
        - Active receipt of anti-B cell therapies (e.g. rituximab, ocrelizumab, obinutuzumab), high-dose systemic steroids (=20mg prednisone equivalent daily for at least 14 days), alkylating agents (e.g. cyclophosphamide, cisplatin), antimetabolites (e.g. methotrexate, 5-FU) or anti-TNF agents (e.g. infliximab, adalimumab)

      **Such patients, upon receipt of a third dose of a COVID-19 vaccine may or may not adequately respond to vaccination. Case-by-case evaluation with an expert is recommended.

Dose: **500mg IV x 1 dose of sotrovimab.** There are insufficient data to recommend the IM route[2] (see #5).

Patients should be informed that sotrovimab does not have full Health Canada approval for this indication and consent should be obtained (see #6).

Role of Sotrovimab in treatment of COVID-19

Sotrovimab is a monoclonal antibody that neutralizes the spike protein of the SARS-COV-2 virus, preventing entry into human cells and replication. Sotrovimab is active against variants of concern Alpha to Delta. It is not yet known if sotrovimab is able to neutralize the new variant of concern Omicron.

Evidence Summary

Sotrovimab has been evaluated in a single peer-reviewed, double blind, randomized-placebo controlled, manufacturer-sponsored trial (COMET-ICE)[1]. In this trial, 1057 patients with mild symptoms of COVID-19 and at least one risk factor for disease progression were randomized to receive a single dose of sotrovimab 500mg IV compared to placebo. The primary endpoint was a composite outcome of hospitalization for >24 hours or death within 29 days of the receipt of the infusion. Out of the 528 patients who received sotrovimab, 6 met the primary endpoint of hospitalization or death vs. 30 of the 529 who received placebo (1% vs. 6%; p<0.001; ARR=5%, NNT=20). There were only 2 deaths observed (placebo arm); the primary endpoint was driven entirely by hospitalizations.

Secondary outcome results demonstrated that sotrovimab significantly reduced progression to severe/critical respiratory COVID-19 compared with placebo (1 vs. 5% p=0.002). Sotrovimab did not reduce length of stay or ICU-bed-days. The proportion of patients reporting adverse events was similar between treatment groups; sotrovimab was well tolerated, and no safety concerns were identified; 6 patients in each placebo and sotrovimab groups experienced mild to moderate infusion reactions. The recommended observation time is 1 hour.

While COMET-ICE included only adults ≥ 18 years, the manufacturer has submitted sufficient data to Health Canada for the Authorization to include pediatric patients 12-17 years old weighing at least 40 kgs[5]. Pregnant patients were excluded from the trial and there are no safety or efficacy data of sotrovimab in pregnancy.

Drug Supply

In the context of the COVID-19 Pandemic, recommendations seek to allocate the most effective or scientifically proven drug therapies to patients or group of patients meeting the clinical criteria with the highest needs and the greatest likelihood of benefit. Recommendations on how to allocate scarce drug therapies are beyond the scope of this document. (Ethical Framework for Allocating Scarce Drug Therapies During COVID-19) http://www.bccdc.ca/Health-Professionals-Site/Documents/Drug_Scarcity_Framework.pdf

Practice Point #1: Definition of mildly ill

Mildly ill patients are those who are not requiring hospital-level care due confirmed COVID-19 and who:

- Have signs and symptoms of COVID-19 (e.g. shortness of breath, fever, cough), AND
- Do not require supplemental oxygen support (e.g. low or high flow oxygen), AND
- Have oxygen saturation ≥94% on room air

Patient Location

Patients who are candidates for sotrovimab are usually ambulatory (e.g. recovering at home) and are not hospitalized. However, mildly ill patients can also reside in Long Term Care, present to the Emergency

Department, or be screened during an admission for other reasons. Mildly ill patients may also be part of nosocomial outbreaks or receive a diagnosis of COVID-19 during a hospitalization for a different diagnosis.

The health care setting where sotrovimab may be administered will vary by health authority and is outside of the scope of this practice guide. Clinicians are encouraged to consult with their local COVID-19 clinical experts and/or health care leadership for logistical considerations.

Evidence Summary

Sotrovimab has only been evaluated in mildly ill patients (COMET-ICE)[1] and has received Health Canada approval under an Interim Order for use in this population only[5]. While another monoclonal antibody treatment REGEN-COV (casirivimab + imdevimab) has been studied in severely ill patients, these data are not generalizable to sotrovimab.[4] Studies of monoclonal antibodies in asymptomatic patients for post-exposure prophylaxis (PEP) are currently underway; however, there are insufficient clinical and cost-effectiveness data to support the use of sotrovimab in the setting of PEP.

Practice Point Summary: Sotrovimab can be considered in patients with a confirmed SARS-COV-2 infection who are mildly ill from symptoms of COVID-19.

Practice Point #2: Timing of administration from symptom onset

Five to 10 days after symptom onset, unimmunized patients begin producing antibodies as part of the innate immune response. Therefore, the benefit of exogenous anti-COVID-19 antibodies to neutralize the virus and prevent replication is only effective within this timeframe, after which additional antibodies have no effect.

Evidence Summary

In the COMET-ICE trial, patients who were 5 days or less from symptom onset at the time of *eligibility screening* were considered for participation in the trial.[1] The study drug or placebo infusion was administered within the next 24 hours, meaning all patients in COMET-ICE received the study drugs within 6 days of symptom onset. A follow-up study (COMET-TAIL) expanded the window of receipt of sotrovimab to 7 days; the primary outcome of progression to hospitalization or death was comparable in COMET-TAIL to COMET-ICE indicating that the 7-day window from symptom onset is reasonable[2]. Furthermore, other monoclonal antibody treatments for COVID-19 (e.g. REGEN-COV; bamlanivimab-casirivimab) studied for the same indication used a cut off of 7 days from symptom onset for enrolment. The product monograph does not specify the precise symptom window for administrion[5].

Practice Point Summary: Sotrovimab can be considered in patients who can receive the drug within 7 days of symptom onset.

Practice Point #3: Risk factors

The benefit of sotrovimab in mildly ill patients is proportional to the number of risk factors or co-morbidities for disease progression present. Patients who are most likely to experience a reduction hospitalization need to have at least one risk factor for sotrovimab to be considered.

Evidence Summary

In COMET-ICE, the study population represented patients at high risk for COVID-19 progression to hospitalization or death.[1] As such, enrolment in the trial was limited to patients who:

- Who had ≥1 **risk factor** that puts them at an increased risk for disease progression such as:
    - age 55 years or older
    - diabetes mellites treated with medication
    - obesity (BMI >30 kg/m^2)
    - chronic kidney disease (eGFR, <60 ml/min)
    - congestive heart failure (NYHA class II, III, or IV)
    - chronic respiratory conditions such as COPD or moderate to severe asthma

These risk factors comprise trial inclusion criteria. Other significant co-morbidities may also be used at the discretion of the clinician (e.g. immunocompromise, auto-immune diseases etc.). Other studies of anti-COVID monoclonal antibodies in this clinical setting used very similar, if not identical inclusion criteria. In the trial, most participants had 1 co-morbidity (56%).

Relationship between comorbidities and risk of hospitalization and death

The number of risk factors is proportional to the magnitude of benefit of monoclonal antibodies. Local and real-world data suggest that age is, by far, the greatest predictor of hospitalization and death and older patients benefit more from intervention.[3] An observational cohort study depicting real world experience with outpatient use of monoclonal antibodies, including sotrovimab, used a Monoclonal Antibody Screening Score to assess patients' risk factors and calculated the absolute risk reduction depending on the score.[3] The MASS uses the following point system: age ≥65 (2 points), BMI ≥35 kg/m^2 (1 point), diabetes mellitus (2 points), chronic kidney disease (3 points), cardiovascular disease in a patient ≥55 years (2 points), chronic respiratory disease in a patient ≥55 years (2 points), hypertension in a patient ≥55 years (1 point), and immunocompromised status (3 points). Patients who had a MASS score of 1 or 2 had an absolute risk reduction of hospitalization of 2.3% and 4.6%, for a NNT of 43 and 22 respectively, which mirrors the patient population and ARR of COMET-ICE. However, patients who had a MASS of ≥ 4 had a 25.7% risk reduction for an NNT of 4. This means that an elderly patient with diabetes (MASS = 4), is 10 times more likely to benefit from monoclonal antibody treatment than a younger patient with obesity only (MASS = 1). In settings of drug scarcity or limited resources, a higher MASS, especially in those 65 year or older, can be considered for priority assignment of sotrovimab or be used in cost-effectiveness assessments.

Practice Point Summary: Sotrovimab can be considered in patients with at least one risk factor for disease progression. A higher number of co-morbidities is associated with a greater absolute benefit.

Practice Point #4: Vaccination status

Unvaccinated patients are at the highest risk of hospitalization or death from COVID-19. COMET-ICE included only those without previous vaccination or infection, who were the most likely to benefit from exogenous antibodies.[1] The benefit of sotrovimab in vaccinated individuals has not been characterized but is likely much smaller. Patients who were partially vaccinated (received 1 of 2 doses) were included in a subsequent trial of sotrovimab (COMET-TAIL)[2].

There are also patients who are known to be unlikely to respond to vaccination based on severe immunocompromise and are not adequately protected despite being immunized. Such patients can also receive sotrovimab.

Current criteria for eligibility for sotrovimab are patients who:

- Are **unvaccinated or partially unvaccinated** (received 0 or 1 of 2 COVID-19 vaccine doses) with no prior history of COVID-19 infection OR
- Are **unlikely to adequately respond to vaccination** despite two COVID-19 vaccine doses* due to:
    - Being a bone marrow transplant (BMT) recipient, OR
    - Having received a solid organ transplant (SOT) and receiving immunosuppression, OR
    - Having received a hematopoietic stem cell transplant (HSCT) in the last 2 years
    - Having an primary immunodeficiency, OR
    - Receiving treatment for an active hematological malignancy
    - Receiving B-cell depleting agents such as anti-CD20 or anti-CD22 agents (e.g. rituximab, ocrelizumab, obinutuzumab) within the past year
    - *Such patients, once they have received a third dose of a COVID-19 vaccine, may or may not adequately respond to immunization. Case-by-case evaluation with an expert is recommended in these situations. Serology results will likely be required.

Criteria that define patients unlikely to adequately respond to vaccination were developed by National Advisory Committee for Immunization (NACI) and adopted by the Province to prioritize this vulnerable group of patients for third doses of the COVID-19 vaccine.

Practice Point Summary: Patients eligible for sotrovimab are those who are unvaccinated, inadequately vaccinated or unlikely to adequately respond to vaccines.

Practice Point #5: Dose of Sotrovimab

The COMET-ICE trial used a single dose of sotrovimab 500mg IV in 100ml NS infused over 1 hour, followed by a 1-hour observation period.[1] This dose and administration guidance is currently reflected in the product monograph. The drug is supplied as a single use 500mg vial.

The manufacturer is currently evaluating the IM route in a phase II/III randomized-controlled trial, COMET-TAIL[2]. Patients were assigned to receive sotrovimab 500mg IV, 500mg IM and 250mg IM in a 1:1:1 ratio. The 500mg IM (but not 250mg) dose is showing signs of benefit, but these findings are based on a press release and data obtained by the manufacturer. A final evaluation of the 500mg IM dose will be possible in early 2022.

Practice Point Summary: The recommended regimen of sotrovimab is a single 500mg dose administered IV; the IM route is currently being evaluated.

Practice Point #6: Informed consent for sotrovimab

As stated by the manufacturer, the use of sotrovimab is permitted under an interim authorization delivered in

accordance with section 5 of the COVID-19 Interim order (IO), pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.[6]

The interim authorization is associated with Terms and Conditions that need to be met by the sponsor to ascertain the continued quality, safety, and efficacy of the product. For further information on an authorization under this pathway, clinicians can refer to Health Canada's IO Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19[6].

Practice Point Summary: Patients should be informed that sotrovimab does not have full Health Canada approval for this indication and consent should be obtained.

References:

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