Invasive fungal infections are associated with significant morbidity and mortality in transplant recipients. Not only are transplant recipients more susceptible to these infections due to their immunocompromised state, but treatment itself can pose its own challenges. Azole antifungals are frequently chosen to prevent or treat these infections. Concomitant use of azole antifungals and immunosuppressants such as calcineurin inhibitors (CNI) and mammalian target of rapamycin (mTOR) inhibitors can result in clinically significant drug interactions since azole antifungals inhibit cytochrome P450 (CYP450) enzymes that metabolize these immunosuppressants. Anticipation of these interactions enables clinicians to use these agents together and minimize toxicities and/or supratherapeutic immunosuppressant concentrations when initiating azole antifungal therapy. When the azole antifungal is discontinued, awareness of the drug-drug interactions can prevent sub-therapeutic immunosuppressant concentrations. In this article, we offer strategies for managing these clinically meaningful drug-drug interactions.

The CYP450 enzyme system, particularly the 3A4 isozyme, is responsible for the oxidation of both CNI and mTOR inhibitors. Importantly, azole antifungal agents inhibit CYP450 3A4 and inhibit immunosuppressant metabolism. Another key component of these interactions involves P-glycoprotein (P-gp). As an active transport protein, P-gp has the potential to affect drug bioavailability by either decreasing absorption or increasing elimination.

Both CYP450 enzymes and P-gp are found within the gastrointestinal tract and the liver. The presence of these elimination pathways creates a hurdle for immunosuppressants after oral administration as they are eliminated in the gut prior to systemic absorption. The process of drug elimination in the gut prior to systemic absorption is termed first pass metabolism. Inhibiting these proteins in the gut results in more immunosuppressant being available for systemic absorption.

The full effect of inhibition for both CYP450 and P-gp is typically seen within the first week after the azole antifungal is initiated. Therefore, monitoring of cyclosporine, tacrolimus, sirolimus, and everolimus levels 2-3 times per week for 1-2 weeks is recommended. Upon discontinuation of the azole antifungal agent, the effect can last 7-10 days depending on the half-life of the offending agent, the relative degree of 3A4 inhibition, and the dose of the azole. Higher doses of azole antifungal agents may be associated with more clinically significant drug-drug interactions. Thus, treatment doses are typically more problematic than prophylactic doses. For example, fifty milligrams of fluconazole did not significantly affect tacrolimus concentrations in kidney transplant recipients, while higher doses significantly inhibit CYP450.

Table 1 (below) provides preemptive dosing strategies based upon the available...
literature and prescribing information for patients who currently maintain stable trough concentrations of CNI and mTOR inhibitors. As new agents become available, awareness of the underlying mechanisms involved in these drug-drug interactions allow for judicious use of immunosuppressants and azole antifungals concomitantly. Of note, no clinically significant drug interactions exist among antiproliferatives, polyclonal, or monoclonal antibodies when used concomitantly with azole antifungal agents. Steroids have been known to exacerbate certain fungal infections, but no drug-drug interactions are described in the literature.

In the perioperative period, antifungal prophylaxis is commonly initiated at the same time as immunosuppression, when patients have not yet achieved therapeutic immunosuppressant concentrations. Judicious monitoring of immunosuppressant concentrations is warranted in the perioperative period. Current guidelines indicate clotrimazole troches are one of the more common agents used to prevent mucocutaneous candidiasis. Given the limited evidence regarding interactions between immunosuppressants and clotrimazole, routine monitoring of immunosuppressant concentrations is crucial, as the effects of the enzymatic inhibition may not be recognized until discontinuation of the prophylaxis. This principle holds true for other azole antifungals as well. Dosing strategies are offered for initiation of azole therapy, however upon discontinuation of the azole, monitoring of immunosuppressant plasma concentrations must guide clinicians to appropriate dose adjustments. Therefore, we recommend obtaining CNI and mTOR inhibitor concentrations 2-3 times per week for a minimum of 2 weeks following discontinuation of azole antifungal therapy to minimize the chance of subtherapeutic immunosuppressant concentrations and subsequent rejection. Based upon dosage adjustments and interpatient variability, additional monitoring may be warranted.

Predicting drug-drug interactions can be very challenging depending on the degree of inhibition of metabolic enzymes when azole therapy is initiated. The recommendations provided here offer preemptive dosing strategies for immunosuppressants at the initiation of azole therapy as well as monitoring considerations upon discontinuation of the azole.

Table1. Initial recommended dosing strategies of concomitant azole antifungal agents and immunosuppressants when initiating azole antifungal agents and stable immunosuppressant concentrations have been achieved.
a. Consider judicious monitoring of immunosuppressant concentrations if utilizing fluconazole >100mg daily
b. Concomitant administration not recommended by package label without sufficient published data to support concomitant use
c. Concomitant administration contraindicated according to package label without sufficient published data to support concomitant use
d. Concomitant administration contraindicated according to package label with published literature to guide management of drug-drug interaction

Disclosure Statement
The authors have no conflicts of interest to disclose.

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