Alberta Health Services
COVID-19 Scientific Advisory Group

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Short Communication

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Since this brief was written in September 2021, the evidence regarding the effectiveness of sotrovimab against some variants of COVID-19 has advanced and the policies regarding its usage in Alberta have changed substantially. It is possible that future variants will respond to this medication; however, this review should be considered as background information only and not be used to guide clinical practice.

Safety and Effectiveness of Sotrovimab in High Risk Populations

Context

- Sotrovimab is a SARS-CoV-2 neutralizing monoclonal antibody (biologic) therapy that has recently been approved by Health Canada as a treatment for COVID-19. The medication has been purchased by the Government of Canada for distribution to provinces and territories starting in October 2021.
- Clinical trial data suggests that use of sotrovimab within 5 days of symptom onset in unvaccinated outpatients with documented COVID-19 with risk factors for severe disease can reduce the risk of progression to requiring hospitalization (Gupta et al., 2021).
- A major limitation to the use of this medication is the requirement of IV administration over a time period of two hours (one-hour infusion, one-hour observation). In Alberta, initial capacity will be limited to 20-30 patients per day, administered by the Mobile Integrated Health program of Emergency Medical Services.
- Alberta's criteria for sotrovimab use in this initial phase are as follows:
  RT-PCR-confirmed COVID-19 infection if they can receive the treatment 5 or fewer days after symptom onset, AND they are:
  a. *Aged 65 years or older AND unvaccinated, defined as not having received any doses of an approved COVID-19 vaccine, OR*
  b. *Have received solid organ transplant or stem cell transplant, regardless of vaccination status*.
- This brief compiles the existing clinical trial evidence and also summarizes guidance from other jurisdictions regarding sotrovimab use, specifically to identify signals of reduced effectiveness or harm in populations with risk factors for severe COVID-19. This is a rapidly changing field, and the findings of this brief may change as evidence becomes available.

Key Messages

- One interim study report (n=583) showed that use of sotrovimab, a pansarbecovirus neutralizing monoclonal antibody, **as a single 500 mg iv infusion given within 5 days of symptom onset**, reduced the risk of hospitalization from 7% (21 participants in placebo) to 1% (3 participants in treatment group) in unvaccinated patients who had any of the following risk factors for progression to severe COVID-19:

a. Age over 55 years, OR
b. Age over 18 years with one of: diabetes for which medication was warranted; obesity (BMI >30); chronic kidney disease (eGFR <60 ml per minute per 1.73 m2 of body-surface area); congestive heart failure (NYHA II, III, or IV); chronic obstructive pulmonary disease, or moderate-to-severe asthma.

- Vaccinated individuals, pregnant people and severely immunocompromised individuals[i] were excluded from the trial so results are not generalizable to those groups.
- Most study subjects (~90%) were enrolled based on age >55 or obesity.
- There was no safety signal identified with adverse events reported in 17% of patients in the Sotrovimab group (2% serious), and 19% of those in the placebo group (6% serious). Most of the serious adverse events were COVID-19 hospitalizations, and none were considered related to Sotrovimab.
- At present, evidence from the COMET-ICE trial supports offering sotrovimab to moderate and low-risk patients; however, no safety signals arise from patients with high-risk comorbidities and this population may derive the most benefit from this medication.

Summary of Clinical Trial Evidence

As of November 2021, one published randomized controlled trial has examined the efficacy and safety of Sotrovimab (Gupta et al., 2021). The COMET-ICE trial is a double-blinded, randomized, multicenter, placebo-controlled clinical trial conducted in patients with risk factors early in the course of mild (non-hospitalized) COVID-19 infection. Patients were recruited between August 2020 and March 2021 in the US, Canada, Brazil, and Spain. Included patients were adults diagnosed with COVID-19 with onset of symptoms in the prior 5 days and at high risk of progression of COVID-19 (defined as age ≥ 55 years, obesity, diabetes requiring medication, kidney disease, congestive heart failure, COPD, and moderate to severe asthma). Median age of participants was 53 years, with 22% of participants older than 65 and 11% of participants older than 70 years. No information about the participants' vaccination status was reported. A total of 583 patients were randomized to placebo and treatment groups, and treatment with Sotrovimab within 5 days of symptom onset (60% within 3 days) was found to result in an 85% reduction in the composite endpoint of hospitalization or death due to any cause, occurring 1% of patients in the Sotrovimab group versus 7% in the placebo group (p=0.002). One patient (in the placebo group) died, and all five patients admitted to ICU were in the placebo group, with two requiring mechanical ventilation and a third declining intubation and subsequently dying. No subgroup analysis of efficacy was reported.

The COMET-ICE trial also evaluated safety, and adverse events were reported in 17% of patients in the Sotrovimab group (2% serious), and 19% of those in the placebo group (6% serious). Most of the serious adverse events were COVID-19 hospitalizations, and none were considered related to Sotrovimab. The only mild or moderate adverse event to occur in more than 1% of Sotrovimab patients was diarrhea. Infusion-related reactions were comparable at 1% in each group; one patient experienced moderate dyspnea related to Sotrovimab treatment that was considered related to the infusion. Limitations of this study include the small number of hospitalizations in the Sotrovimab group (meaning it is not possible to determine if Sotrovimab is less effective in some patient subgroups); the relatively small sample size to identify rare (<1%) safety signals; and lack of secondary endpoint analysis.

No other clinical trials yet published have examined Sotrovimab, though several are ongoing (Table 1). Results from the recently completed BLAZE-4 trial (NCT04634409) and interim results from nearly-completed trials will likely be available to inform patient prioritization

decisions in the next 6-12 months.

Guidance from other Canadian Jurisdictions

Ontario

The Ontario Science Table examined the evidence for Sotrovimab, as well as the combined antibody therapy of Casirivimab + Imdevimab in their October brief on these monoclonal antibody therapies (Bailey et al., 2021). For patients with mild COVID-19 infection, their report concludes that Sotrovimab is equivalent to, but harder to administer than Casirivimab + Imdevimab combination therapy. This guidance does not recommend neutralizing antibody therapy in patients with previous COVID-19 infection or full vaccination unless they are immunocompromised, and prefers REGEN-COV over sotrovimab with the following indications:

1. Confirmed, symptomatic COVID-19, AND
2. Are within 7 days of onset of any COVID-19 symptom, AND
3. Have at least one of the following risk factors: age > 50, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease, chronic liver disease, immunosuppression, or receipt of immunosuppressants

British Columbia

The BCCDC guidance does not recommend the use of monoclonal antibody therapy in pregnancy, but the October 20, 2021 therapeutic recommendation update states: Monoclonal antibodies (mAbs; Bamlanivimab/etesevimab, REGN-COV2, Sotrovimab, Regdanvimab) IV have shown to reduce hospitalization rates (although not mortality or length of stay) in UNVACCINATED outpatients at high-risk of complications due to comorbidities (age >40 with a comorbidity like obesity or hypertension) (BCCDC, 2021). Due to high vaccination rates and barriers to operationalizing outpatient IV administration outside of clinical trials, the clinical application of these studies is limited. mAbs may be considered on a case-by-case basis in those inadequately immunized (unimmunized, partially immunized or inadequate immune response) with mild disease AND who are at high risk of developing severe COVID-19-related complications. The subcutaneous route has shown similar reductions in viral loads, but clinical data is lacking and would still present operational barriers such as multiple injections and required observation time.

Additional Discussion

Monoclonal antibodies have been safely used in pregnant people for other conditions and thus this therapy may be considered for unvaccinated pregnant people on a case by case basis after a risk-benefit discussion with their care provider. In addition, immunocompromised patients are at high risk of incomplete protection after COVID-19 vaccination, as well as having high risk of severe disease and thus may benefit significantly from administration of neutralizing antibody. Therefore, many treatment guidelines including Alberta's are prioritizing severely immunocompromised patients for antiviral monoclonal antibody therapy regardless of their vaccination status.

[i] "Severely immunocompromised" status included but was not limited to: cancer patients actively receiving immunosuppressive chemotherapy or immunotherapy, those with a solid organ transplant or allogeneic stem cell transplant within the last 3 months, or those having conditions requiring the use of systemic corticosteroids equivalent to ≥0.5 mg/kg of body weight per day of prednisone within 6 weeks of randomization

References

Bailey JJ, Morris AM, Bean S, et al. (2021). Evidence-based recommendations on the use of casirivimab + imdevimab, and sotrovimab for adults in Ontario. *Science Briefs of the Ontario COVID-19 Science Advisory Table*. https://doi.org/10.47326/ocsat.2021.02.45.1.0

BCCDC. (2021). Clinical Reference Group Recommendations: Therapies for COVID-19 [Updated October 19, 2021]. Retrieved from: http://www.bccdc.ca/Health-Professionals-Site/Documents/Recommendation_Therapies_COVID-19.pdf

Cheng, Q., Chen, J., Jia, Q., Fang, Z., & Zhao, G. (2021). Efficacy and safety of current medications for treating severe and non-severe COVID-19 patients: an updated network meta-analysis of randomized placebo-controlled trials. Aging, 13(18), 21866–21902. https://doi.org/10.18632/aging.203522

Gupta, A., Gonzalez-Rojas, Y., Juarez, E., Crespo Casal, M., Moya, J., Falci, D. R., Sarkis, E., Solis, J., Zheng, H., Scott, N., Cathcart, A. L., Hebner, C. M., Sager, J., Mogalian, E., Tipple, C., Peppercorn, A., Alexander, E., Pang, P. S., Free, A., Brinson, C., … COMET-ICE Investigators (2021). Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. The New England journal of medicine, 10.1056/NEJMoa2107934. Advance online publication. https://doi.org/10.1056/NEJMoa2107934

Kreuzberger, N., Hirsch, C., Chai, K. L., Tomlinson, E., Khosravi, Z., Popp, M., ... & Skoetz, N. (2021). SARS-CoV-2-neutralising monoclonal antibodies for treatment of COVID-19. Cochrane Database of Systematic Reviews, (9). https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013825.pub2/full

Siemieniuk, R. A., Bartoszko, J. J., Martinez, J. P. D., Kum, E., Qasim, A., Zeraatkar, D., ... & Brignardello-Petersen, R. (2021). Antibody and cellular therapies for treatment of covid-19: a living systematic review and network meta-analysis. BMJ, 374. https://www.bmj.com/content/374/bmj.n2231

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Table 1. Safety and effectiveness of Sotrovimab in populations at high risk for hospitalization, ICU admission, and mortality from COVID-19

Trial Name	Clinicaltrials.gov identifier	Jurisdiction	Study Population	Comments on safety and effectiveness
ACTIV-3: Therapeutics for Inpatients with COVID-19 (TICO) Currently recruiting	NCT 04501978	Multicentre	Adults (≥18 years) with lab-confirmed COVID-19 Heart failure, neurological conditions, cerebrovascular disease, and thrombotic conditions excluded	No information on Sotrovimab (VIR-7831) yet available
Intramuscular VIR-7831 (Sotrovimab) for Mild/Moderate COVID-19 Estimated completion August 2022	NCT04913675	Multicentre	≥ 12 years AND at high risk of progression of COVID-19 or ≥ 55 years	No information yet available
Safety, Tolerability and Pharmacokinetics of Second Generation VIR-7831 Material in Non-hospitalized Participants With Mild to Moderate COVID-19 (COMET-PEAK) Estimated completion June 2022	NCT04779879	Multicentre	Adults 18-69 years No information about risk factors for severe outcomes	No information yet available
A randomized, open-label, active controlled, parallel group, multicenter phase 3 study to evaluate the efficacy and tolerability of Bamlanivimab and Etesevimab, Casirivimab and Imdevimab, and Sotrovimab versus Standard of Care in patients with mild to moderate COVID-19 disease (AntiCov) Trial ongoing	n/a	Italy / Multicentre	Age ≥ 12 years Unclear if high risk populations are included	No information yet available

Trial Name	Clinicaltrials.gov identifier	Jurisdiction	Study Population	Comments on safety and effectiveness
VIR-7831 for the Early Treatment of COVID-19 in Outpatients (COMET-ICE) Study completed September 2021 Interim results: Gupta et al., 2021	NCT04545060	Multicentre	Participant must be aged 18 years or older AND at high risk of progression of COVID-19* or ≥ 55 years old *Diabetes, obesity, CKD, congestive heart failure, COPD, asthma	No safety signals or differences in effectiveness related to risk factors for severe COVID-19
A Study of Immune System Proteins in Participants With Mild to Moderate COVID-19 Illness (BLAZE-4) Study completed October 2021	NCT04634409	Multicentre	Age 18-65. Two trial arms: Low risk (no comorbs) High risk adult (≥ 65 years, BMI ≥ 35, CKD, diabetes, immunosuppression, Age + CVD, HTN or COPD) High risk kids (Age 12-17 with 85%ile BMI, sickle cell disease, heart disease, neurodevelopmental disorder, medical dependence, asthma, etc.)	No information yet available
AGILE (Early Phase Platform Trial for COVID-19) Currently recruiting; estimated completion April 2022	NCT04746183	Multicentre	Adults ≥ 18 years with at least one well-controlled comorbidity (CVD, chronic lung disease, immune deficiency, diabetes, obesity or hypertension)	No information yet available
UPMC OPTIMISE-C19 Trial, a COVID-19 Study (OPTIMISE-C19) Currently recruiting; estimated completion December 2022	NCT04790786	United States (University of Pittsburgh)	Age ≥ 12 years, COVID-19 positive No comment on risk factors for progression	No information yet available
A Study to Investigate the PK, Safety, and Tolerability of Sotrovimab vs Placebo Administered IV or IM in Japanese and Caucasian Participants Active; estimated completion January 2022	NCT04988152	United States	Age 18-65 Patients with comorbidities are excluded from this trial	No information yet available