Drug-drug interactions between triazole antifungal agents used to treat invasive aspergillosis and immunosuppressants metabolized by cytochrome P450 3A4

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Abstract
 Patients undergoing treatment with immunosuppressant drugs following solid organ or hematopoietic stem cell transplantation are at particular risk for development of serious infections such as invasive aspergillosis. Four triazole antifungal drugs, voriconazole, posaconazole, itraconazole, and isavuconazole, are approved to treat invasive aspergillosis either as first- or second-line therapy. All of these agents are inhibitors of cytochrome P450 3A4, which plays a key role in metabolizing immunosuppressant drugs such as cyclosporine, tacrolimus, and sirolimus. Thus, co-administration of a triazole antifungal drug with these immunosuppressant drugs can potentially increase plasma concentrations of the immunosuppressant drugs, thereby resulting in toxicity, or upon discontinuation, inadvertently decrease the respective concentrations with increased risk of rejection or graft-versus-host disease. In this article, we review the evidence for the extent of inhibition of cytochrome P450 3A4 by each of these triazole antifungal drugs and assess their effects on cyclosporine, tacrolimus, and sirolimus. We also consider other factors affecting interactions of these two classes of drugs. Finally, we examine recommendations and strategies to evaluate and address those potential drug-drug interactions in these patients.

KEYWORDS
cyclosporine, invasive aspergillosis, isavuconazole, itraconazole, posaconazole, sirolimus, tacrolimus, voriconazole

1 | INTRODUCTION

Invasive fungal diseases (IFDs) are a major cause of morbidity and mortality in immunocompromised individuals, such as hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients.1,2 Aspergillus species are responsible for a large proportion of IFDs and can produce a range of acute and chronic conditions.3

Invasive aspergillosis (IA) is the most common IFD in HSCT recipients and has been reported to account for between 40% and 60% of cases.4,5 In SOT recipients, IA is the second most common IFD overall, but the leading IFD in lung transplant recipients.6 Mortality from IA is substantial in both patient populations. In prospective, multicenter, observational studies, the overall 6-week mortality rate among HSCT recipients with IA in North America was 22%5 and 1-year mortality rate in the United States (US) was 75%.4 In a separate prospective, multicenter, observational study, the 1-year mortality rate among SOT
recipients in the US was 41%. Triazole antifungal agents help to fill an important need for efficacious treatments to reduce mortality in these patients.

Triazole antifungal agents have emerged as an important class of drug to treat and prevent IA. Currently, four triazole antifungal agents have a labeled indication that includes treatment or prevention of IA in the US and/or European Union (EU). Voriconazole is available as oral (tablet or oral solution) and intravenous (IV) formulations and is approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of IA in adults and children (FDA, aged ≥12 years; EMA, aged ≥2 years) and the prevention of IFDs (including IA) in HSCT patients (EMA only).

Posaconazole is available as an IV formulation, an oral suspension, or as delayed-release tablets. It is approved by the FDA (patients aged 13 years and older) and EMA (patients aged 18 years and older) as antifungal prophylaxis in patients who are at high risk of developing infections because of being severely immunocompromised, such as HSCT recipients with graft-versus-host disease or those with hematologic malignancies with chemotherapy-induced prolonged neutropenia; it is also approved by the EMA for the treatment of adult patients with IA when amphotericin B or itraconazole cannot be tolerated or has failed. Itraconazole is available in the US as an oral solution or capsules (although IV formulations are available in some other countries) and is approved by the FDA for the treatment of IA in patients intolerant or refractory to amphotericin B. It was approved for use in Europe in the early 1990s, prior to the formation of the EMA, and so labeling information (including indications) is country-specific. Isavuconazol sulfate, the prodrug of isavuconazole (hereafter referred to as isavuconazole throughout, with dosing expressed throughout as isavuconazole equivalents), is available as oral and IV formulations and is approved by the FDA and EMA for the treatment of adult patients with IA.

Transplant recipients are required to take immunosuppressant drugs such as cyclosporine, tacrolimus, sirolimus, or everolimus to prevent graft-versus-host disease or organ rejection; therefore, consideration must be given to potential interactions between immunosuppressive and antifungal agents. The cytochrome P450 3A4 (CYP3A4) pathway plays an important role in the metabolism of these immunosuppressant drugs. Because all triazole antifungal agents approved for the management of IA inhibit CYP3A4 to various degrees, and all except posaconazole are also substrates for CYP3A4 (although each has different substrate affinity), this pathway is a highly relevant potential point of drug-drug interactions in clinical practice. CYP3A4 plays a key role in the metabolism and bioavailability of cyclosporine, tacrolimus, sirolimus, and everolimus (together with CYP3A5, the efflux transporter P-glycoprotein [P-gp], and CYP2C8 [everolimus only], discussed in more detail in later sections). An antifungal treatment that strongly inhibits CYP3A4 will, therefore, increase plasma concentrations of these immunosuppressant agents. CYP3A enzymes are present in the small intestine and liver, and so the route of administration of immunosuppressive drugs is also a key factor that requires consideration when these classes of drugs are used concomitantly. Whereas both intestinal and hepatic enzymes would be major sites of interaction during oral administration, interactions via hepatic CYP3A enzymes would predominate during IV administration. Increases in plasma concentration of immunosuppressive drugs can result in adverse effects. For example, elevated serum concentrations of both cyclosporine and tacrolimus are potentially nephrotoxic and neurotoxic, whereas sirolimus, everolimus, and cyclosporine have been associated with pulmonary toxicity. Furthermore, the extent of immunosuppression (eg, high blood concentrations or use of more than one immunosuppressant agent) has been demonstrated in some SOT patients to be associated with an increased risk for the development of late infections. In addition, intra-patient variability in tacrolimus exposure is associated with an increased risk of acute rejection. In a recent retrospective database analysis of patients from 150 US hospitals between 2005 and 2013, tacrolimus was identified as one of the top 25 drugs for which interactions with both voriconazole and itraconazole were reported in hospitalized patients.

In this article, we review the inhibitory potential of CYP3A4 activity by the triazoles used to treat IA, as illustrated by their effects on the pharmacokinetics of midazolam, a pure CYP3A4 substrate. We then review the interaction profiles of these triazoles with cyclosporine, tacrolimus, and sirolimus as models for immunosuppressant drugs metabolized by CYP3A4 for which interactions with triazole antifungal agents have been best characterized. Finally, we briefly review available evidence for other immunosuppressant agents and examine other factors that require consideration with respect to interactions of these two classes of drugs.

2 | INHIBITION OF CYP3A4 BY TRIAZOLE ANTIFUNGAL AGENTS: MIDAZOLAM PHARMACOKINETICS AS A PROBE FOR CYP3A4 ACTIVITY

Midazolam is an anxiolytic benzodiazepine that is a sensitive in vivo substrate of CYP3A4 and is recommended by the FDA and EMA as a probe to classify whether a drug is an inhibitor of CYP3A4. Use of midazolam as a probe helps to classify the inhibitory potential of the azole drugs on CYP3A4 substrate candidates. Co-administration of an inhibitor of CYP3A4 with midazolam increases its exposure, as measured by the area under the time–concentration curve (AUC), or decreases the clearance. As per classifications of the FDA and EMA, an agent that increases the AUC by ≥5-fold (or decreases CL by >80%) is considered a strong inhibitor, an agent that increases the AUC by ≥2-fold but <5-fold (or decreases clearance by 50%-80%) is considered a moderate inhibitor, and an agent that increases the AUC by ≥1.25-fold but <2-fold (or decreases clearance by 20%-50%) is considered a weak inhibitor. Studies of the effects of voriconazole, posaconazole, itraconazole, and isavuconazole on midazolam pharmacokinetics are examined below, although direct comparisons cannot necessarily be inferred because the concentrations of midazolam were not always identical. Furthermore, whereas measurement of circulating concentrations of metabolites such as α-hydroxymidazolam is useful to confirm changes in the metabolic rate of CYP3A4, not all studies have assessed that.
In a randomized, open-label, crossover study conducted in 10 healthy subjects, oral voriconazole (400 mg twice daily [BID] on Day 1 and 200 mg BID on Day 2) was co-administered with single doses of either oral midazolam 7.5 mg or IV midazolam 0.05 mg/kg (Day 2). When co-administered with oral midazolam, voriconazole increased the AUC extrapolated to infinity (AUC$_{0-\infty}$) of midazolam by 10.3-fold and the maximum plasma concentration (C$_{\text{max}}$) by 3.8-fold (Figure 1A). The AUC$_{0-\infty}$ ratio of α-hydroxymidazolam to midazolam decreased from 0.30 to 0.07 ($P < .001$). When an IV dose of midazolam was co-administered with voriconazole, the geometric mean AUC$_{0-\infty}$ of midazolam increased only 3.6-fold, and the AUC$_{0-\infty}$ ratio of α-hydroxymidazolam to midazolam decreased from 0.11 to 0.05 ($P < 0.01$). Plasma clearance of a single IV dose of midazolam decreased by > 70%, and the terminal half-life ($t_{1/2}$) was prolonged almost 300% in the presence vs absence of voriconazole.

Studies of co-administration of midazolam and posaconazole have assessed effects of oral posaconazole on both oral and IV formulations of midazolam. In a randomized, open-label, crossover study in 13 healthy subjects administered oral posaconazole 200 mg tablets once daily (QD) for 10 days, the AUC until the time of last measurable concentration (AUC$_{0-\text{last}}$) of midazolam following a single 0.05 mg/kg IV dose on Day 10 increased approximately 2-fold. In a separate randomized, open-label, crossover study of posaconazole oral suspension (200 mg BID and 400 mg BID) in 12 healthy subjects, the AUC$_{0-\text{last}}$ of midazolam following a 2 mg oral dose increased by approximately 4-fold and 5-fold in the 200 mg and 400 mg dosing groups, respectively, whereas the C$_{\text{max}}$ increased approximately 2-fold in both dosing groups (Figure 1B). In that study, the AUC$_{0-\text{last}}$ of a single dose of IV midazolam 0.4 mg increased approximately 5-fold and 7-fold in the 200 mg and 400 mg BID posaconazole groups, respectively.

**FIGURE 1** Pharmacokinetics of oral midazolam when co-administered with triazole antifungal agents. (A) Midazolam (7.5 mg) with oral voriconazole (400 mg twice daily [BID] on first day and 200 mg BID on second day) or without pretreatment. (B) Midazolam (2 mg) alone or with posaconazole 200 mg BID or posaconazole 400 mg BID (inset shows expanded Y axis). (C) Midazolam (7.5 mg) with once-daily (QD) oral itraconazole 200 mg or placebo. (D) Midazolam (3.0 mg) with oral isavuconazole (200 mg three times a day [TID] for 2 days followed by 200 mg QD for 9 days) (inset shows expanded Y axis). Figures reproduced or adapted (with permission, where required) from: (A) Saari et al.$^{30}$; (B) Krishna et al.$^{32}$; (C) Olkkola et al.$^{34}$; (D) Townsend et al.$^{39}$
which was similar to the extent of increase observed with oral midazolam, whereas the $C_{\text{max}}$ increased 2-fold in both posaconazole dose groups. In another randomized, parallel-group, open-label study in 35 healthy subjects, the AUC$_{\text{0-∞}}$ of a single 2 mg oral dose of midazolam increased 3.1-fold, 4-fold, and 5.7-fold when co-administered with posaconazole oral suspension 50, 100, and 200 mg QD, respectively; the $C_{\text{max}}$ increased 2-fold, 2.4-fold, and 2.7-fold, respectively.33

Co-administered itraconazole at a dose subtherapeutic for treatment of IA (100 mg QD) and therapeutic doses (200-400 mg QD) has been shown to result in marked increases in the AUC$_{\text{0-∞}}$ and $C_{\text{max}}$ of midazolam. In a double-blind, randomized, crossover study, Olkkola and colleagues34 administered oral itraconazole (200 mg; therapeutic dose), ketoconazole (400 mg; a strong CYP3A4 inhibitor), or placebo to nine healthy subjects for 4 days. Following co-administration of itraconazole with oral midazolam 7.5 mg on Day 4, the AUC$_{\text{0-∞}}$ of midazolam increased 10-fold and the $C_{\text{max}}$ increased 3-fold relative to placebo (Figure 1C). In a separate randomized, double-blind, crossover study in 12 healthy volunteers, the AUC$_{\text{0-∞}}$ of midazolam administered orally after the last of four daily doses of 100 mg oral itraconazole was increased almost 6-fold and the $C_{\text{max}}$ was increased approximately 2.5-fold.35 In a third open-label study in nine healthy subjects, the AUC$_{\text{0-∞}}$ of midazolam following a 7.5 mg oral dose increased 8-fold when administered 2 hours after oral itraconazole 100 mg QD and 2.6-fold when administered 4 days after the last dose of itraconazole.36 The AUC$_{0-19\text{h}}$ ratio of $\alpha$-hydroxymidazolam to midazolam was also significantly decreased ($P < .005$), although the extent of the decrease was not reported. A fourth study assessed the effects of itraconazole on both oral and IV midazolam in a randomized, double-blind, crossover study in 12 healthy volunteers.37 Subjects randomized to itraconazole (200 mg QD) or placebo for 6 days also received an oral 7.5 mg dose of midazolam on Day 1 and Day 6 as well as 0.05 mg/kg IV midazolam on Day 4 (all midazolam doses administered 2 hours after itraconazole or placebo). Compared with placebo, the AUC$_{\text{0-∞}}$ of midazolam on Day 1 was increased approximately 3.5-fold and the $C_{\text{max}}$ was increased approximately 1.8-fold by co-administration of itraconazole. Following the IV dose of midazolam on Day 4, its clearance was reduced 69% and the t$_{1/2}$ was more than doubled by itraconazole compared with placebo, although the exposure was not affected as markedly as following the oral dose. After the Day 6 dose of oral midazolam, the AUC$_{\text{0-∞}}$, $C_{\text{max}}$, and t$_{1/2}$ were approximately doubled compared with the Day 1 oral dose, which was consistent with a 4-fold higher plasma concentration of itraconazole on Day 6 compared with Day 1. It is not clear whether the inhibition of CYP3A4 in these studies is entirely attributable to the parent itraconazole compound because hydroxymitraconazole, a metabolite of itraconazole, also has been shown to be a potent CYP3A4 inhibitor in vitro.38

The effects of isavuconazole on midazolam pharmacokinetics have been examined in one study. In an open-label study, 23 healthy subjects received an oral dose of 3 mg midazolam followed by administration of oral isavuconazole for 10 days (200 mg three times a day [TID] loading dose for 2 days, then 200 mg BID for another 8 days); a second 3 mg oral dose of midazolam was administered on Day 10.39 Compared with the exposure of midazolam in the absence of isavuconazole, midazolam AUC$_{\text{0-∞}}$ increased by 2-fold following co-administration (Figure 1D). In addition, co-administration with isavuconazole was associated with a 1.7-fold increase in the $C_{\text{max}}$ of midazolam and its t$_{1/2}$ was prolonged by 60%. The AUC$_{\text{0-∞}}$ ratio of $\alpha$-hydroxymidazolam to midazolam was decreased by approximately one-third, from 0.33 to 0.20, although no statistical test of this difference was performed.

As discussed above, the FDA provides categorization of the relative strength of CYP inhibitors according to their effects on recognized substrates based on study results provided to them by the pharmaceutical companies.40 As per those criteria, voriconazole, posaconazole, and itraconazole are all considered strong inhibitors of CYP3A isoenzymes ($\geq$5-fold increases in midazolam AUC), whereas isavuconazole is considered a moderate inhibitor ($\geq$2-fold but $<5$-fold increase in midazolam AUC). The effects of oral formulations of these antifungal agents on midazolam exposure are less pronounced with IV midazolam than oral midazolam. That is likely to reflect inhibition of intestinal CYP3A isoenzymes by the orally administered inhibitor, which would decrease first-pass metabolism of orally administered midazolam to a greater extent. The apparent dose responsiveness of CYP3A inhibition demonstrated with posaconazole appears to reflect submaximal inhibition potential of CYP3A4 with lower exposure to that agent. It is also worth noting that considerable variability of exposure has been found with the oral suspension formulation of posaconazole, which in turn prompted the more recent development of delayed-release tablets,41 but interactions of that formulation with CYP3A isoenzymes have not been reported.

3 EFFECTS OF TRIAZOLE ANTIFUNGALS ON THE PHARMACOKINETICS OF CYCLOSPORINE, TACROLIMUS, AND SIROLIMUS

Consistent with their inhibitory effects on CYP3A4, all of these triazoles have been demonstrated to increase the exposure of co-administered cyclosporine, tacrolimus, and sirolimus. Nevertheless, the potency of inhibition for each of voriconazole, itraconazole, posaconazole, and isavuconazole varies with respect to these immunosuppressant drugs.

3.1 Voriconazole

Studies and prescribing information indicate that concurrent administration of voriconazole increases the exposure concentrations of these immunosuppressant drugs modestly or markedly (Table 1).8,10–13,42–47. In seven kidney transplant recipients who completed a randomized, double-blind, placebo-controlled, crossover study, 7.5 days of oral voriconazole administration (200 mg BID) increased the AUC for the dosing interval (AUC$_{\text{0-τ}}$) of oral cyclosporine (150-375 mg/day) by 1.7-fold.45 In an analysis of 21 HSCT recipients, initiation of voriconazole treatment (oral or IV) was also found to increase the concentration/dose ratio of cyclosporine from 86.0 to 120.2 and that of tacrolimus from 595.9 to 890.7.48 However, others have reported
that the effects of voriconazole on cyclosporine or tacrolimus concentrations may be highly variable and may not be related to plasma concentrations of voriconazole.\textsuperscript{59,52} Although other published data on the quantitative effects of tacrolimus are scarce, labeling information for voriconazole indicates that, in healthy subjects, the AUC\textsubscript{0-\infty} and C\textsubscript{\text{max}} of a single 0.1 mg/kg dose of tacrolimus were increased approximately 3-fold and 2-fold, respectively, by oral voriconazole (400 mg BID for 1 day, then 200 mg BID for 6 days).\textsuperscript{7,8}

One of the earliest indications of an interaction of voriconazole with sirolimus was a case report in which two kidney transplant recipients required dose reductions of 75%-88% for sirolimus with concurrent voriconazole treatment.\textsuperscript{51} A retrospective database analysis of HSCT recipients concluded that a 90% reduction in initial sirolimus dose was required for safe administration of voriconazole in these patients.\textsuperscript{52} A separate retrospective analysis suggested that safe co-administration of sirolimus and voriconazole required a number of different considerations, including which agent the patient received first, the sirolimus dosage and concentrations, concurrent diseases, and other factors affecting CYP3A activity.\textsuperscript{53} For example, patients already receiving voriconazole may not require large "loading doses" when initiating sirolimus treatment. For patients already receiving low doses of sirolimus (0.5-2 mg/day), a 50% dose reduction might be sufficient when initiating voriconazole treatment if plasma sirolimus concentrations are ≤12 ng/mL. The FDA and EMA labeling information indicates that co-administration of voriconazole increases the AUC 11-fold and the C\text{max} 7-fold, and concurrent use of voriconazole with sirolimus is contraindicated.\textsuperscript{7,8}

### 3.2 | Posaconazole

A number of clinical studies and the prescribing information for posaconazole suggest that concurrent administration of this triazole antifungal agent modestly or markedly increases exposure of these immunosuppressant drugs (Table 1). One study assessed four heart transplant recipients on an established regimen of cyclosporine and found that co-administration of 200 mg/day oral posaconazole (tablet) for 10 days increased the AUC\textsubscript{0-\infty} by 1.3-fold.\textsuperscript{43} Those investigators also assessed the effect of posaconazole at 400 mg BID (oral suspension) for 7 days on a single dose of 0.05 mg/kg oral tacrolimus in 36 healthy subjects. The AUC\textsubscript{0-\infty} of tacrolimus increased 4.8-fold with co-administration of posaconazole. In another study in 41 blood and marrow transplant recipients, the dose of cyclosporine was not initially reduced when administering concurrent prophylactic treatment with oral posaconazole (200 mg oral suspension TID); instead, dose concentrations were monitored and adjusted to remain in the therapeutic range for cyclosporine.\textsuperscript{54} After 30 days, the mean cyclosporine dose was reduced from 3.09 to 1.58 mg/kg/day; the cyclosporine concentration/dose ratio increased from 82.1 to 172.6. Further quantitative information for the effects of posaconazole on tacrolimus are provided in FDA and EMA prescribing information, which state that posaconazole increases the AUC and C\text{max} of tacrolimus by 3.6-fold and 1.2-fold, respectively.\textsuperscript{9,10}

The effects of posaconazole on sirolimus exposure were assessed in a study of 12 healthy subjects.\textsuperscript{44} Compared with 2 mg sirolimus
alone, co-administration with posaconazole after 16 days at 400 mg BID increased the C_{max} and AUC of sirolimus by 6.7-fold and 8.9-fold, respectively. In a retrospective analysis of 15 HSCT recipients who received sirolimus (median dose 2 mg/day), 14 of whom also received tacrolimus (median dose 2.3 mg/day), posaconazole was initiated as prophylaxis or treatment of IFD for a median of 78 days.\(^7\) Dosing of the immunosuppressant drugs was reduced empirically at the onset of posaconazole treatment (sirolimus, median 50% reduction; tacrolimus, median 33% reduction). Although trough concentrations of tacrolimus remained relatively stable before and after initiation of posaconazole treatment (medians, 5.3 and 5.2 ng/mL, respectively), six patients had trough concentrations of sirolimus >12 ng/mL. Only one of those patients experienced an adverse event potentially related to elevated sirolimus concentrations, and so the authors concluded that concurrent use of sirolimus and posaconazole was well tolerated when the dose was empirically reduced 33%-50% and trough concentrations carefully monitored. However, as with voriconazole, co-administration of posaconazole with sirolimus is contraindicated in both FDA and EMA prescribing information.\(^9.\)\(^10\)

### 3.3 | Itraconazole

Available data indicate that itraconazole markedly increases the exposure of all three immunosuppressant drugs (Table 1). Three small studies have provided evidence of increased concentrations of cyclosporine or tacrolimus in HSCT recipients treated with itraconazole. In an open-label study with 17 evaluable HSCT recipients, IV itraconazole (200 mg BID for 2 days) increased the mean C_{max} of cyclosporine (n = 8) and tacrolimus (n = 9) by approximately 1.8-fold each after 48 hours.\(^5\) A retrospective analysis of HSCT recipients found that concentration/dose ratios of cyclosporine and tacrolimus (combined analysis) were increased from 62.5 (ng/mL)/(mg/kg) to 121.1 (ng/mL)/(mg/kg) within 7-10 days of initiating treatment with 200 mg QD oral itraconazole.\(^3\) In a third open-label study in 16 HSCT recipients treated with either cyclosporine or tacrolimus (n = 8 each), itraconazole (oral solution) was administered at 200 mg BID for 2 days, then QD from 30 to 100 days after transplantation.\(^4\) Exposure was not reported in this study, but after 7 days of co-administration, the dose-adjusted blood concentrations of cyclosporine and tacrolimus prior to the Day 7 dose of each were increased 2.7- and 5.6-fold, respectively. Reduction of the dose of each (cyclosporine, 66.5% of starting dose; tacrolimus, 33.7% of starting dose) also reduced the dose-adjusted blood concentrations in all except one tacrolimus-treated patient with a genotype of CYP3A5 that is associated with enhanced metabolism of tacrolimus. Several case reports have indicated increased concentrations of sirolimus with concurrent itraconazole treatment\(^5\)\(^7\)\(^9\)\(^11\); FDA prescribing information also indicates this effect, but no quantitative information is provided.\(^1\)

### 3.4 | Isavuconazole

Information on the effects of isavuconazole on these immunosuppressant drugs is derived from three clinical studies in healthy adults (cyclosporine 300 mg, n = 24; tacrolimus 5 mg, n = 24; sirolimus 2 mg, n = 22)\(^5\) (Table 1). In each of these studies, isavuconazole was administered as 200 mg TID for 2 days, then 200 mg QD thereafter. Co-administration of isavuconazole increased the AUC_{0-24 h} and C_{max} of cyclosporine 1.3-fold and 1.1-fold, respectively, whereas increases with tacrolimus were in 2.3-fold and 1.4-fold, respectively, and increases with sirolimus were 1.8-fold and 1.7-fold, respectively. These data are also contained in EMA prescribing information for isavuconazole,\(^1\) although FDA prescribing information only mentions an approximately 2-fold increase of tacrolimus and sirolimus.\(^1\)

### 3.5 | Relative impact on co-administered immunosuppressant drugs

Comparisons between the effects of these triazoles on the pharmacokinetics of immunosuppressant drugs must be made with caution because no head-to-head studies have been conducted. Moreover, the subjects included in each study were not necessarily comparable (eg, transplant recipients vs healthy subjects), not all studies tested the approved clinical dosing regimen, and in many cases, the available information is incomplete. Furthermore, the effects of triazole antifungal agents on immunosuppressant drugs may involve other CYP isoenzymes and/or transporters (see next section). Nevertheless, available data indicate that isavuconazole is a less potent inhibitor of CYP3A4 compared with these other triazole antifungal agents. Thus, among the triazole drugs currently approved to treat IA, isavuconazole appears to have a more manageable interaction profile with respect to these immunosuppressant drugs, although as the most recently approved member of its class, clinical experience is limited.

### 3.6 | Other factors requiring consideration

Although interactions of these three immunosuppressant drugs with triazole antifungal drugs are the most studied, other immunosuppressive drugs are available and so their interactions need to be considered. As also mentioned above, everolimus is metabolized by CYP3A4 and it is also a substrate for the efflux transporter P-gp (see below). Although interactions of everolimus with triazole antifungal agents have not been systematically studied, case reports and retrospective analyses have described dramatic increases in everolimus concentrations and associated adverse effects when administered with voriconazole or posaconazole.\(^6\)\(^\text{a}\)\(^6\)\(^\text{b}\) Synthetic corticosteroids are commonly used to treat a variety of inflammatory conditions, and the metabolism of most or all involves CYP3A4 isoenzymes.\(^6\)\(^\text{a}\)\(^6\)\(^\text{b}\),\(^6\)\(^\text{c}\) However, interpretation of CYP3A4-mediated drug-drug interactions may be complicated because those agents in turn can affect the expression of CYP genes via effects on the glucocorticoid receptor.\(^6\)\(^\text{a}\) Nevertheless, one study reported a 2.5-fold increase in the AUC_{0-24 h} of oral methylprednisolone (single 48 mg dose) when co-administered with itraconazole (400 mg on Day 1, then 200 mg QD for 3 days),\(^6\)\(^\text{a}\) and labeling of voriconazole indicates that co-administration with prednisone (the pro-drug of prednisolone) increases the AUC_{0-24 h} prednisolone by 34%.\(^7\)\(^\text{b}\) On the other hand, isavuconazole (200 mg TID for 2 days, then
200 mg QD thereafter) had little effect on prednisolone following a single 20 mg dose of prednisone (AUC₀-∞ increased 8%).

Notwithstanding the importance of the direct effects of triazole antifungal agents on CYP3A4, their interactions may also involve other metabolic pathways, and the unique pharmacokinetic properties of each agent are also a factor that should be considered. For example, voriconazole is primarily metabolized by CYP2C19, with contributions by CYP3A4 and CYP2C9. Voriconazole exhibits non-linear pharmacokinetics such that exposure increases disproportionately with increasing dosages. That may be due in part to saturable metabolism, although more recent evidence suggests that it may instead (or in addition) be related to dose-dependent autoinhibition of CYP3A4 activity. In any event, considerable inter- and intra-subject variability in plasma concentrations of voriconazole has been observed and is at least partly due to allelic variants of the CYP2C19 gene that confer reduced or enhanced enzyme activity in subjects characterized as poor or extensive/ultra-rapid metabolizers, respectively. At a given dose of voriconazole, clearance in poor metabolizers is reduced, thus resulting in increased plasma concentrations of voriconazole. In turn, this could potentially lead to adverse effects, including elevated concentrations of immunosuppressant drugs metabolized by CYP3A4. The same dose in extensive or ultra-rapid metabolizers would result in lower plasma concentrations of voriconazole that would be less likely to affect CYP3A4-mediated metabolism but may not be sufficient to confer therapeutic benefit.

Uptake and efflux transporters can also influence the pharmacokinetics of drugs as they have the potential to alter their distribution and/or clearance. Given that most immunosuppressive agents are also substrates of the P-gp efflux transporter, effects of triazole antifungal drugs on P-gp are also an important clinical consideration. Voriconazole does not appear to have any effect on P-gp-mediated transport of \( N \)-methyl-quinidine (NMQ) transport in vitro or P-gp-mediated digoxin transport in vivo. In contrast, posaconazole and itraconazole both strongly inhibit NMQ transport in vitro (IC₅₀ : 3 μM and 2 μM, respectively) and increase plasma concentrations of digoxin in vivo (posaconazole, extent of increase not specified; itraconazole, 80% increase of serum digoxin concentration for 0.25 mg QD digoxin with 200 mg oral itraconazole vs placebo for 10 days). The effect of isavuconazole on P-gp is not as clear. Strong inhibition of NMQ transport (IC₅₀ : 3 μM) has been observed in vitro, but in vitro inhibition of digoxin transport is markedly less (IC₅₀ : 26 μM). Furthermore, plasma exposure of digoxin in vivo was only increased by ~25% with co-administration of the clinically recommended dose of isavuconazole, and a 37% increase in AUC₀-∞ of the P-gp substrate atorvastatin with co-administered isavuconazole was mostly explicable in terms of its moderate inhibition of CYP3A4. On the other hand, the increase in digoxin exposure was unlikely to result from inhibition of CYP3A4 as this enzyme has at most only a minor role in digoxin metabolism, and so some of the effect of isavuconazole on atorvastatin exposure may well have resulted from P-gp inhibition. Nevertheless, these observations suggest that isavuconazole is a weak inhibitor of P-gp in vivo. Thus, plasma concentrations (and corresponding interactions with immunosuppressant drugs) of posaconazole, itraconazole, and to a lesser extent isavuconazole may modulate plasma concentrations of immunosuppressant drugs via interactions with P-gp.

Other concomitant drugs can also affect plasma concentrations of triazole antifungal agents and thereby also potentially affect concentrations of CYP3A4-metabolized immunosuppressant drugs. For example, recent in vitro data suggest that proton pump inhibitors that may be competitive inhibitors of CYP isoenzymes have the potential to increase voriconazole exposure. Co-administration of proton pump inhibitors may also decrease pH-dependent absorption of some formulations of triazole antifungal agents such as itraconazole capsules. In the case of voriconazole, the CYP2C19 allele is also a factor that adds complexity. In another recent study, voriconazole was co-administered with a combination of ritonavir and atazanavir (commonly used as therapy in patients with HIV). Exposure of co-administered voriconazole was moderately reduced in extensive metabolizers, likely reflecting ritonavir-mediated induction of CYP2C19. However, exposure of voriconazole was markedly increased in poor metabolizers, probably because CYP3A4, which is normally more important for voriconazole clearance in subjects having poor or no CYP2C19 activity, was strongly inhibited by both ritonavir and atazanavir. Posaconazole is metabolized primarily via the 1A4 isoenzyme of UDP glucuronosyltransferase (UGT), and isavuconazole is partly metabolized by CYP3A5 (as well as UGT; subsequent to CYP3A4/CYP3A5). and so other concomitant drugs that affect those enzymes can potentially affect plasma concentrations of triazole antifungal agents and thereby also affect concentrations of immunosuppressant drugs.

Finally, the terminal half-life of triazole antifungal agents affects the duration of any potential drug-drug interactions. The terminal half-life of voriconazole is dose-dependent and is approximately 6 hours for an oral 200 mg dose, whereas that of posaconazole is independent of dose at 27 hours. The terminal half-life for itraconazole capsules is 32-48 hours with repeated doses, although the terminal half-lives of itraconazole and the hydroxyitraconazole metabolite for at least one IV formulation are dose-dependent and can extend beyond 150 hours. The terminal half-life of isavuconazole is independent of dose at 130 hours. Thus, any drug-drug interaction involving these triazole antifungal agents might be expected to persist for a longer duration with isavuconazole or some IV formulations of itraconazole compared with either voriconazole or posaconazole. In the case of isavuconazole, its effects on CYP3A4 in vitro involves both inhibition (an effect mediated by direct interactions of the proteins, and so requiring presence of the inhibitor) and induction (an effect on gene expression that can persist after the inducer is eliminated). If this is also true in vivo, this may account for the weaker inhibition of CYP3A4 by isavuconazole compared with the other triazole antifungal agents. Thus, any CYP3A4-mediated drug-drug interaction with isavuconazole could potentially be biphasic in nature during cessation of treatment.

### 3.7 Current recommendations and strategies to address drug-drug interactions

The interactions of triazoles reviewed above with cyclosporine, tacrolimus, and sirolimus have required accompanying recommendations
in product labeling. Both FDA and EMA labeling for these triazole antifungal drugs are largely consistent, and unless otherwise indicated, the discussion points below apply to both.

Labeling for voriconazole emphasizes that increased concentrations of cyclosporine and tacrolimus have been associated with nephrotoxicity, and so patients should be monitored for the development of abnormal renal function.\textsuperscript{7,8} Empirical dose reductions are recommended for both cyclosporine (reduce to one-half) and tacrolimus (reduce to one-third) when initiating treatment with voriconazole, and concentrations of cyclosporine or tacrolimus should be carefully monitored during and after cessation of treatment. As mentioned above, concurrent use of voriconazole with sirolimus is contraindicated.

Labeling for posaconazole also cautions about nephrotoxicity associated with elevated concentrations of cyclosporine (EU)\textsuperscript{10} or both cyclosporine and tacrolimus (US).\textsuperscript{7} Labels do not mention monitoring renal function in that context, although it would seem a reasonable measure. When initiating treatment with posaconazole, empirical dose reductions are recommended for both cyclosporine (reduce to three-quarters) and tacrolimus (reduce to one-third). As with the recommendations for voriconazole, frequent monitoring of cyclosporine or tacrolimus concentrations is also recommended during and at discontinuation of posaconazole treatment so that the dose can be adjusted accordingly. Concurrent use of posaconazole with sirolimus is contraindicated in FDA labeling, and although not contraindicated in the EMA label, a recommendation for very frequent monitoring of trough concentrations of sirolimus is included for instances in which it may be unavoidable.

As discussed above, approval for itraconazole was obtained prior to the formation of the EMA, and so labeling is not provided by the EMA but rather by individual country members of the EU. In FDA labeling, a "use with caution" warning is included for cyclosporine, tacrolimus, and sirolimus, which includes suggestions to monitor for signs and symptoms of side effects and to consider dose reductions.\textsuperscript{11} The label does not mention therapeutic drug monitoring, although that would seem prudent.

Labeling for isavuconazole in the US also includes a "use with caution" warning for cyclosporine, tacrolimus, and sirolimus, and mentions the possibility of serious side effects in the kidney or brain associated with elevated concentrations of these immunosuppressant drugs.\textsuperscript{12} Neither US or EU labeling recommends empirical dose reductions of any of these immunosuppressant drugs when initiating isavuconazole treatment, but both recommend that their concentrations be monitored and adjusted as needed.\textsuperscript{12,13}

Recommendations from medical societies regarding co-administration of triazole antifungal drugs with immunosuppressant drugs are largely consistent with product labeling. For example, in 2013 (prior to the availability of isavuconazole), the American Society of Transplantation Infectious Diseases Community of Practice guidelines emphasize the potential need for dose reductions of cyclosporine and tacrolimus during treatment of IA with triazole antifungal drugs, and the contraindication of voriconazole use with sirolimus.\textsuperscript{84} More recent guidelines on therapeutic drug monitoring issued by the European Conference on Infections in Leukaemia (2015)\textsuperscript{95} include the need for monitoring of all of these triazole antifungal agents in the setting of potential drug-drug interactions. In other recent recommendations from the Infectious Diseases Society of America (2016), it is recommended to obtain serum trough concentrations for both the triazole antifungal drugs (voriconazole, posaconazole, itraconazole, and possibly isavuconazole) and any potentially interacting drugs, which includes cyclosporine, tacrolimus, and sirolimus.\textsuperscript{86}

Recently, a six-step strategy was recommended to evaluate and respond to the potential for drug-drug interactions of triazole antifungal agents with immunosuppressant drugs.\textsuperscript{87} The first step involves prediction of such interactions based on the underlying pharmacologic mechanisms using resources such as the summary of product characteristics or drug compendia. Second, the identification of any interactions should be informed by the extent and quality of evidence in the medical literature. Third, the magnitude of any potential interaction should be determined from available evidence, and include consideration of any other concomitant medications. Fourth, classification of risk should take into account the narrow therapeutic window for immunosuppressant drugs. Fifth, patient-related factors such as disease status and comorbidities that might affect drug exposure should be taken into account. Finally, having followed these steps, clinicians may need to consider the possibility of discontinuing treatment with the triazole drug, switching to a nonazole medication, empirically decreasing the dose of the immunosuppressant drug, or decreasing the dose based on therapeutic drug monitoring.

4 | CONCLUSIONS

Triazole antifungal agents are an important part of the physician's armamentarium against IA in immunocompromised patients. Although the potential for interactions with immunosuppressant drugs is an additional consideration in SOT and HSCT recipients, in some cases monitoring and adjustment of the dose of an immunosuppressant drug during and at discontinuation of treatment with an approved triazole antifungal drug is sufficient to address any concerns. Nevertheless, there are some combinations of triazole antifungals and immunosuppressant drugs for which the risks outweigh the benefits, such that they are contraindicated. It is, therefore, essential that the interaction profile of an antifungal treatment is a key element in treatment decisions for patients with IA.

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CONFLICTS OF INTEREST

A. Groll has received grants from Gilead; Merck, Sharp & Dohme; Pfizer and Schering-Plough; is a consultant to Astellas, Basilea, Gilead,
Merck, Sharp & Dohme and Schering-Plough, and served at the speakers’ bureau of Astellas, Basilea, Gilead, Merck, Sharp & Dohme, Pfizer, Schering-Plough, and Zeneus/Cephalon. R. Townsend and A. Desai are full-time employees of Astellas Pharma Global Development, Inc. N. Azie was a full-time employee of Astellas Pharma Global Development, Inc. at the time of this review. M. Jones, M. Engelhardt, and A-H. Schmitt-Hoffmann are full-time employees of Basilea Pharmaceutica Ltd. R. Brüggemann has served as a consultant to Astellas Pharma Inc., F2G, Gilead Sciences, Merck Sharpe and Dohme Corp., and Pfizer Inc. and has received grants from Astellas Pharma Inc., Gilead Sciences, Merck Sharpe and Dohme Corp., and Pfizer Inc.

**AUTHOR CONTRIBUTIONS**

All authors contributed to drafting the review and provided final approval to submit.

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