NEW DRUGS, HOT TOPICS, & PANEL DISCUSSION

Updates from the Transplant Pharmacist

PANEL MEMBERS

- Kimberly Harrison, PharmD, BCPS, BCTXP
  - Heart Transplant Clinical Pharmacist, Vanderbilt University Medical Center
- Nikita Wilson, PharmD, BCPS, MMHC
  - Kidney/Pancreas Transplant Clinical Pharmacist, Vanderbilt University Medical Center
- Carissa Garza, PharmD, MMHC
  - Liver Transplant Clinical Pharmacist, Vanderbilt University Medical Center

DISCLOSURE

- The speakers have nothing to disclose relevant to this presentation.
- Presentation will include discussion of off-label uses of medications in solid organ transplant.

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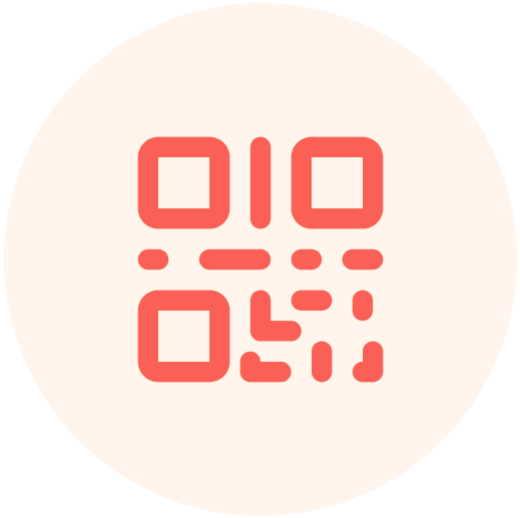

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What is your experience with the new CMV drug maribavir?

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MARIBAVIR (LIVENCITY™)

FDA Approval Date: Nov 2021

- Only available through a limited specialty pharmacy network

Indication

- Treatment of CMV refractory to treatment with other anti-virals
- Adults & pediatrics ≥ 12yo & ≥ 35kg

Mechanism

- pUL97 kinase inhibitor (halts viral replication)
- Active against UL97 and UL54 mutations
- Resistance has been reported

Livencity [package insert]. Lexington, MA: Takeda Pharmaceuticals America, Inc; 2022.

MARIBAVIR (LIVENCITY™)

Formulations

- 200mg tablets (okay to crush or disperse in water for per tube administration)

Dosing

- 400mg PO BID with or without food
- No renal or hepatic dose adjustments (not studied in ESRD or severe hepatic disease)

Side Effects

- Taste disturbance (resolves while on therapy)

Drug Interactions

- 3A4 substrate/weak inhibitor
  - Close monitoring of immunosuppressants
  - Higher doses required when used with carbamazepine, phenytoin or phenobarbital
- Pgp/BCRP inhibitor

Livencity [package insert]. Lexington, MA: Takeda Pharmaceuticals America, Inc; 2022.

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What is your center's approach to utilizing nirmeltravir/ritonavir (Paxlovid) for the treatment of COVID?

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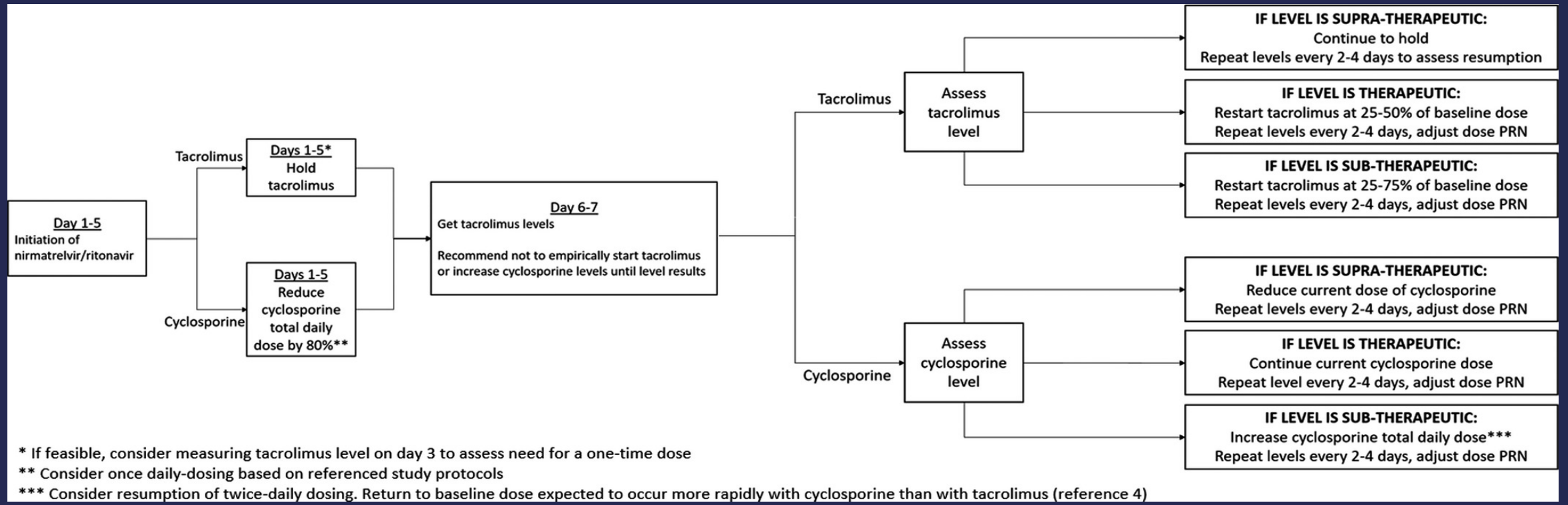
NIRMATRELVIR/ RITONAVIR (PAXLOVID™)

- **FDA EUA Approval Date**: Dec 2021
- **Indication:**
  - Treatment of mild-to-moderate COVID-19 at high risk for progression to severe disease, including hospitalization and death
  - Agre≥ 12yo & ≥ 40kg
- **Mechanism:**
  - Nirmatrelvir: SARS-CoV-2 protease inhibitor w/ ritonavir booster
- **Dosing:**
  - Nirmatrelvir 300mg BID + Ritonvair 100mg BID for 5 days
  - Requires renal dose adjustment
- **Adverse Effects:**
  - Dysgeusia, diarrhea
  - Reports of anaphylaxis and hypersensitivity reactions
- **Drug Interactions:**
  - Strong 3A4 inhibitor

Paxlovid [package insert]. Pfizer, Sept 2022.

SALERNO ET AL

- 25 adult SOT taking tacrolimus (n=21), cyclosporine (n=4), everolimus (n=3), sirolimus (n=1)



Outcome: 4/25 required hospitalization, no deaths, 1 supratherapeutic trough level

Am J Transplant. 2022;22:2083–2088. Am J Transplant. 2022;22(7):1925-1926

AST STATEMENT ON ORAL ANTIVIRAL THERAPY FOR COVID-19 FOR SOT 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.

Kumar D, Humar A, Ison MG, et al. AST statement on oral antiviral therapy for COVID. Available at https://www.myast.org/sites/default/files/AST%20Statement%200n%20Oral%20Antiviral%20Therapy%20for%20 COVID%20Jan%204%20%282%29.pdf. Accessed October 10, 2022

NIH COVID TREATMENT GUIDELINES: DRUG-DRUG INTERACTIONS BETWEEN RITONAVIR-BOOSTED NIRMATRELVIR (PAXLOVID) AND CONCOMITANT MEDICATIONS

- Drug interactions that can be safely managed should not preclude the use of this medication

Prescribe Alternative COVID-19 Therapy

For these medications, management strategies are not possible or feasible, or the risks outweigh the potential benefits.

Anticonvulsants
- Carbamazepine
- Phenobarbital
- Phenytoin
- Primidone

Anti-infectives
- Glecaprevir/pibrentasvir
- Rifampin
- Rifapentine

Immunosuppressants
- Voclosporin

Cardiovascular
- Amiodarone
- Clopidogrel[a,b]
- Disopyramide
- Dofetilide
- Dronedarone
- Eplerenone
- Flecainide

Cardiovascular, continued
- Ivabradine
- Propafenone
- Quinidine

Neuropsychiatric
- Clozapine
- Lurasidone
- Midazolam (oral)
- Pimozide

Pulmonary hypertension
- Sildenafil
- Tadalafil
- Vardenafil

Miscellaneous
- Bosentan
- Certain chemotherapeutic agents[c]
- Ergot derivatives
- Lumacaftor/ivacaftor
- St. John's wort
- Tolvaptan

https://www.covid19treatmentguidelines.nih.gov/. Accessed October 10, 2022

NIH COVID TREATMENT GUIDELINES

- The use of another COVID-19 therapy may need to be considered. These immunosuppressants have significant drug-drug interaction potential with ritonavir, and **they should not be used if close monitoring, including therapeutic drug monitoring, is not feasible**. Consult a patient's specialist providers before coadministering these immunosuppressants and ritonavir-boosted nirmatrelvir. See the American Society of Transplantation statement for more information.

Temporarily Withhold Concomitant Medication, if Clinically Appropriate		
Withhold these medications during ritonavir-boosted nirmatrelvir treatment and for at least 2–3 days after treatment completion. They may need to be withheld for longer if the patient is an adult of advanced age or the medication has a long half-life. If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.		
Anticoagulants • Rivaroxaban[d] **Anti-infectives** • Erythromycin **BPH**	**Immunosuppressants**[e] • Everolimus • Sirolimus • Tacrolimus **Lipid-modifiers**	**Neuropsychiatric** • Suvorexant • Triazolam[g] **Erectile dysfunction** • Avanafil

Adjust Concomitant Medication Dose and Monitor for Adverse Effects		
Consult the Liverpool COVID-19 Drug Interactions website or the Ontario COVID-19 Science Advisory Table for specific dosing recommendations.[i] If the dose of the concomitant medication cannot be adjusted, withhold the medication (if clinically appropriate) or use an alternative concomitant medication or COVID-19 therapy.		
Anticoagulants • Apixaban • Dabigatran • Edoxaban **Anti-infectives** • Clarithromycin • Itraconazole • Ketoconazole	**Erectile dysfunction** • Sildenafil • Tadalafil • Vardenafil **Immunosuppressants** • Cyclosporine[e] • Dexamethasone[j] • Fedratinib	**Neuropsychiatric**, continued • Diazepam[g] • Estazolam[g] • Flurazepam[g] • Iloperidone • Lumateperone • Pimavanserin • Quetiapine

https://www.covid19treatmentguidelines.nih.gov/. Accessed October 10, 2022

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What is your go-to medication for treatment of migraines or headaches in transplant patients?

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CALCITONIN GENE-RELATED PEPTIDE (CGRP) ANTAGONISTS

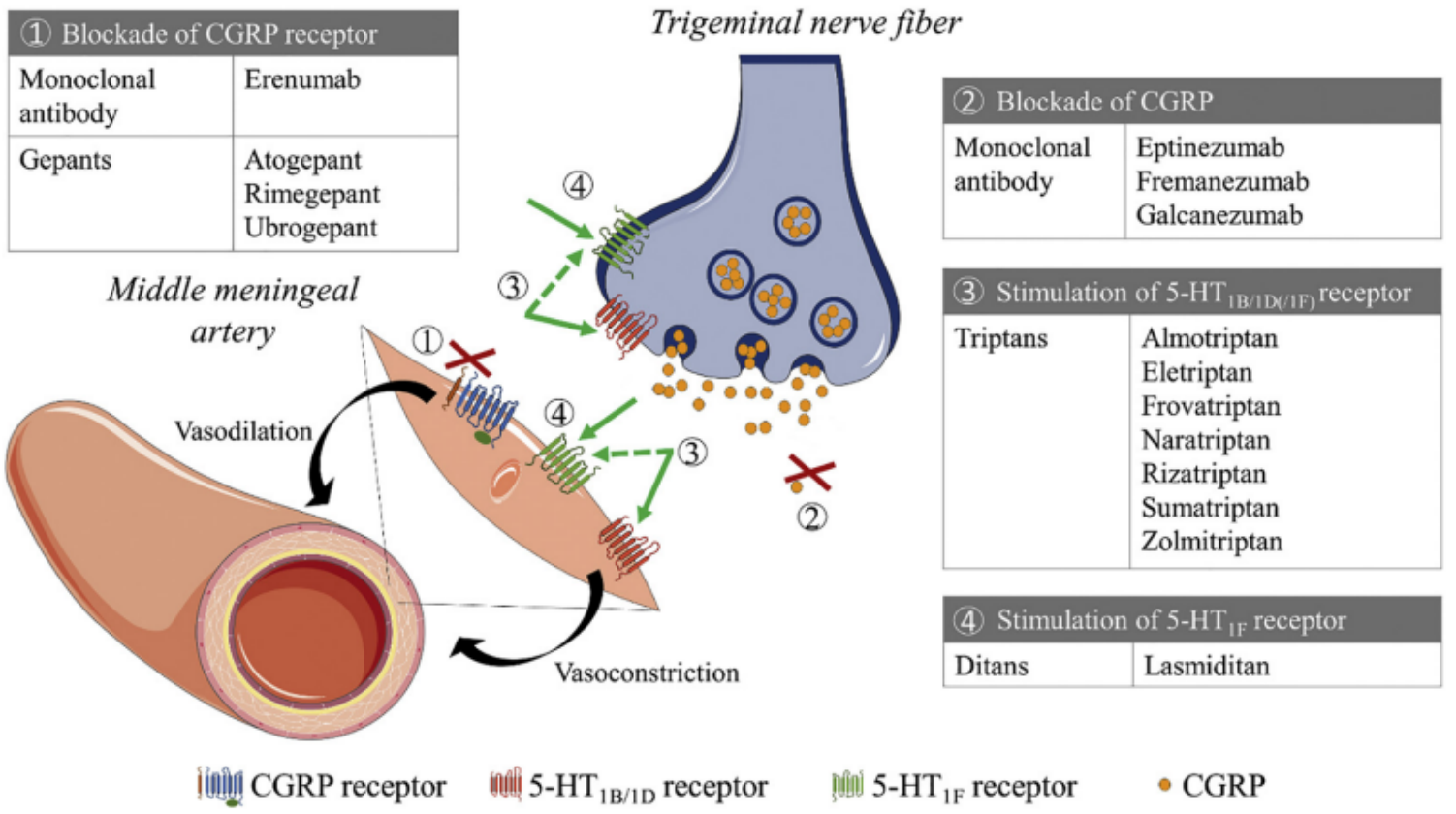

Fig. 1. Overview of migraine-specific medications and their possible targets. Migraine drugs can act through blockade of CGRP or its receptor or by stimulation of 5-$HT_{1B/1D/1F}$ receptors.

Pharmacology & Therapeutics. 2020;211:107528.

AVAILABLE CGRP ANTAGONISTS

Drug Name	Type of Treatment	Route	Medication Target
Atogepant (Qulipta)	Prevention	Oral	CGRP receptor antagonist
Erenumab (Aimovig)	Prevention	SubQ	CGRP receptor antagonist (mAb)
Rimegepant (Nurtec)	Prevention Treatment	Oral Oral	CGRP receptor antagonist
Ubrogepant (Ubrelvy)	Treatment	Oral	CGRP receptor antagonist
Eptinezumab (Vyepti)	Prevention	IV	CGRP ligand antagonist (mAb)
Fremanezumab (Ajovy)	Prevention	SubQ	CGRP ligand antagonist (mAb)
Galcanezumab (Emgality)	Preventtion	SubQ	CGRP ligand antagonist (mAb)

mAb: monoclonal antibody

Pharmacology & Therapeutics. 2020;211:107528.

CGRP ANTAGONISTS

Adverse Effects

- Injection site reactions (injectables)
- Hypertension (Aimovig)
- Theoretical concern for cardiac side effects

Drug Interactions

- Limited effect on other agents

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Which maintenance immunosuppressive medication do you have the most trouble with getting approved through insurance?

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MEDICATION ACCESS

TABLE 1 Maintenance immunosuppressants with on- or off-label indications.

	CNI				Steroids	Antimetabolites			mTORi		Co-stimulation inhibitors
		Tacrolimus				MPA					
	CyA-ME	IR-TAC	ER-TAC	LCPT	Prednisone	MMF	MPS	Azathioprine	Sirolimus	Everolimus	Belatacept
Kidney	FDA	FDA	FDA	FDA	FDA±	FDA	FDA	FDA	FDA	FDA	FDA
Pancreas	OFF-LABEL	OFF-LABEL	†	†	†	OFF-LABEL	†	OFF-LABEL	†	†	†
Liver	FDA	FDA	†	†	OFF-LABEL	FDA	OFF-LABEL	OFF-LABEL	†	FDA	†
Intestine	†	OFF-LABEL	†	†	†	†	†	†	†	†	†
Heart	FDA	FDA	†	†	FDA±	FDA	OFF-LABEL	OFF-LABEL	OFF-LABEL	OFF-LABEL	†
Lung	OFF-LABEL	FDA	†	†	†	OFF-LABEL	OFF-LABEL	†	†	†	†

Abbreviations: †, neither FDA-approved nor endorsed by Micromedex and/or AHFS-DI ± delayed-release formulation only; CNI, calcineurin inhibitors; CyA-ME, cyclosporine, microemulsion; ER-TAC, extended-release tacrolimus; FDA, FDA-approved indication; IR-TAC, immediate release tacrolimus; LCPT, LCP-tacrolimus; MMF, mycophenolate mofetil; MPA, mycophenolic acid; MPS, mycophenolate sodium; mTORi, mammalian target of rapamycin inhibitors; OFF-LABEL, endorsed by CMS-approved compendia Micromedex and/or AHFS. CMS-approved compendia accessed March 2022.

Nelson J, Alvey N, Bowman L, et al. Pharmacotherapy. 2022;42(8):599-633.

NEW CONSENSUS RECOMMENDATIONS

PHARMACOTHERAPY

SPECIAL ARTICLE

Consensus recommendations for use of maintenance immunosuppression in solid organ transplantation: Endorsed by the American College of Clinical Pharmacy, American Society of Transplantation, and International Society for Heart and Lung Transplantation: An executive summary

Joelle Nelson[1,2,3] | Nicole Alvey[4,5] | Lyndsey Bowman[6] | Jamie Schulte[7] | Maria Cristina Segovia[8] | Jennifer McDermott[9,10] | Helen S. Te[11] | Nikhil Kapila[8] | Deborah Jo Levine[12] | Robert L. Gottlieb[13] | Jose Oberholzer[14] | Maya Campara[15,16]

Nelson J, Alvey N, Bowman L, et al. Pharmacotherapy. 2022;42(8):599-633.

NELSON J, ALVEY N, BOWMAN L, ET AL. PHARMACOTHERAPY. 2022;42(8):599-633.

2. Are extended-release formulations of tacrolimus as effective as immediate release (IR-TAC) formulation?
   - 2.1. *Recommendation (1A kidney; 1B liver; 1C heart).* Once daily, extended-release formulations of tacrolimus are equally efficacious as IR-TAC for the prevention of acute rejection and patient and allograft survival.
   - 2.2. *Recommendation (1B kidney, pancreas, liver; 1C heart; 2D lung).* Kidney, liver, heart, and lung transplant recipients on LCP-tacrolimus (LCPT) have comparable tacrolimus exposure as those receiving IR-TAC with a reduced mean total daily dose (TDD). Pancreas and lung transplant recipients on extended-release tacrolimus (ER-TAC) had comparable tacrolimus exposure compared to those on IR-TAC.
   - 2.3. *Recommendation (2C pancreas).* Despite similar exposure, at 12 months, LCPT-treated patients experienced less biopsy poven acute rejection (BPAR) without affecting patient or allograft survival.
   - 2.4. *Recommendation (2D intestine).* There are limited data for ER-TAC use in intestine transplantation. However, there is no evidence of harm when used in this population.

1. *Is MPA the superior antimetabolite in preventing allograft rejection and/or loss at 12 months?*
   - 6.1. *Recommendation (2B kidney).* There may be benefit to the use of MPA over azathioprine for the prevention of acute rejection.
   - 6.2. *Recommendation (1C pancreas, 1B liver).* MPA is more effective than azathioprine in reducing acute rejection rates at 12 months.
   - 6.3. *Recommendation (2D intestine).* Despite an absence of studies directly comparing MPA to azathioprine, MPA has been adopted as a standard component of early M-IMS in this population in lieu of azathioprine.
   - 6.4. *Recommendation (1B heart).* MPA has demonstrated better patient and allograft survival over azathioprine with a decreased incidence and severity of acute rejection.
   - 6.5. *Recommendation (2C lung).* Comparative data have variable results although there are some observational and cohort data demonstrating less acute rejection with MPA as compared to azathioprine and potential benefit in switching to MPA in the setting of BOS.

TRANSPLANT MEDICATION ACCESS GUIDE

American Society of Transplantation Transplant Pharmacy Community of Practice

&

American College of Clinical Pharmacy Immunology/Transplant Practice and Research Network

Medication Access Workgroup

Medication	Company	Program Types	Resource
Astagraf XL (tacrolimus XL)	Astellas	Copay Card	Astellas Cares
Cellcept (mycophenolate mofetil)	Genentech	Copay Card, or Patient Assistance through the Genentech Access to Care Foundation	Patient Assistance for CellCept® (mycophenolate mofetil)
Cresemba (isavuconazole)	Astellas	7-Day Quick Start, Copay Card, Patient Assistance	CRESEMBA Support Solutions
Gengraf (cyclosporine modified)	AbbVie	Patient Assistance	myAbbVie Assist
Envarsus XR (tacrolimus XR)	Veloxis	Free 30 Day Trial, Copay Card, Patient Assistance	Veloxis Financial Support

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What other resources do you use for help with medication access?

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PANEL DISCUSSION

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Audience Q&A Session

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Panel Discussion

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