AST Statement on Oral Antiviral Therapy for COVID-19 for Organ Transplant Recipients

The FDA has given Emergency Use Authorization (EUA) for two oral antivirals (Nirmatrelvir/Ritonavir (Paxlovid);Pfizer and Molnupiravir (Lagevrio); Merck) for treatment of COVID-19. The purpose of this statement is to provide a framework for use of these antivirals in organ transplant recipients.

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.
3. Based on the above, early use of either an appropriate monoclonal antibody or outpatient intravenous remdesivir may be preferable in transplant outpatients as first-line therapy to prevent progression.

Preamble

Both nirmatrelvir/ritonavir (Paxlovid) and Molnupiravir are meant to be used as outpatient therapy for COVID-19, for high-risk patients early in disease (within 5 days of symptom onset). Because data to date indicates that molnupiravir is likely less effective than monoclonal antibody with activity against circulating variants or nirmatrelvir/ritonavir, it should be considered a second line drug if more effective alternatives are available and can be safely administered. There are no data on the use of either antiviral for pre-exposure or post-exposure prophylaxis or in hospitalized patients with severe COVID-19 and these uses are excluded in the EUA.

Considerations for Use

Transplant recipients are in the category of patients at high risk of COVID-19 disease and will be eligible for outpatient antivirals. Oral antivirals could also be used early post-symptom onset for patients admitted for another reason that contract COVID. Given that initial supply of antivirals is likely to be limited, prioritization for those at increased risk of disease due to age, comorbidity, type of transplant seems reasonable. We also recommend that providers consider other therapies available for early disease and shown to reduce progression to severe disease. These include monoclonal antibodies or early treatment with intravenous remdesivir. These treatments may also obviate concerns of drug interactions with oral antivirals (see below).

Drug Interactions and Safety

Paxlovid has the potential for drug interactions with immunosuppression based on the mechanism of action of ritonavir. Ritonavir is a common medication used as part of the treatment regimen for HIV and is a potent inhibitor of CYP3A. The inhibition with ritonavir may be maximum 2-3 days after exposure and last 3-4 days after it is discontinued. Limited

experience with ritonavir in the HIV+ transplant setting suggests that CNI levels can increase significantly and doses of CNI as well as mTOR inhibitors need to be adjusted. Azole antifungals are also CYP3A inhibitors and therefore patients who are already on azole antifungals may require less dose adjustment of CNI. Paxlovid is a 3C-like protease inhibitor. We also note that historically, when 3C protease inhibitors have been used for other viral infections, monotherapy with 3C protease inhibitors has resulted in the development of viral resistance. Thus, the risk of emergent resistance in SARS-CoV-2 may be higher in immunosuppressed patients. For molnupiravir, there is a theoretical risk that it may promote mutations in the spike protein of SARS-CoV-2.

The following table provides a comparison of the two drugs:

	Nirmatrelvir/Ritonavir (Paxlovid)	Molnupiravir (Lagevrio)
Mechanism of Action	Inhibits the main protease of SARS-CoV-2. Given with ritonavir to boost levels	Nucleoside analog targets RdRp of SARS-CoV-2 and introduces mutations in viral RNA
Population	Age ≥12 years and ≥40kg Mild to moderate COVID-19 and high risk of progression to hospitalization or death	Age ≥18 years Mild to moderate COVID-19 and high risk of progression to hospitalization or death. Less preferred option.
Dose	Nirmatrelvir 300mg po BID plus Ritonavir 100mg po BID 5 day course	800mg po BID 5 day course
Efficacy (high risk population)	89% for hospitalization or death in phase 2/3 RCT	30% for all cause hospitalization or death in a phase III RCT when given within the first 5 days of symptom onset
Drug Interactions	Ritonavir will increase levels of drugs metabolized by P450 CYP3A and increase levels of sirolimus, everolimus, tacrolimus, cyclosporin** Multiple other interactions including antifungals and anticoagulants (see FDA sheet)	None known
Potential strategy related to immunosuppression interaction*	1. Consider monoclonal antibody or IV remdesivir x 3 days in order to avoid need for Paxlovid 2. Adjust CsA significantly (e.g. reduce dose **to** 20% (one-fifth) of current dose. Close monitoring of levels recommended. 3. Reduce dose substantially or hold tacrolimus. Close monitoring of levels recommended (e.g. In HIV+ transplant	Not applicable

	patients on Ritonavir, doses of 0.5mg Tacrolimus per week have been used). 4. For sirolimus, a similar approach is needed	
Common side effects	Dysgeusia, diarrhea	Diarrhea, Nausea, Anemia
Renal/Hepatic function adjustment	For GFR 30-60 mL/min, reduce dose to nirmatrelvir 150mg BID with Ritonavir 100mg BID Not recommended if GFR <30 mL/min or with severe hepatic impairment (Child-Pugh Class C)	No dose adjustment required but not studied in CKD
Pregnancy	Contraindicated	Contraindicated
Activity vs. Variants	All known variants	All known variants

*This is only a suggested strategy. Consult with local pharmacist. Only use Paxlovid if CNI/mTOR levels can be monitored during COVID infection and treatment. Drug interaction may differ if patients are on other drugs that inhibit CYP3A such as azole antifungals. Patients on belatacept or other non-CNI, non-mTOR based regimens would be better candidates for Paxlovid. Also consider patient's individual risk of rejection.

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