

ALTERNATIVE VIEWPOINTS

Factors Influencing the Magnitude and Clinical Significance of Drug Interactions between Azole Antifungals and Select Immunosuppressants

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The manuscript by Dr. Saad and her colleagues¹ is a good reference for transplant practitioners reviewing the potential for drug-interactions between azole antifungals and selected immunosuppressants.¹ The authors clearly state that they are discussing “selected” immunosuppressants but they also include several references that thoroughly review azole drug-interactions. However, it is imperative for healthcare practitioners to understand the potential for drug misadventures when combining azoles with other immunosuppressants not listed in this review.¹

Corticosteroids have been a mainstay in clinical immunosuppression since their inception in solid organ transplantation (SOT) in the 1960s. Although corticosteroid withdrawal is advantageous due to the long-term metabolic adverse events, these agents are still frequently utilized in many induction, maintenance and acute rejection treatment regimens. One, often overlooked, characteristic of corticosteroids is their ability to affect the cytochrome P450 system (CYP) and P-glycoprotein (P-gp). Dexamethasone and prednisolone are known inducers of CYP and P-gp in animal models, in vitro studies and human trials.^{2–4} Conversely, methylprednisolone is an inhibitor of CYP.⁴ However, neither pharmacokinetic studies nor case-reports have documented an impact of corticosteroids on the pharmacokinetic parameters of the azole antifungals. It is important to understand the theoretic potential for decreased azole concentrations when using

them in conjunction with dexamethasone or prednisolone, or increased concentrations when used concomitantly with methylprednisolone. The impact of the azoles on the pharmacokinetics of the corticosteroids has been well documented and is reviewed in Table 1.

Another aspect to be considered in patients receiving immunosuppressants is pharmacodynamic drug-interactions. Dr. Saad and her colleagues defined pharmacodynamic drug-interactions as “additive, synergistic or antagonistic interactions that can affect efficacy or toxicity.”¹ Table 1 details some real or theoretical safety concerns when combining azoles and immunosuppressive agents. However, the impact of immunosuppressants on the efficacy of antifungal therapy should also be addressed. Immunosuppression in SOT recipients is an inescapable risk factor for infectious complications. The extent of immunosuppression is greatly influenced by the number, type and dosage of immunosuppressive medications employed. Conversely, some immunosuppressants have antifungal properties. Table 2 outlines the impact of the immunosuppressants on fungal infections.

Overall, the manuscript by Saad and colleagues is an excellent review of the azoles’ impact on the calcineurin inhibitors and sirolimus. This reference will aid in understanding the mechanism and significance of drug-interactions with these medications. However, clinical immunosuppression is often attained by utilizing multi-drug regimens, potentially containing immunosuppressants that were not reviewed by Dr. Saad and her colleagues. It is the hope of this practitioner, that this short overview will bridge that gap.

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Table 1. Pharmacokinetic and Pharmacodynamic Drug Interactions between the Azoles and Immunosuppressants not Discussed by Saad et al.⁵⁻⁷

| Drug Class / Drug | Pharmacodynamic Interactions | Pharmacokinetic Interactions |
|-------------------|--|--|
| Fluconazole | <i>Hepatic:</i> co-administration of CyA, TAC or sirolimus and fluconazole may increase the risk for hepatic insufficiency. ^a | <i>Corticosteroids:</i> concomitant use of fluconazole and prednisone can result in an increase prednisone concentrations. ⁸ |
| Itraconazole | <i>Cardiovascular:</i> congestive heart failure and peripheral edema have been reported with the use of IV itraconazole. These effects may be worsened by the sodium and water retention properties of the corticosteroids. ^a <i>GI:</i> in one clinical study in liver transplant recipients, when combined with maintenance immunosuppressants (CyA or TAC, AZA or MPA and corticosteroids) itraconazole had a much higher incidence of both upper and lower GI adverse events compared to fluconazole. ¹⁵ <i>Hepatic:</i> co-administration of CyA, TAC or sirolimus and itraconazole may increase the risk for hepatic insufficiency. ^a | <i>Corticosteroids:</i> itraconazole has been shown to increase the concentrations of methylprednisolone, dexamethasone and prednisolone when given concomitantly. ⁹⁻¹⁴ |
| Posaconazole | <i>Metabolic:</i> adrenal insufficiency has been rarely reported with posaconazole. Concomitant use of this agent with the corticosteroids could increase the risk for or worsen this adverse event. ^a <i>Neurologic:</i> co-administration of posaconazole with either CyA or TAC has resulted in seizures in two patients. No additional convulsions were reported following the discontinuation of posaconazole. ¹⁶ <i>Hepatic:</i> co-administration of CyA, TAC or sirolimus and posaconazole may increase the risk for hepatic insufficiency. ^a | No pharmacokinetic drug interactions reported between posaconazole and the corticosteroids, MPA or AZA. |
| Voriconazole | <i>Hepatic:</i> co-administration of CyA, TAC or sirolimus and voriconazole may increase the risk for hepatic insufficiency. ^a | <i>Corticosteroids:</i> prednisolone AUC is increased 11–34% when co-administered with voriconazole. ^{14, 17} |

^a literature is not available for these pharmacodynamic drug interactions; however an interaction can be theorized based off of their mechanisms of toxicity.

AUC = overall exposure; AZA = azathioprine; CyA = cyclosporine; MPA = mycophenolic acid; TAC = tacrolimus

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Table 2. Impact of immunosuppressants on invasive fungal infections.

| Agent(s) | Clinical Effect |
|---|--|
| <i>Immunosuppressants with Antifungal Properties</i> | |
| Calcineurin Inhibitors | Calcineurin phosphatase influences growth, morphology and virulence of several fungi. The calcineurin inhibitors possess potent anti-cryptococcal properties, but also have some activity against <i>Candida</i> and <i>Aspergillus</i> . ¹⁸ |
| Mycophenolic Acid | It appears that mycophenolic acid only has activity against <i>Pneumocystis jiroveci</i> , most likely through inhibition of inosine monophosphate dehydrogenase. ¹⁸ |
| Sirolimus | TOR kinases are found in several fungi and promote cell proliferation. Sirolimus has activity against fungi dependent on TOR activity, including <i>Candida</i> , <i>Cryptococcus</i> , <i>Fusarium</i> , <i>Penicillium</i> , <i>Saccharomyces</i> and <i>Schizosaccharomyces</i> . ¹⁸ |
| <i>Immunosuppressants that Increase the Risk for IFIs</i> | |
| ALAs | Use of ALAs is an independent risk factor for the development of fungal infections, particularly invasive aspergillosis. ^{19–21} |
| Corticosteroids | A direct relationship between high-dose steroids (suppression of macrophage function), exposure to <i>Aspergillus</i> conidia and subsequent development of <i>Aspergillus</i> infections has been reported. ^{22, 23} |
| All Immunosuppressant (not including steroids) | Neutropenia is common due to the myelosuppressive effects of immunosuppressive therapies and is a major risk factor for the development of fungal infections. ²⁴ |

ALAs = antilymphocyte antibodies; TOR = Target of Rapamycin

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Authors' Reply

We appreciate the comments of Dr. Gabardi and appreciate his insightful thoughts into the known or potential pharmacokinetic and pharmacodynamic interactions between corticosteroids and azole antifungal agents. As he notes, our article was focused on the potential for drug interactions only between azole antifungal agents and select immunosuppressants (specifically, calcineurin inhibitors and sirolimus). We selected these immunosuppressive agents as our focus because of their high potential for increased adverse

effects due to drug interactions, and the clinical and pharmacokinetic literature support to document these interactions. Given the space constraints of the journal, we elected to discuss in detail only select studies with each agent, in order to illustrate important concepts; the majority of the article was devoted to an overview and discussion of the mechanisms of interactions (particularly, pharmacokinetic ones via cytochrome P450 and p-glycoprotein). These same concepts can, of course, be applied to corticosteroids and (to a lesser extent) mycophenolate, as was done for the corticosteroids in the very nice summary table

provided by Dr. Gabardi. It is our hope that clinicians will apply these concepts not only for “known” interactions, (i.e., documented in the literature), but also when considering the potential for newer agents for which little

literature documentation of drug interactions is available.

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