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Comprehensive information about medications, biologics, nutrients, and drug therapy

Formulary Information

mTOR Inhibitor Interactions with Azole Antifungals

By: Sarah Petite, Pharm.D.

Introduction: The mammalian target of rapamycin (mTOR) inhibitors, sirolimus (Rapamune®) and everolimus (Zortress®) are immunosuppressants that may be utilized in solid organ transplant recipients.[1,2] These medications, which are cytochrome P450 (CYP) 3A4 substrates, have a narrow therapeutic index and are subject to many different serious drug interactions. The strong CYP3A4 inhibition caused by several members of the azole antifungal class may be particularly concerning since coadministration with mTOR inhibitors can lead to an increased risk of mTOR-associated toxicity. The potential for serious consequences of increased mTOR exposure associated with concurrent use of some azole antifungals has led to this drug combination being classified as contraindicated in the various package inserts and many drug information databases.[3] However, the contraindication is not absolute and there are clinical scenarios when mTOR inhibitors and azole antifungals can be used together. Knowledge of the degree of CYP3A4 inhibition and required empiric dose reductions can help guide pharmacists through the management of this interaction. A summary of the management options is provided in Table 1.

mTOR Inhibitor Dosage Modification Not Needed with Fluconazole: Fluconazole is classified as a category D interaction with sirolimus and everolimus. However, nearly 80% of fluconazole is eliminated unchanged in the urine and the metabolism is not heavily reliant on hepatic mechanisms.[3] Due to the low hepatic clearance, there are no empiric mTOR inhibitor dose reductions required. However, there have been reports of increased mTOR inhibitor concentrations following fluconazole initiation.[4] Therefore, therapeutic drug levels of the mTOR inhibitor

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Pregnancy Categories: When an "A" Doesn't Make the Grade

By: Della Bahmandar, Pharm.D.

Introduction: On December 3, 2014, the Food and Drug Administration (FDA) issued a final rule which changes the way pregnancy and breastfeeding labeling information is presented for prescription medications.[1] The new labeling recommendation was created in response to decades of criticism of the oversimplification and ambiguous nature of the current pregnancy-risk category system. The new labeling rule requires the replacement of the current pregnancy-risk category letters of A, B, C, D, and X with three updated subsections displayed in the product's package insert. These subsections will contain more detailed information regarding the drug's effects on pregnancy, lactation, and fertility and are designed to improve risk versus benefit assessments. The new labeling system will also provide clinical consideration of potential risks of not treating a given condition during pregnancy or breastfeeding. Scheduled to take effect on

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should be closely monitored to ensure levels remain within goal range for the given organ and time frame post-transplantation.

mTOR Inhibitor Dosage Reductions with Concurrent Itraconazole: Itraconazole is a category D interaction with sirolimus and category X interaction with everolimus.[3] Despite these warnings to avoid use of itraconazole with these medications, there are case reports of the use of sirolimus with itraconazole after empiric mTOR inhibitor dose reductions of 75% to 90%.[4,5] The available dosage forms of the mTOR inhibitors are described in Table 2 to help guide these empiric dose reductions. The use of everolimus and itraconazole is not well reported in the literature and recommendations for empiric everolimus dose reductions are extrapolated from reports of concurrent use of voriconazole and posaconazole.

Voriconazole and Posaconazole: Is Concomitant Use with mTOR Inhibitors Allowed? Both sirolimus and everolimus are category X drug interactions with voriconazole and posaconazole.[3] Although these are considered contraindicated drug combinations, there may be clinical scenarios requiring concomitant use. Case reports provide guidance on the successful use of either voriconazole or posaconazole with mTOR inhibitors through dramatic empiric dose reductions of the mTOR inhibitors by up to 90%.[4,6,7]

The Bottom Line: If the clinical scenario requires concomitant use of mTOR inhibitors and azole antifungals, the drug-drug interaction does not necessarily prevent concurrent use. No dosage adjustment of a mTOR inhibitor is needed when given along with fluconazole. For itraconazole, voriconazole, and posaconazole, the pharmacist should evaluate if the mTOR inhibitor dosage has already been adjusted. If the dosage adjustment has been made, concomitant use can occur. However if it is unclear or no dose adjustment has been made, the prescriber or transplant clinical pharmacist should be contacted.

References:

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Table 1: Drug Interaction Management [3-7]

Medication	Drug Interaction Category	Management
Fluconazole	D	No empiric dose reduction
Itraconazole	Sirolimus: D Everolimus: X	Empiric dose reduction of mTOR inhibitor by 75-90%
Voriconazole	X	Empiric dose reduction of mTOR inhibitor by 75-90%
Posaconazole	X	Empiric dose reduction of mTOR inhibitor by 75-90%

mTOR=mammalian target of rapamycin
Category D drug interaction=Consider therapy modification
Category X drug interaction=Avoid combination

Table 2: mTOR Inhibitor Dosage Forms[3]

Medication	Available Dosage Forms
Sirolimus (Rapamune®)	Tablets: 0.5 mg, 1 mg, 2 mg Oral solution: 1 mg/mL
Everolimus (Zortress®)*	Tablets: 0.25 mg, 0.5 mg, 0.75 mg

mTOR=mammalian target of rapamycin
*Everolimus is also available as an oral chemotherapy medication branded as Afinitor®

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June 30, 2015, manufacturers of newly approved drugs will be required to use this labeling immediately, while new labeling will be phased in gradually for previously approved products.[1]

Why is the FDA Taking Action? In 1979, the FDA adopted the Pregnancy Category System to provide clinicians with an assessment of the risk of teratogenicity of drugs during pregnancy.[2] During that time, medications were less commonly used during pregnancy, in part due to the perception that pregnant women were young and healthy and did not require drug therapy. However, recent data suggest that 70% of women use at least one prescription medication during pregnancy, with approximately 50% using four or more medications.[3,4]

Problems with Our Current System: In regards to the pregnancy-risk category letter system, there have been several notable concerns. First, it does not reflect the effects of drug exposure at various times of pregnancy.[2,5] For example, lisinopril, which was classified under category D, does not appear to present a significant risk during the first trimester, but fetal exposure in the second/third trimester is associated with severe toxicity, including death.[6] Next, it is frequently misinterpreted that the successive categories represent increasing severity of malformation.[2,5] For example, lisinopril falls under a lower pregnancy-risk category than oral contraceptives which are classified as category X without documented teratogenicity.[5,7] Finally, it can be misconstrued that all medications in the same pregnancy-risk category carry equal risk.[2,5] For example, warfarin and oral contraceptives are both listed as category X; however, warfarin carries up to a 25% risk of serious defects, whereas oral contraceptives carry a low absolute risk of fetal harm.[6,7]

Whole New Look: To address these concerns, the FDA has proposed the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR will provide guidance regarding the creation of subsections in the package insert which will contain more detailed information about the effect of the medication on pregnancy, lactation, and fertility.[1,8] The first subsection, labeled *Pregnancy*, will include pertinent information related to the use of the drug during pregnancy such as dose adjustments, maternal and fetal disease-associated risk, adverse reactions affecting the mother and/or fetus, and the effect of the drug on labor and delivery. Additionally, information on pregnancy exposure registries may be included. The second subsection, *Lactation,* will include information on the presence of the drug in breast milk and its effects on the breast-fed child and on milk production. The third subsection, *Females and Males of Reproductive Potential*, will provide information when pregnancy testing and/or contraception is required and will include data, when available, regarding the effects of the drug on fertility.

Things to Keep a Closer Eye On: Companies will be required to remove the pregnancy letter categories from the labeling of all prescription drugs and biological products and, in some cases, revise the product labeling with the updated subsections. The pregnancy-risk category must be removed and replaced with the new subsections within 3 to 5 years for drugs approved on or after June 30, 2001, while the pregnancy-risk category of drugs approved before June 30, 2001 will be required to be removed within 3 years, but the replacement with the new subsections for those older medications will remain voluntary.[8] Labeling for over-the-counter (OTC) medicines will not change, as OTC drug products are not affected by the PLLR. During the implementation phase, the current pregnancy categorization and the new labeling system will both be in effect, which may lead to some confusion. In summary, the long-awaited shift away from the FDA's pregnancy-risk category labeling has arrived and practitioners must begin to acclimate to the new system which will ultimately serve to support and enhance clinical decision-making in the pregnant and breastfeeding populations.

References:

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Additions to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Alemtuzumab (Lemtrada®)	Monoclonal Antibody	Treatment of multiple sclerosis	Restriction: Restricted to the Department of Neurology for treatment of multiple sclerosis **for outpatient use only**
Blinatumomab (Blincyto®)	Antineoplastic Agent	Philadelphia chromosome relapsing/remitting B-cell precursor ALL	Restriction: Restricted to the Department of Hematology and Medical Oncology
Clevidipine (Cleviprex®)	Calcium Channel Blocker	Hypertension	N/A
Hydroxyethyl Starch (Voluven®)	Volume Expander	Plasma Volume Expander	Restriction: Restricted to use in ORs and PACU Note: Hetastarch (Hextend® was removed from the CCHS Formulary)
Nivolumab (Opdivo®)	Antineoplastic Agent	Treatment of unresectable/ metastatic melanoma	Restriction: Restricted to the Department of Hematology and Medical Oncology **for outpatient use only**
Pirfenidone (Esbriet®)	Antifibrotic Agent	Treatment of idiopathic pulmonary fibrosis	Restriction: Restricted to initation of therapy to providers from the Respiratory Institute. Note: There are no restrictions for continuation of therapy
Tenecteplase (TNKase®)	Thrombolytic Agent	Treatment of STEMI in patients who cannot undergo primary PCI	N/A

ALL=Acute Lymphoblastic Leukemia OR=Operating Room N/A=Not applicable
STEMI=ST-elevation Myocardial Infarction PACU=Post-anesthesia Care Unit PCI=Percutaneous Coronary Intervention

Formulary Update

Medications Removed from the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
CiproHC® (ciprofloxacin and hydrocortisone otic suspension)	Antibiotic/ Corticosteroid Otic	Treatment of Acute Otitis Externa	Ciprofloxacin and dexamethasone ophthalmic solution administered via the otic route according to the CCHS CiproDex® therapeutic substitution instructions will be utilized
Formoterol Inhaler (Foradil®)	Long-acting Beta$_2$ Agonist	Treatment of Asthma and COPD	Arformoterol (Brovana®) nebulized solution will be used as the CCHS Formulary Agent
Hetastarch (Hextend®)	Volume Expander	Plasma Expander	Voluven® will be used as the CCHS Formulary Agent
Optison®	Contrast Agent	Used for ECHO Contrast	Definity® will be used as the CCHS Formulary Agent
Vasolex® (Peru,Trysin, Castor Oil)	Topical Skin Protectant	Wound Care	Vasolex® is not FDA-approved and lacks evidence for use as a topical skin protectant. Alternative agents include petrolatum jelly and topical moisturizers.

COPD=Chronic Obstructive Pulmonary Disease ECHO=Echocardiography FDA=Food and Drug Administration

Changes in Restrictions in the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Dexmedetomidine (Precedex®)	Sedative	To treat agitation in the Intensive Care Setting	Restriction: Restricted to adults in the MICU and CCU for failure to wean from the ventilator due to agitation. Addition of CCU is the modification in the restriction.*
Incobotulinumtoxin A (Xeomin®)	Neuromuscular Blocker Agent	Cervical Dystonia Glabellar Lines	Restriction: The restriction was expanded to include cosmetic use for glabellar lines **for outpatient use only**
Intravenous Immune Globulin (IVIG)	Blood Product Derivative	Various FDA– and non-FDA indications	Restriction Criteria will expand to include these non-FDA approved uses: AIDP, myasthenia gravis, and dermatomyositis

AIDP=Acute Inflammatory Demyelinating Polyneuropathy CCU=Coronary Care Unit MICU=Medical Intensive Care Unit
*Other restrictions for this agent can be found in Lexi-Comp.

Formulary Update

Changes in Restrictions in the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Ramucirumab (Cyramza®)	VEGFR-2 antagonist	Treatment of non-small cell lung cancer Treatment of advanced gastric cancer	Restriction: Restriction expanded to include use in combination with docetaxel for non-small cell lung cancer restricted to the Department of Hematology and Medical Oncology **for outpatient use only**

VEGFR-2=Vascular Endothelial Growth Factor Receptor-2

Additions to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Docosanol 10% Cream (Abreva®)	Topical Antiviral Agent	Treatment of cold sores or fever blisters	N/A
Human Papillomavirus 9-valent Vaccine, Recombinant (Gardasil 9®)	Inactivated Vaccine	Prevention of human papillomavirus infection	N/A
Meningococcal Group B Vaccine (Bexsero®)	Inactivated Vaccine	Prevention of meningococcal infection	Restriction: Restricted for use in patients aged 10 to 25 years with anatomical or functional asplenia, including patients with sickle cell anemia, complement component deficiency, or at risk from meningococcal B disease outbreaks.
Romiplostim (Nplate®)	Colony Stimulating Factor	Chronic Immune Thrombocytopenia	Restriction: Restricted for use to the Department of Pediatric Hematology and Oncology for patients with refractory immune thrombocytopenia who have failed at least two other therapies.

N/A=Not applicable

Formulary Update

Medications Removed from the Pediatric CCHS Formulary and Therapeutic Interchanges			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Topical Acyclovir	Topical Antiviral	Treatment of cold sores	Docosanol 10% cream is more cost-effective
CiproHC® Otic Solution (ciprofloxacin/ hydrocortisone	Antibiotic/ Corticosteroid	Otitis Externa	Ciprofloxacin and dexamethasone ophthalmic solution administered via the otic route according to the CCHS CiproDex® therapeutic substitution instructions will be utilized.
Nystatin Topical Powder	Antifungal Agent	Mucocutaneous infections	Therapeutic interchange to miconazole 2% topical powder
Vasolex® (trypsin,balsam peru, castor oil)	Topical Skin Protectant	Wound Care	Vasolex® is not FDA-approved and lacks evidence for use as a topical skin protectant. Alternative agents include petrolatum jelly and topical moisturizers.

FDA=Food and Drug Administration