UHN Ajmera Transplant Centre

PAXLOVID USE IN TRANSPLANTATION AND MANAGEMENT OF DRUG-DRUG-INTERACTIONS WITH IMMUNOSUPPRESSION

This document is not meant to be all inclusive. Please refer to Transplant Infectious Disease service and Transplant Pharmacy team for further guidance as needed.

KEY POINTS

1. Nirmatrelvir/ritonavir (Paxlovid) will be challenging to use in many transplant patients due to significant drug interactions and the difficulty with therapeutic drug monitoring in outpatients with active COVID-19 infection.
2. Molnupiravir appears to have relatively low efficacy and has not been evaluated in transplant recipients and is not approved in Canada.
3. **Based on the above, early use of either an appropriate monoclonal antibody or outpatient intravenous remdesivir is preferable in transplant outpatients as first-line therapy to prevent progression.**
4. In some patients, alternative therapies may not be possible. Paxlovid may be considered in these situations or if supply of other therapies is not available.

DOSING RECOMMENDATIONS

The recommended dosage for Paxlovid is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all three tablets taken together orally twice daily for 5 days**.** Paxlovid (both nirmatrelvir and ritonavir tablets) can be taken orally with or without food. The tablets should be swallowed whole and not chewed, broken, or crushed.

Renal impairment

eGFR	Dose Recommendation
≥ 60 mL/min	No dose adjustment required
≥ 30 to < 60 mL/min	Reduce dose to 150 mg nirmatrelvir and 100 mg ritonavir (i.e. 50% dose reduction on nirmatrelvir)
< 30 mL/min	Not recommended

Hepatic impairment

Paxlovid is not recommended for use in patients with severe hepatic impairment (Child Pugh Class C).

MANAGEMENT OF PAXLOVID INTERACTIONS WITH IMMUNOSUPPRESSANTS

Suggested management of drug interactions of Paxlovid with calcineurin inhibitors (CNI) and mammalian target of rapamycin inhibitors (mTORi) in recipients of solid organ or hematopoietic stem cell transplants are described in Table 1 below.

Recommendations are based on the following considerations:

- pharmacology and pharmacokinetics of the individual immunosuppressive agents
- well-established potency of CYP 3A inhibition with ritonavir and magnitude of interaction with CNI/mTORi
- onset, peak and duration of CYP 3A inhibitory effects of ritonavir
- patient safety – to minimize risk of toxicity associated with CNI/mTORi over-exposure and to avoid over-immunosuppression in the setting of viral infection

Checklist:

1. Hold or adjust all CNI and mTORi at time of Paxlovid initiation as outlined below.
2. Start Paxlovid at the time interval described below from time of last dose of CNI or mTORi.
3. Check CNI or mTORi level as described below and restart / adjust when appropriate.

Table 1: Paxlovid Initiation and Immunosuppressant Management Guidelines

Immunosuppressant	Starting Paxlovid	When to Check Level and Re-Start/Adjust Immunosuppressant
Tacrolimus • Immediate release (Prograf, generics)	Hold tacrolimus and start Paxlovid 12 hours* from last dose of immediate release tacrolimus. Hold tacrolimus throughout 5 days Paxlovid treatment course.	Check level 1-2 days after last dose of Paxlovid. If level therapeutic or subtherapeutic, resume tacrolimus at 25-75% of baseline dose. Repeat level every 2-4 days and adjust dose PRN. If level supra-therapeutic, continue to hold tacrolimus and repeat level in 2-4 days to assess resumption.
Tacrolimus • Extended release (Advagraf) • Prolonged release (Envarsus)	Hold tacrolimus and start Paxlovid 24 hours* from last dose of extended or prolonged release tacrolimus. Hold tacrolimus throughout 5 days Paxlovid treatment course.	
Cyclosporine (Neoral, generics)	Reduce cyclosporine total daily dose by 80%* and start Paxlovid in 12 hours. Consider switch to once daily dosing. Continue with 80% cyclosporine dose reduction throughout 5 day Paxlovid treatment course.	Check level 1-2 days after last dose of Paxlovid. If level subtherapeutic, increase cyclosporine dose. Consider resumption of twice daily dosing. If level therapeutic, continue with current cyclosporine dose. If level supra-therapeutic, reduce or hold current cyclosporine dose. In all cases, repeat level in 2-4 days and continue to adjust dose PRN.
Sirolimus (Rapamune)	Hold sirolimus and start Paxlovid 24 to 48 hours* from last sirolimus dose. Hold sirolimus throughout 5 day Paxlovid treatment course.	Check level 1-2 days after last dose of Paxlovid. If level therapeutic or subtherapeutic, resume sirolimus at 50% of baseline dose. Repeat level every 7 days and adjust dose PRN. If level supra-therapeutic, continue to hold sirolimus and repeat level in 5-7 days to assess resumption.
Everolimus	Hold everolimus and start Paxlovid 12 hours* from last everolimus dose. Hold everolimus throughout 5 day Paxlovid treatment course.	Check level 1-2 days after last dose of Paxlovid. If level therapeutic or subtherapeutic, resume everolimus at 25-50% of baseline dose. Repeat level every 2-4 days and adjust dose PRN. If level supra-therapeutic, continue to hold everolimus and repeat level in 2-4 days to assess resumption.

*High risk of CNI/mTORi toxicity if initiating Paxlovid in the setting of supra-therapeutic CNI/mTORi level. If level suspected or confirmed as supra-therapeutic, recommend to further delay initiation of Paxlovid where possible.

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