CST statement on the use of Monoclonal Antibodies against SARS-CoV-2 for prophylaxis and update on early outpatient therapy for COVID-19 in SOT recipients

1- Tixagevimab and cilgavimab (Evusheld, AZD7442) for preexposure prophylaxis

AZD7442 is a long-acting combination of two monoclonal antibodies targeted against the surface spike protein of SARS-CoV-2, used to prevent COVID-19. In the PROVENT Phase III clinical trial there was a 77 % reduction in the risk of developing symptomatic COVID-19 compared to placebo, with protection from the virus continuing for at least six months.

Administration: Two intramuscular injections in the gluteal area

Data are still lacking in the transplant population and with the Omicron Variant; however preclinical data suggest that AZD7442 still maintains some neutralizing activity against the Omicron variant

In the United States, AZD7442 has been granted Emergency use authorization (EUA) for >=12 years of age, >40 kilograms (88 pounds) in weight for those with moderate to severely compromised immune systems or history of severe adverse reactions to a COVID-19 vaccine and/or component(s) of those vaccines

Health Canada has received the application for *Evusheld* on 11-03-2021 (currently under review).

If approved in Canada, we expect to have a limited supply, and hence transplant centers should consider allocating it based on risk factors for severe outcomes from COVID-19 (see below) and for individuals with increased risk of exposure (education workers, health care providers, living in LTCF or community living).

Below are some considerations for SOT at increased risk for severe outcomes:

-Lung transplant

-Age > 60

- 2 or more comorbidities (BMI>30, CKD, DM, COPD/bronchiectasis, CAD and other heart disease, neurocognitive disorders)

-Received B cell depleting therapy (Rituximab), T- cell depletion (ATG, Alemtuzumab), Belatecept within the past 6 months

- Anti-RBD seronegative after primary series (3 doses of vaccines). Access to anti-RBD might not be available to all SOT in all provinces, and therefore serology should be used only in centers where it is accessible to the majority of SOT recipients.

Evusheld should NOT be used as a replacement for vaccination. SOT recipients should continue to practice infection prevention measures (masking, social distancing, hand hygiene) and encourage household contacts to be vaccinated and get their booster doses.

2- Consideration for Early Outpatient therapy for COVD-19 in SOT

The below antivirals and monoclonal antibodies have been studied in non-hospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression, and showed a decrease in hospitalization and/or death compared to placebo. Most of these trials were performed before the emergence of the Omicron VOC, and did not include vaccinated individuals, thus it is difficult to generalize the efficacy data to vaccinated population. SOT recipients were not included in these trials but are at high risk of COVID-19 disease progression. The agents below are expected to be active against the Omicron VOC.

Preferred

1- Sotrovimab

Sotrovimab is a monoclonal antibody approved and available in Canada for the treatment of early SARS-COV-2 infection in patients at high risk of hospitalization. The COMIT-ICE trial in outpatients with mild to moderate COVID-19 at high risk of hospitalization showed a 79% reduction in the need for hospitalization >24h or death when patients received Sotrovimab compared to placebo. Sotrovimab appears to retain neutralizing ability against Omicron. Administration should be within 7 days of onset of symptoms.

Administration: 500 mg intravenously once over 1 hour with a 1 hour observation period after infusion.

Alternatives:

2- Remdesivir

Remdesivir is a direct-acting nucleotide prodrug inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase. In the recent PINTREE trial, a 3-day course of remdesivir during early COVID-19 illness had an acceptable safety profile and resulted in an 87% lower risk of hospitalization or death compared to placebo.

Administration: intravenously once daily for 3 days (200 mg first dose and 100 mg day 2 and 3).

3- PAXLOVID (awaiting Health Canada approval)

PAXLOVID, a combination of nirmatrelvir (PF-07321332) and ritonavir tablets, is a SARS-CoV-2 protease inhibitor antiviral that inhibits viral replication. In the EPIC-High risk trial, there was 89% reduction in COVID-19-related hospitalization or death when PAXLOVID was given within 5 days of illness to high risk individuals with mild to moderate COVID -19 disease.

It has been granted EUA in the USA. Health Canada has received the application, which is under review

Administration: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all 3 tablets taken together orally twice daily for 5 days. Renal adjustment is required for renal impairment.

Co-administration of PAXLOVID, a CYP3A inhibitor, with other drugs may result in potentially significant drug interactions. These include and are not limited to immunosuppression, antiarrhythmics (amiodarone), anticoagulants (rivaroxaban, warfarin), anticonvulsants, and statins. There are further considerations if the patient is also on an azole antifungal (voriconazole). The interactions with Calcineurin Inhibitors and mTOR inhibitors may be particularly problematic and significant dose adjustments are needed. Therapeutic drug monitoring is recommended, but may be challenging in patients with active COVID infection. **For this reason, other therapies such as monoclonal antibody or outpatient remdesivir may be a preferred option in most transplant patients.**

Drug Class	Effect	Comments
Calcineurins inhibitors	Î Cyclosporin Î Tacrolimus	TDM monitoring concentration of CNI is recommended **Avoid use when TDM is not feasible**

MTOR inhibitors	ÎÎ Sirolimus ÎÎ Everolimus	TDM monitoring concentration of Sirolimus is recommended **Avoid use when TDM is not feasible**

4. **Molnupiravir (awaiting Health Canada approval)**

Molnupiravir is a prodrug of the antiviral ribonucleoside analog N-hydroxycytidine (NHC) and inhibits viral replication by causing an accumulation of errors in the viral genome leading to inhibition of replication. In the Phase 3 MOVe-OUT trial in at risk, non-hospitalized adult patients with mild-to-moderate COVID-19 there was 30% reduction in hospitalization compared to placebo. Molnupiravir should not be used in pregnant or lactating individuals. There is a theoretical risk of SARS-CoV-2 mutant development in patients with prolonged replication due to its mode of action. **Overall the efficacy of Molnupiravir appears low compared to other treatment options and so it may be less preferable**. Molnupiravir should only be used when the other options cannot be used.

It has been granted FDA EUA in the USA for adults >=18 years of age. Health Canada has received the application, which is under review.

Administration: Molnupiravir 800 mg orally (4 x200 mg twice a day) for 5 days.

References:

1. U.S. Food and Drug Administration. FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD™ (tixagevimab co-packaged with cilgavimab). Available at: https://www.fda.gov/media/154701/download. Accessed 22 December 2021
2. Gupta A, Gonzalez-Rojas Y, Juarez E; et al COMET-ICE Investigators. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. N Engl J Med. 2021 Nov 18;385(21):1941-1950. doi: 10.1056/NEJMoa2107934. Epub 2021 Oct 27. PMID: 34706189
3. ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. Lancet Infect Dis. 2021 Dec 23:S1473-3099(21)00751-9. doi: 10.1016/S1473-3099(21)00751-9. Epub ahead of print. PMID: 34953520; PMCID: PMC8700279.
4. Gottlieb RL, Vaca CE, Paredes R et al; GS-US-540-9012 (PINETREE) Investigators. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. N Engl J Med. 2021 Dec 22. doi: 10.1056/NEJMoa2116846. Epub ahead of print. PMID: 34937145.
5. U.S. Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid™. Available at: https://www.fda.gov/media/155050/download. Accessed 22 December 2021.
6. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-additional-phase-23-study-results
7. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et. al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med 2021: Available at: https://www.nejm.org/doi/10.1056/NEJMoa2116044 [Epub ahead of print 16 December 2021]

8. U.S. Food and Drug Administration. Fact Sheet for Patients And Caregivers: Emergency Use Authorization (EUA) Of Molnupiravir For Coronavirus Disease 2019 (COVID-19). Available at: https://www.fda.gov/media/155055/download. Accessed 28 December 2021.