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FUNGAL INFECTIONS IN TRANSPLANTATION (S SHOHAM, SECTION EDITOR)

Interpretation and Understanding of Clinical Drug Interactions Between Azoles and Immunosuppressants in Solid Organ Transplant Recipients

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Abstract

Purpose of Review The aim of this paper is to discuss clinical interactions between the azole antifungals and the commonly used immunosuppressants for the prevention of rejection in solid organ transplant recipients.

Recent Findings Drug–drug interactions between azole antifungals and immunosuppressants have largely been reported in healthy subjects or the hematopoietic stem cell transplant (HSCT) population. Data is emerging evaluating these interactions in solid organ transplant recipients.

Summary Drug–drug interactions between azole antifungals and immunosuppressants occur at or near the same magnitude as in healthy subjects or the HSCT population. Factors affecting these drug–drug interactions include the influence of the interacting agents on CYP enzymes, the doses of the drugs administered, and the route of administration of both the azoles and immunosuppressants. Care and caution should be exercised when managing solid organ transplant patients receiving medications from both classes.

Keywords Azoles · Antifungals · Immunosuppression · Interactions · Solid organ transplant

Introduction

Fungal infections are a significant complication in solid organ transplant recipients. The cumulative incidence of disease is approximately 3% in the first year after transplantation, with the majority of the disease comprised of candidiasis, aspergillosis, and cryptococcal infections [1]. The management of these infections can be complicated by drug–drug interactions that take place between immunosuppressant (IS) medications (e.g., calcineurin inhibitors, mTOR inhibitors) and the azole antifungals, the primary antifungal agents used to prevent and treat a wide variety of fungal disease. This review takes an in-depth look at the clinical management of drug–drug interactions that take place between these classes of medications in solid organ transplant recipients. First, we will describe the mechanisms responsible for the interactions, followed by a discussion of the drug classes affected. We will then summarize the available data for each individual antifungal agent and how they affect immunosuppressant pharmacokinetics starting with azoles used for treatment, followed by those used for prophylaxis, and finishing with those used for pharmacokinetic boosting.

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The Cytochrome P450 System

The cytochrome (CYP) P450 enzymes are heme proteins responsible for a variety of mechanisms in the body, but most notably are involved in the metabolism of endogenous substrates [2, 3]. A vast majority of these metabolic interactions occur in the liver, with resultant reactions namely being the inhibition or induction of drugs. While nearly 60 CYP genes have been documented in humans, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 are most responsible for drug metabolism [2]. CYP3A4 accounts for the majority of all interactions between the azole antifungals

and immunosuppressants, closely followed by CYP2C9 and CYP2C19.

Drugs may either induce, inhibit, or act as substrates of the CYP450 enzyme system. Inducers of the enzyme system will increase the amount of activity of the enzymes, thereby leading to a reduction in drug concentration levels of the affected medication. Conversely, inhibitors of the enzyme systems will decrease the amount of activity of the enzymes leading to increases in the drug concentration levels of the affected medications. Both induction and inhibition are dependent on the dose and concentration of the agent that is instigating the reaction. Substrates of the enzyme system are specific moieties that undergo metabolism by one or more of the CYP enzymes. It is important to note that inducers and inhibitors exert their effects in differing manner with regard to onset and duration. Inducers will achieve their maximum effects after approximately 2 weeks, while inhibitors can exert their effect after a single dose [2–5, 6•]. Duration of effect is the same, with effects of induction taking at least 2 weeks to subside. Inhibitors, on the hand, cease their influence within a week after drug removal.

The azole antifungals are both substrates and inhibitors of the CYP enzyme system, whereas the calcineurin inhibitors (cyclosporine, tacrolimus) and mTOR inhibitors (sirolimus, everolimus) are substrates only. The resultant adverse effect is an increase in serum levels of the immunosuppressants. This is problematic since the known complications of elevated levels of these agents include nephrotoxicity, neurotoxicity, and hypertension.

P-Glycoprotein

Active transporters also play a critical role in drug metabolism. One such example is P-glycoprotein (P-gp), an ATP-dependent efflux pump that regulates the absorption and elimination of drugs [3, 7]. P-gp is found at high concentrations in the kidney, liver, small intestines, and colon. Some of the azole antifungals, calcineurin inhibitors, and mTOR inhibitors are affected to some degree by P-gp. Because P-gp and the CYP enzymes are distributed throughout the same areas of the body, it is difficult to differentiate the degree of the interaction by each individual component.

The Azole Antifungals

The azole antifungals have been used in solid organ transplant patients for antifungal prophylaxis, treatment, and pharmacokinetic boosting. The azoles bind to 14-α-demethylase, which prevents the conversion of lanosterol to ergosterol, an essential component of the fungal cell membrane. This leads to loss of fungal membrane activity. 14-α-Demethylase is also a component of the fungal CYP450 enzyme system. Differences in drug–drug interactions can be attributed to varying specificity of fungal CYP450 compared with mammalian CYP450 [8•, 9]. Other differences that affect CYP450 activity include the dose of the antifungal as well as the route of administration. Due to the presence of CYP enzymes and P-gp in the lining of the stomach, liver, and intestines, oral therapy often provides a greater degree of interaction than IV administration. Please see Table 1 for a summary of information on the azole antifungal agents with calcineurin and mTOR inhibitors.

For the purposes of this review, fluconazole, voriconazole, posaconazole, and itraconazole will be included as agents primarily used for treatment. Clotrimazole and fluconazole will be discussed as agents often used for antifungal prophylaxis. Itraconazole, a broad-spectrum triazole, will not be discussed in this writing due to withdrawal of the IV formulation from the US market and its overall limited use in the solid organ transplant population. Finally, ketoconazole will be discussed for the purposes of pharmacokinetic boosting of immunosuppressant serum levels.

Agents Used for Treatment of Invasive Fungal Infections

Fluconazole

Fluconazole is the least potent inhibitor of the available azoles used for the treatment of fungal infections. Unlike the other azoles to be discussed, fluconazole undergoes minimal hepatic metabolism with > 90% of the drug eliminated through the urine. It exhibits noncompetitive inhibition of CYP2C9, CYP2C19, and CYP3A4. Fluconazole has been shown to interact with both tacrolimus and cyclosporine in a dose-dependent manner [10, 11•]. In a small case series including both kidney–pancreas and bone marrow transplant recipients, those receiving 100 mg of fluconazole daily had no increase in their dose:concentration ratio [10]. Conversely, patients taking fluconazole doses > 200 mg daily had a 125% increase in the dose:concentration ratio by day 3. This trend persisted and continued to increase through 4 weeks of therapy, and modifications to cyclosporine doses were made. Similar to cyclosporine, tacrolimus levels were increased when given in combination with fluconazole for the management of esophageal candidiasis [11•]. In a single case report in a stable renal transplant recipient, dose-normalized tacrolimus levels were increased 5.5-fold after IV fluconazole was administered. This further increased to 7.4-fold when fluconazole was changed to oral administration, providing additional clinical evidence that that route of administration is a factor when assessing drug–drug interactions with the azoles in solid organ transplant recipients.

Significant increases in sirolimus levels have also been observed when given in combination with fluconazole [12]. A 49-year-old male experiencing delayed graft function after

Table 1 Interactions between azole antifungals and immunosuppressants

Azole antifungal	Mechanism of interaction	Strength of interaction	Immunosuppressants affected	Resultant interaction	How to manage interaction
Clotrimazole	CYP3A4 inhibition	++	CSA, TAC, SRL, EVR	Increased IS levels	CSA, TAC, SRL, EVR: More frequent TDM with initiation or discontinuation; no empiric dose adjustments recommended
Fluconazole	CYP2C9, CYP3A4 inhibition	++	CSA, TAC, SRL, EVR	Increased IS levels	CSA, TAC: Therapeutic drug monitoring of calcineurin inhibitor SRL, EVR: Pre-emptive dose reduction of 25–50%
Voriconazole	CYP2C9, CYP2C19, CYP3A4 inhibition	+++	CSA, TAC, SRL, EVR	Increased IS levels	CSA: Decrease CSA dose by 50% when starting voriconazole TAC: Decrease TAC dose by 66% when starting voriconazole SRL: Contraindication, although literature supports 80–90% dose reduction EVR: No data; will need to decrease EVR dose
Posaconazole	CYP3A4, P-gp inhibition	+++	CSA, TAC, SRL, EVR	Increased IS levels	CSA: Decrease CSA dose by 25% when starting posaconazole TAC: Decrease TAC dose by 66% when starting posaconazole SRL: Contraindicated per package labeling; may decrease dose by 90% with close monitoring EVR: No data; will need to decrease EVR dose
Isavuconazole	CYP3A4 inhibition	++	CSA, TAC, SRL, EVR	Increased IS levels	CSA, TAC: Therapeutic drug monitoring of calcineurin inhibitor SRL: Empiric SRL dose reduction likely EVR: No data available
Ketoconazole	CYP3A4 inhibition	+++	CSA, TAC, SRL, EVR	Increased IS levels	CSA, TAC, SRL, EVR: Empiric dose reductions of 50–75% with twice weekly TDM to evaluate need for further adjustments

CSA cyclosporine, *TAC* tacrolimus, *SRL* sirolimus, *EVR* everolimus

renal transplant was switched from cyclosporine to sirolimus to minimize calcineurin inhibitor toxicity and levels were maintained at approximately 10 ng/mL. The patient was started on fluconazole 200 mg PO daily for the management of esophageal candidiasis and the sirolimus dose was reduced by 25% pre-emptively. Additional dose reduction to 50% of the sirolimus starting dose was ordered, but trough concentrations continued to rise, peaking at 35.5 mcg/mL 1 week after fluconazole was initiated. Pre-emptive dose decreases for everolimus, another mTOR inhibitor, are also necessary based on limited available data [13].

Voriconazole

Voriconazole undergoes extensive hepatic metabolism predominantly through CYP2C19, followed closely by CYP2C9 and CYP3A4 [14]. Less than 2% of the drug is excreted in the urine. Of note, significant polymorphisms in CYP2C19 exist, and voriconazole exposure can be increased fourfold in patients who are poor metabolizers. Further complicating this issue is the fact that voriconazole exhibits nonlinear kinetics and levels are highly variable between patients.

Voriconazole is both a strong inhibitor and a substrate of the three aforementioned enzymes, and causes significant increases to other medications that are substrates of CYP2C9, CYP2C19, and CYP3A4. Interactions with cyclosporine, tacrolimus, and sirolimus are documented in a number of case series [15–19•]. In a retrospective analysis of more than 120 solid organ transplant (kidney and lung) recipients, 100 patients received concurrent tacrolimus and voriconazole for the management of invasive aspergillosis [17]. Dose-corrected trough concentrations of tacrolimus increased by a factor of 5.0 ± 2.7 (range 1.0–20.2); this data supports the empiric dose reduction by 66% for tacrolimus recommended in the voriconazole package labeling, although authors noted that additional tacrolimus dose decreases would likely be necessary [17, 20]. Unfortunately, voriconazole therapeutic drug monitoring (TDM) was not provided during this analysis to assess any impact of the level of voriconazole on tacrolimus kinetics. Similar to fluconazole, the route of administration also has an impact on the degree of interaction. In a single case report of a patient undergoing liver transplant, a 30% reduction in the tacrolimus dose was necessary when IV voriconazole was given in combination with oral tacrolimus to maintain therapeutic levels (6–7 mcg/mL) [16]. When voriconazle was changed to oral administration, the tacrolimus levels climbed to 10–11 mcg/mL, necessitating further dose reductions. Of note, the drug–drug interaction between voriconazole and a new, prolonged-released tacrolimus product has also been evaluated in healthy volunteers [19•]. An increase in exposure with the prolonged-release tacrolimus was significantly less as well as less variable compared with the immediate release product.

There is no documented clinical data discussing the use of voriconazole in combination with sirolimus in solid organ transplant recipients; however, there is a case series of 67 patients who underwent hematopoietic stem cell transplant and received the combination of agents [18]. Patients received both sirolimus and voriconazole concurrently for at least 110 days, with the median daily reduction in sirolimus dose of 90%. Median sirolimus serum levels were 5.8 ng/mL before co-administration of voriconazole and 6.1 ng/mL after co-administration with the dose

reduction. While the voriconazole package labeling suggests the coadministration of these two agents is contraindicated, there is evidence that they may be safely managed when given in combination.

Posaconazole

The CYP enzymes have no role in the metabolism of posaconazole [8]. Rather, it is glucoronidated in the liver by UDP-glucuronyl-transferase (UGT) and largely excreted as unchanged drug through the feces. Posaconazole is an inhibitor of CYP3A4 and P-gp. One significant consideration for posaconazole use is the formulation being given. For nearly a decade, the only formulation available was an oral suspension that had poor and highly variable absorption. In 2014, an extended-release tablet was approved for use, with improved bioavailability and absorption. These improvements lead to changes in dosing strategies and will certainly impact the kinetics of co-administered medications.

The effects of oral posaconazole on the pharmacokinetics of both cyclosporine and tacrolimus are well-described [21]. Heart transplant recipients who had been receiving cyclosporine for at least 15 months without dose modifications in the previous 6 weeks were given posaconazole 200 mg as two 100-mg tablets daily for 10 days. Cyclosporine exposure increased with concurrent posaconazole administration, requiring 14–29% dose reductions in cyclosporine dosing. Data was extrapolated to mimic clinically relevant dosing and the predicted increase in cyclosporine exposure was consistent with what has been demonstrated with co-administration of other azoles. Cyclosporine should be reduced by 75% when posaconazole is initiated. In this same study, healthy adults were given a single oral dose of tacrolimus on days 1 and 14, and posaconazole oral suspension (400 mg twice daily) with high-fat meals on days 8 through 14. Co-administration of tacrolimus and posaconazole resulted in 121% and 358% increases in tacrolimus C_{max} and $AUC_{0-\infty}$, respectively. Tacrolimus dosing should be pre-emptively reduced by 30% when starting concurrent posaconazole.

In the same retrospective series discussed above of greater than 120 patients who were either kidney or lung recipients, 26 of them received posaconazole for invasive aspergillosis with concurrent tacrolimus [17]. The daily tacrolimus dose was reduced by a factor of 3.7 ± 2.0 (range 0.7–10.0) during posaconazole therapy, which was a lesser extent than observed between the tacrolimus and voriconazole. Unfortunately, posaconazole TDM was not done during this study so the effect of posaconazole levels on the tacrolimus pharmacokinetics is unknown.

Data for concomitant use of posaconazole and sirolimus is limited to a single case report describing salvage therapy for the treatment of rhinocerebral mucormycosis after patient intolerance to tacrolimus and amphotericin [22]. Goal sirolimus concentrations were 6–8 ng/mL and the dose of sirolimus was empirically reduced by 83%. Thirteen sirolimus levels were drawn during the time period in which therapy overlapped, with a mean sirolimus trough concentration 7.1 ng/mL (4.3 to 11.8 ng/mL). The authors suggest reducing sirolimus doses by 60–75% when initiating in patients with goal sirolimus troughs < 10 ng/mL and by 30–50% in patients whose goal levels are 10–15 ng/mL.

Isavuconazole

Isavuconazole is administered as the prodrug isavuconazonium sulfate and is rapidly hydrolyzed by plasma esterases to isavuconazole [23]. Isavuconazole is metabolized by CYP3A4 and CYP3A5, with additional transformation by UGT, and is an inhibitor of CYP3A4 and CYP3A5 which will increase the levels of those enzyme substrates. Of note, the mean plasma half-life is 110–130 h which may lead to prolonged drug–drug interaction effects.

A summary of phase I clinical trial data presented pharmacokinetic interactions between isavuconazole and multiple immunosuppressants including tacrolimus, sirolimus, and cyclosporine in healthy adults [24]. Single oral doses of tacrolimus 5 mg, sirolimus 2 mg, and cyclosporine 300 mg were administered, while isavuconazole was provided at the clinical dose of 200 mg orally three times daily for 2 days, followed by 200 mg orally daily. Isavuconazole increased the AUC of tacrolimus, sirolimus, and cyclosporine by 125%, 84%, and 29%, respectively. C_{max} values of tacrolimus, sirolimus, and cyclosporine were 42%, 65%, and 6% higher, respectively. Authors noted that although isavuconazole does alter the pharmacokinetics of a number of immunosuppressants, it is not nearly to the same degree as the other previously discussed azoles.

Fifty-five consecutive solid organ transplant (kidney, liver, lung, and heart) recipients were assessed retrospectively to investigate the need for empiric dose reduction in tacrolimus when given in combination with isavuconazole [25]. Patients received isavuconazole for at least 21 days for prophylaxis while receiving tacrolimus, and were followed for at least 40 days after isavuconazole was stopped. The per-patient tacrolimus concentration:dose ratio decreased by a median of 13%; however, this was largely driven by the liver recipients in the group, who had a 36% decrease. Once isavuconazole was discontinued, the average tacrolimus dose increased 1.3-fold. Investigators determined there was no need for empiric dose reduction of tacrolimus when co-administering with isavuconazole, but rather followed tacrolimus TDM and adjusted doses accordingly.

Agents Used for Fungal Prophylaxis

Antifungal prophylaxis strategies for solid organ transplant recipients vary based on multiple factors including selection of antifungal agent, duration of prophylaxis, and use of

universal versus targeted therapy. Additionally, the type of organ transplanted, as well as patient-specific risk factors, impacts antifungal prophylaxis regimens. For the purposes of this review, we will focus on two azoles commonly used to prevent *Candida* infections after solid organ transplant.

Clotrimazole

Clotrimazole troches, which dissolve in the mouth, are routinely used for prevention of oral candidiasis in solid organ transplant recipients. Despite dissolution of clotrimazole troches in the mouth and limited systemic absorption, this product has been found to significantly increase serum concentrations of immunosuppressants.

In a case report of a liver transplant recipient, pharmacokinetic studies demonstrated a twofold increase in AUC of tacrolimus when administered in combination with clotrimazole [26]. In a prospective study, renal transplant recipients on tacrolimus were randomized to receive clotrimazole or nystatin for prophylaxis of oral candidiasis. Tacrolimus serum concentrations were significantly elevated in the clotrimazole group compared with the nystatin group on days 3, 5, and 7 [27].

Fluconazole

As described above in the treatment section, fluconazole is a potent inhibitor of CYP2C9, CYP2C19, and CYP3A4 and interacts with tacrolimus and cyclosporine in a dose-dependent manner [10, 11].

Doses of fluconazole for prevention of *Candida* infection after solid organ transplant are typically lower doses (100–200 mg/day) than those used to treat invasive fungal infections resulting in a less profound drug–drug interaction with cyclosporine and tacrolimus. Although the magnitude of the interaction will be less significant and does not necessitate empiric dose changes, monitoring of immunosuppressant serum concentrations is important when initiating or discontinuing fluconazole prophylaxis to reduce the risk of drug-related toxicities with supratherapeutic levels or the risk of organ rejection with subtherapeutic levels.

Agents Used for Pharmacokinetic Boosting

Ketoconazole

Among the triazoles, ketoconazole is the most potent inhibitor of CYP3A4 causing significant increases in serum levels of calcineurin inhibitors and mTOR inhibitors. Specifically, co-administration of sirolimus or everolimus with ketoconazole has been associated with 10-fold and 15-fold increases in the AUC of the mTOR inhibitors [28, 29]. Due to the potency of the interaction between ketoconazole and these immunosuppressants, an empiric dose reduction of cyclosporine, tacrolimus, sirolimus, or everolimus by 50% or more is recommended along with careful TDM of the immunosuppressant following ketoconazole initiation. In clinical practice, the significance of these drug–drug interactions has been utilized to reduce total daily doses of CNIs and mTOR inhibitors, thus minimizing costs associated with these immunosuppressants.

In a prospective, randomized trial of 100 living donor renal transplant recipients, ketoconazole was administered in combination with cyclosporine to purposefully elevate cyclosporine blood levels resulting in reduced medication costs for patients while maintaining graft function and patient safety. When the oral dose of ketoconazole 100 mg/day was initiated, the cyclosporine total daily dose was reduced by 25–50% and further adjusted based on twice weekly cyclosporine TDM [30]. A similar study evaluating co-administration of ketoconazole and tacrolimus was conducted at the same transplant center and reported a reduction in tacrolimus dose, cost, and improvement in graft function [31]. Two small studies involving renal transplant recipients reported on prescribing ketoconazole in combination with either sirolimus or everolimus to boost the mTOR inhibitor trough levels resulting in a reduction of total daily doses to 0.25–0.5 mg/day for sirolimus and 0.75–0.9 mg/day for everolimus, thus making the mTOR inhibitor prescriptions affordable for patients [32, 33].

Although the use of ketoconazole to elevate drug concentrations of immunosuppressants can be beneficial to patients as a way to reduce drug costs, there is an increased risk of rejection if ketoconazole is discontinued without appropriate dose adjustments to the CNI or mTOR inhibitor.

Conclusion

The treatment and prevention of fungal infections is a complex process that involves dose reduction of many of the immunosuppressants used to prevent rejection in solid organ transplant recipients. Interactions between the azole antifungals and immunosuppressants are influenced by the doses given, the CYP isoenzymes involved, and the formulation of medication administered. TDM of both the azole antifungals and immunosuppressants is key to preventing morbidity and mortality in this population.

Compliance with Ethical Standards

Conflict of Interest Kathryn Dzintars and Lindsey Toman declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Shoham S, Marr K. Invasive fungal infections in solid organ transplant recipients. Future Microbiol. 2012;7(5):639–55. https://doi.org/10.2217/fmb.12.28.
2. Manikandan P, Nagini S. Cytochrome P450 structure, function and clinical significance: a review. Curr Drug Targets. 2018;19:38–54.
3. Saad AH, DePestel DD, Carver PL. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. Pharmacotherapy. 2006;26:1730–44.
4. Nivoix Y, Leveque D, Herbrecht R, Koffel J, Beretz L, et al. The enzymatic basis of drug-drug interactions with systemic triazole antifungals. Clin Pharmacokinet. 2008;47:779–92.
5. Groll AH, Townsend R, Desai A, Azie N, Jones M, Engelhardt M, et al. Drug-drug interactions between triazole antifungal agents used to treat invasive aspergillosis and immunosuppressants metabolized by cytochrome P450 3A4. Transpl Infect Dis. 2017;19:e12751.
6.• Sparkes T, Lemonovich TL, on behalf of the AST Infectious Diseases Community of Practice. Interactions between anti-infective agents and immunosuppressants – Guidelines from the American Society of Transplantation Infectious Diseases Community Practice. Clin Transplant. 2019;33:e13510 **The American Society of Transplantation's Infectious Diseases subgroup published clinical guidelines for the management of drug–drug interactions between anti-infective agents, including antifungals, and immunosuppressants.**
7. Leopoldo M, Nardulli P, Contino M, Leonetti F, Luurtsema G, et al. An updated review on P-glycoprotein inhibitors. *Expert Opin Ther Patents*. 2019;29:455–61.
8.• Bellman R, Smuskiewicz P. Pharmacokinetics of antifungal drugs: practical implications for optimized treatment of patients. *Infection*. 2017;45:737–79 **Excellent review on the clinical relevance of the pharmacokinetics of the azole antifungals used clinically for the treatment and prevention of invasive fungal infections.**
9. Nett JE, Andes DR. Antifungal agents: spectrum of activity, pharmacology, and clinical indications. ID Clin N Am. 2016;30:51–83.
10. Lopez-Gil JA. Fluconazole-cyclosporine interaction: a dose-dependent effect? Ann Pharmacother. 1993;27:427–30.
11.• He J, Yu Y, Yin C, Liu H, Zou H, et al. Clinically significant drug-drug interaction between tacrolimus and fluconazole in stable renal transplant recipient and literature review. *J Clin Pharm Therapeutics*. 2020;45:264–9 **Clinical data describing the concurrent use of fluconazole and tacrolimus for the management of candida esophagitis in a renal transplant recipient.**
12. Cervelli MJ. Fluconazole-sirolimus drug interaction. Transplantation. 2002;10:1477–8.
13. Pea F, Baccarani U, Tavio M, Cojutti P, Adani GL, Londero A, et al. Pharmacokinetic interaction between everolimus and antifungal triazoles in a liver transplant patient. Ann Pharmacother. 2008;42:1711–6.
14. Scott LJ, Simpson D. Voriconazole: a review of its use in the management of invasive fungal infections. Drugs. 2007;67:269–98.
15. Romero AJ, Le PP, Nilsson LG, Wood N. Effect of voriconazole on the pharmacokinetics of cyclosporine in renal transplant patients. Clin Pharmacol Ther. 2002;2001(71):226–34.
16. Spriet I, Grootaert V, Meyfroidt G, Debaveye Y, Willems L. Switching from intravenous to oral tacrolimus and voriconazole leads to more pronounced drug-drug interaction. Eur J Clin Pharmacol. 2013;69:737–8.
17. Vanhove T, Bouwsma H, Hilbrands L, Swen JJ, Spriet I, Annaert P, et al. Determinants of the magnitude of interaction between tacrolimus and voriconazole/posaconazole in solid organ transplant recipients. Am J Transplant. 2017;17:2372–80.
18. Ceberio I, Dai K, Devlin SM, Barke JN, Castrol-Malaspina H, et al. Safety of voriconazole and sirolimus coadministration after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2015;50:438–43.
19.• Huppertz A, Ott C, Bruckner T, Foerster KI, Burhenne J, et al. Prolonged-release tacrolimus is less susceptible to interaction with strong CYP3A4 inhibitor voriconazole in healthy volunteers. Clin Pharm Ther. 2019;106:1290–8 **Data assessing the extent of a drug–drug interaction between prolonged-release tacrolimus and voriconazole in healthy subjects.**
20. VFend®(Voriconazole) [package insert]. Pfizer. New York, NY. May 2011.
21. Sansone-Parsons A, Krishna G, Martinho M, Kantesaria B, Gelone S, Mant TG. Effect of oral posaconazole on the pharmacokinetics of cyclosporine and tacrolimus. Pharmacotherapy. 2007;27:825–34.
22. Deyo JC, Nicolsen N, Lachiewicz A, Koslowski T. Salvage treatment of mucormycosis post-liver transplant with posaconazole during sirolimus maintenance therapy. J Pharm Practice. 2017;30:261–5.
23. Shirley M, Scott LJ. Isavuconazole: a review in invasive aspergillosis and mucormycosis. Drugs. 2016;76:1647–57.
24. Groll AH, Desai A, Han D, Howieson C, Kato K, et al. Pharmacokinetic assessment of drug-drug interactions of isavuconazole with immunosuppressants cyclosporine, mycophenolic acid, prednisolone, sirolimus, and tacrolimus in healthy adults. Clin Pharmacol Drug Dev. 2016;6:76–85.
25. Rivosecchi RM, Clancy CJ, Shields RK, Ensor CR, Shullo MA, et al. Effects of isavuconazole on the plasma concentrations of tacrolimus among solid organ transplant patients. Antimicrobial Agents Chemother. 2017;61:e00970–17.
26. Mieles L, Venkataramanan R, Yokoyama I, Warty VJ, Starzl TE. Interaction between FK506 and clotrimazole in a liver transplant recipient. Transplantation. 1991;52(6):1086–7.
27. Vasquez EM, Pollak R, Benedetti E. Clotrimazole increases tacrolimus blood levels: a drug interaction in kidney transplant patients. Clin Transpl. 2001;15:95–9.
28. Pfizer Wyeth Pharmaceuticals LLC. Rapamune (sirolimus) United States prescribing information. PA: Philadelphia; January 2020.
29. Novartis Pharmaceuticals Corporation. Zortress (everolimus) United States prescribing information. NJ: East Hanover; January 2018.
30. El-Groudy AE, Sobh MA, Hamdy AF, Ghoneim MA. A prospective, randomized study of coadministration of ketoconazole and cyclosporine A in kidney transplant recipients: ten-year follow-up. Transplantation. 2004;77(9):1371–6.
31. El-Dahshan KF, Bakr MA, Donia AF, Badr AE, Sobh MA. Ketoconazole-tacrolimus coadministration in kidney transplant recipients; two-year results of a prospective randomized study. Am J Nephrol. 2006;26:293–8.
32. Thomas PP, Manivannan J, John GT, Jacob CK. Sirolimus and ketoconazole co-prescription in renal transplant recipients. Transplantation. 2003;77(3):474–5.
33. Gonzalez F, Espinoza M, Herrera P, Rocca X, Reynolds E, Lorca E, et al. Everolimus versus azathioprine in a cyclosporine and ketoconazole based immunosuppressive therapy in kidney transplant:3-year follow-up of an open-label, prospective, cohort, comparative clinical trial. Transplant Proc. 2010;42:270–2.