Canadian Society of Transplantation
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**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 (updated August 2023)**

**1- Tixagevimab and cilgavimab (Evusheld, AZD7442) for preexposure prophylaxis** is no longer recommended since the proportion of Omicron sublineages, circulating in Canada, with suspected resistance to Evusheld is very high.

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

The below antivirals and monoclonal antibodies were originally 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 sublineages and did not include vaccinated individuals, thus it is difficult to generalize the efficacy data to vaccinated population. Since then, multiples single center observational studies have shown benefit of early outpatient therapy (within 7 days of symptom onset) in SOT.

**Preferred**

**Sotrovimab** should NO longer be used as first line therapy due the very high proportion of circulating Omicron sublineages with suspected resistance.

**1- Remdesivir**

Remdesivir is a direct-acting nucleotide prodrug inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase. In the PINTREE trial, a 3-day course of remdesivir had an acceptable safety profile and resulted in an 87% lower risk of hospitalization or death compared to placebo. A Canadian study of 210 solid organ transplant recipients with COVID showed that remdesivir, when given as an outpatient early after symptom onset, significantly decreased the hospitalization rate (Hazard ratio 0.12, 95%CI 0.03-0.57).

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

**2- PAXLOVID**

PAXLOVID, a combination of nirmatrelvir/ritonavir (N/T) tablets, is a SARS-CoV-2 protease inhibitor antiviral that inhibit viral replication before viral RNA 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.

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 interaction.** These include and are not limited to immunosuppression, antiarrhythmic (amiodarone), anticoagulant (rivaroxaban, warfarin), anticonvulsants, antifungals (voriconazole), and statins. The interactions with Calcineurin Inhibitors (CNI) and mTOR inhibitors may be particularly problematic and significant dose adjustments are needed. Therapeutic drug monitoring (TDM) is strongly recommended, but may be challenging in patients with active COVID infection. A review of published literature in SOT patients that received N/T showed that a variety of strategies were used to modify immunosuppression during treatment. Regardless of strategy, TDM must be available if N/T is prescribed to an organ transplant recipient with COVID. CNI toxicity has resulted in patients where CNIs were continued during N/T use.

**For this reason, other therapies such as outpatient remdesivir is the preferred option in most transplant patients.**

| Drug Class | Effect | Comments |
|---|---|---|
| Calcineurin inhibitors | Î Cyclosporin<br>Î Tacrolimus | TDM monitoring concentration of CNI is recommended<br>**Avoid use when TDM is not feasible** |
| mTOR inhibitors | ÎÎ Sirolimus<br>ÎÎ Everolimus | TDM monitoring concentration of Sirolimus is recommended<br>**Avoid use when TDM is not feasible** |

3. **Molnupiravir – Not available in Canada**

| Version number | Effective date | Modification |
|---|---|---|
| 1 | January 12, 2022 | |
| 2 | May 20, 2023 | 1. Evusheld no longer recommended<br>2. Under Consideration for early therapy<br>- Sotrovimab no longer be used as first line |

**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.
9. Solera JT, Árbol BG, Bahinskaya I, Marks N, Humar A, Kumar D. Short-course early outpatient remdesivir prevents severe disease due to COVID-19 in organ transplant recipients during the omicron BA.2 wave. Am J Transplant. 2023 Jan;23(1):78-83. doi: 10.1111/ajt.17199. Epub 2023 Jan 11. PMID: 36148607; PMCID: PMC9538117.
10. Solera JT, Árbol BG, Alshahrani A, Bahinskaya I, Marks N, Humar A, Kumar D. Impact of Vaccination and Early Monoclonal Antibody Therapy on Coronavirus Disease 2019 Outcomes in Organ Transplant Recipients During the Omicron Wave. Clin Infect Dis. 2022 Dec 19;75(12):2193-2200. doi: 10.1093/cid/ciac324. PMID: 35445690; PMCID: PMC9278130.
11. Dewey KW, Yen B, Lazo J, Seijo L, Jariwala R, Shah RJ, Quan D, Carpenter B, Paul Singer J, Breen K, Hays S, Florez R. Nirmatrelvir/ritonavir Use With Tacrolimus in Lung Transplant Recipients: A Single-center Case Series. Transplantation. 2023 May 1;107(5):1200-1205. doi: 10.1097/TP.0000000000004394. Epub 2022 Oct 28. PMID: 36525555; PMCID: PMC10125013.
12. Tang Y, Li Y, Song T. Optimizing the use of nirmatrelvir/ritonavir in solid organ transplant recipients with COVID-19: A review of immunosuppressant adjustment strategies. Front Immunol. 2023 Apr 4;14:1150341. doi: 10.3389/fimmu.2023.1150341. PMID: 37081880; PMCID: PMC10111375.