REVIEW

Role of isavuconazole in the treatment of invasive fungal infections

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Abstract: Despite recent advances in both diagnosis and prevention, the incidence of invasive fungal infections continues to rise. Available antifungal agents to treat invasive fungal infections include polyenes, triazoles, and echinocandins. Unfortunately, individual agents within each class may be limited by spectrum of activity, resistance, lack of oral formulations, significant adverse event profiles, substantial drug–drug interactions, and/or variable pharmacokinetic profiles. Isavuconazole, a second-generation triazole, was approved by the US Food and Drug Administration in March 2015 and the European Medicines Agency in July 2015 for the treatment of adults with invasive aspergillosis (IA) or mucormycosis. Similar to amphotericin B and posaconazole, isavuconazole exhibits a broad spectrum of in vitro activity against yeasts, dimorphic fungi, and molds. Isavuconazole is available in both oral and intravenous formulations, exhibits a favorable safety profile (notably the absence of QTc prolongation), and reduced drug–drug interactions (relative to voriconazole). Phase 3 studies have evaluated the efficacy of isavuconazole in the management of IA, mucormycosis, and invasive candidiasis. Based on the results of these studies, isavuconazole appears to be a viable treatment option for patients with IA as well as those patients with mucormycosis who are not able to tolerate or fail amphotericin B or posaconazole therapy. In contrast, evidence of isavuconazole for invasive candidiasis (relative to comparator agents such as echinocandins) is not as robust. Therefore, isavuconazole use for invasive candidiasis may initially be reserved as a step-down oral option in those patients who cannot receive other azoles due to tolerability or spectrum of activity limitations. Post-marketing surveillance of isavuconazole will be important to better understand the safety and efficacy of this agent, as well as to better define the need for isavuconazole serum concentration monitoring.

Keywords: isavuconazole, azole, antifungal, aspergillosis, Mucormycetes, mucormycosis

Introduction

Despite recent advances in both diagnosis and prevention, the incidence of invasive fungal infections (IFIs) continues to rise.[1,2] The most common fungal pathogens associated with invasive disease in humans include *Candida* spp., *Aspergillus* spp., and Mucormycetes.[3] Invasive candidiasis is the fourth most common health care-associated bloodstream infection in the US, and is associated with a 47% attributable mortality rate.[4,5] Invasive aspergillosis (IA) is one of the most common life-threatening IFIs in immunocompromised patients, most notably in patients with hematologic malignancies or hematopoietic stem cell transplantations.[6] The incidence of IA in hematopoietic stem cell transplantation patients has been reported as high as 15% with mortality rates ranging from 50%–90% at 1 year.[2,6] Similar to IA, mucormycosis is most frequently diagnosed in patients with hematologic malignancies and those who received solid organ or hematologic stem cell transplantation. While not as prevalent

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as IA and invasive candidiasis (10–50-fold less frequent, respectively), the increasing number of breakthrough infections with Mucormycetes reported in patients receiving mold-active agents (eg, voriconazole and echinocandins) is concerning.[7,8]

Available antifungal agents to treat IFIs include polyenes, triazoles, and echinocandins. For years, amphotericin B (a polyene) was the treatment of choice for serious, life-threatening IFIs. However, given its significant adverse event profile (most notably nephrotoxicity, infusion reactions, and electrolyte disturbances), its use has declined given the availability of safer alternatives in select infections.[9] Despite these limitations, lipid-based formulations of amphotericin B have remained the treatment of choice for select IFIs. This includes mucormycosis, due (in part) to the lack of in vitro activity of most antifungals against these pathogens.[7] Since the 1990s, triazoles have provided an alternative to amphotericin B for treatment of many IFIs. Fluconazole represents a viable treatment option for many susceptible *Candida* spp.; however, widespread use as empiric therapy for all forms of invasive candidiasis has recently been limited by the emergence of azole-resistant spp.[4] Voriconazole replaced amphotericin B as the preferred therapy for IA.[10] However, adverse events, drug–drug interactions, and both inter- and intra-patient pharmacokinetic variability (resulting in the need for serum concentration monitoring) complicate its use.[9] Unlike other triazoles, posaconazole is often used in sequence after amphotericin B therapy in patients with mucormycosis or as primary therapy in patients unable to tolerate amphotericin B.[7] Limited clinical experience with posaconazole in these patient populations, along with the caution against using the intravenous (IV) formulation in patients with a creatinine clearance (CrCl) <50 mL/min, have been barriers to its widespread use. The echinocandins (caspofungin, micafungin, and anidulafungin) were introduced in the mid-2000s, and have most often been used to treat invasive candidiasis and refractory IA.[4,11] Despite widespread use of the echinocandins over the past decade, they are limited by their lack of oral formulations and absence of activity in vitro against Mucormycetes.

Isavuconazonium sulfate (Cresemba; Astellas Pharma US, Inc.; Northbrook, IL, USA) is a second-generation triazole approved by the US Food and Drug Administration (FDA) in March 2015 and the European Medicines Agency in July 2015. Isavuconazonium sulfate is the prodrug of isavuconazole (the active moiety), thus the latter terminology will be used throughout this review (except where noted). Isavuconazole exhibits a broad spectrum of activity in vitro against yeasts, dimorphic fungi, and molds (notably

Aspergillus spp. and Mucormycetes).[12] Available in both oral and IV formulations, isavuconazole currently has approved indications for the treatment of adults with IA and mucormycosis.[12] The primary aim of this review is to summarize the pharmacologic, kinetic, clinical efficacy and safety characteristics of isavuconazole which best help define its potential role in the management of IFIs.

Pharmacology/spectrum of activity

Similar to other azoles, isavuconazole inhibits the CYP450-dependent enzyme lanosterol 14-alpha-demethylase, encoded by the gene *ERG11*. This enzyme is responsible for producing essential fungal cell wall components through conversion of lanosterol to ergosterol.[12,13] As a result, fungal cell membrane fluidity and asymmetry are compromised. This leads to membrane dysfunction and arrested fungal growth.

Isavuconazole has demonstrated in vitro activity against a variety of fungal species including *Candida*, *Cryptococcus*, *Aspergillus*, and Mucormycetes (see Table 1). Among a variety of *Candida* spp., the minimum inhibitory concentration for 90% of isolates (MIC_{90}) generally ranges from 0.25–0.5 mcg/mL based on Clinical and Laboratory Standards Institute (CLSI) methodology.[14,15] However, several species (including *Candida glabrata* and *Candida krusei*) displayed elevated MIC values against isavuconazole (2 mcg/mL and 1 mcg/mL, respectively).[14,15] No apparent decline in in vitro activity was observed against *Candida* isolates over a 3-year period.[15] Non-*Candida* yeasts are also generally susceptible to isavuconazole. For example, the MIC_{90} against a collection of *Cryptococcus neoformans* isolates was 0.12 mcg/mL.[14] When compared to the activity of voriconazole and posaconazole, the in vitro activity of isavuconazole is comparable against the majority of *Candida* spp. as well as non-*Candida* yeasts, and is more active than fluconazole. One notable exception is *Candida guilliermondii* where both voriconazole and posaconazole exhibited lower MIC_{90} values than isavuconazole (2 mcg/mL, 2 mcg/mL and 8 mcg/mL, respectively).[14]

Isavuconazole is active in vitro against common *Aspergillus* spp., including *Aspergillus fumigatus* and *Aspergillus flavus* with an MIC_{90} of 1 mcg/mL for both organisms (using CLSI methods).[14,16] *Aspergillus niger* exhibits reduced susceptibility to isavuconazole, with an MIC_{90} of 4 mcg/mL. Overall, isavuconazole MICs for *Aspergillus* spp. are comparable to the activity of both voriconazole (0.5 mcg/mL) and posaconazole (0.5 mcg/mL).

Several studies have evaluated the activity of isavuconazole vs non-*Aspergillus* molds, specifically the Mucormycetes. A study which included Mucormycetes isolates (n=72)

Table 1 In vitro activity of isavuconazole against select pathogenic fungi

Organism	Isolates (n)	Isavuconazole			References
		MIC_{50}*	MIC_{90}*	Range*	
Candida spp.					
C. albicans	621	0.015	0.03	≤0.008 to >8	14
C. glabrata	235	0.5	2	0.03–8	14
C. parapsilosis	197	0.06	0.12	≤0.008–1	14
C. tropicalis	110	0.06	0.25	0.015–4	14
C. krusei	37	0.5	1	0.12–4	14
C. lusitaniae	33	0.03	0.06	≤0.008–0.12	14
C. dubliniensis	31	0.015	0.015	≤0.008–0.015	14
Aspergillus spp.					
A. fumigatus	926	0.5	1	0.06 to ≥8	14
A. flavus	454	0.5	1	0.125–4	14, 16
A. niger	218	1	2	0.06 to >8	14, 16
A. terreus	390	0.25	0.5	0.06–2	14, 16
A. nidulans	106	0.125	1	0.06–1	14, 16
Other					
Cryptococcus neoformans	69	0.6	0.12	≤0.008–0.5	14
Rhizomucor	9	1	–	0.5–1	17
Lichtheimia spp.	17	1	–	0.5–2	17
Rhizopus spp.	32	1	–	0.5–4	17
Mucor spp.	13	4	–	1–8	17

Notes: *Concentration in mcg/mL; –, data not reported.
Abbreviations: n, number; MIC_{50}, minimum inhibitory concentration for 50% of isolates; MIC_{90}, minimum inhibitory concentration for 90% of isolates.

compared the in vitro activity of isavuconazole against amphotericin B, voriconazole, and posaconazole.[17] Using the European Committee on Antimicrobial Susceptibility Testing and CLSI testing methodologies, isavuconazole MIC_{50} ranged from 1–4 mcg/mL for isolates of Mucormycetes. However, some species (such as *Mucor circinelloides*) displayed reduced susceptibility, with the MIC_{50} ranging from 4–16 mcg/mL. While isavuconazole exhibits higher MIC_{50} values than posaconazole (MIC_{50} ranged from 0.25–1 mcg/mL) against Mucormycetes isolates, the lack of defined breakpoints for these organisms makes the clinical significance of this finding uncertain.

Resistance

Resistance to triazole antifungals among *Candida* spp. continues to be a concern in clinical practice.[13] The primary mechanisms for azole resistance in *Candida* spp. include over-expression of efflux pumps through ABC transporters, major facilitator transporter *MDR1*, and changes in *EGR11* gene encoding for 14-alpha-demethylase enzyme.[13] In an in vitro study, the activity of isavuconazole was compared to fluconazole, itraconazole, posaconazole, and voriconazole among isolates of *Saccharomyces cerevisiae*, *Candida albicans*, and *C. glabrata* exhibiting a variety of azole resistance mechanisms. Over-expression of ABC transporters and mutations in ERG11 accounted for the loss of isavuconazole

activity, while activity was not affected by mutations in *MDR1*.[18] Since the efflux pumps encoded by *MDR1* are selective for fluconazole, isavuconazole could potentially be a useful agent for fluconazole-resistant *Candida* isolates with this mechanism. Unfortunately, *Candida* spp. can often possess multiple resistance genes, and it can be challenging in clinical practice to discern the type and number of resistance mechanisms with current susceptibility testing. While the most common mechanism cited for azole resistance in *Aspergillus* spp. is an alteration in the *Cyp51A* gene, recent reports have described many other potential areas of azole resistance in the absence of *Cyp51A* mutations.[19] In vitro reports have demonstrated isavuconazole cross-resistance in *Aspergillus* isolates with *Cyp51A* mutations resistant to other azole antifungals including itraconazole, posaconazole, and voriconazole.[19]

Pharmacodynamics (animal model)

The pharmacodynamics of isavuconazole have been evaluated in murine models of disseminated candidiasis and aspergillosis infections.[20–23] In vivo murine invasive candidiasis models reported that the 24-hour free-drug area under the time-concentration curve (AUC) over the MIC was most predictive of isavuconazole efficacy (R^2, 0.84).[22] Of note was the observation that isavuconazole AUC/MIC values associated with efficacy were significantly lower for the *C. glabrata*

and *Candida tropicalis* isolates compared to *C. albicans* (*P*=0.04). A similar study evaluated the pharmacodynamic target of isavuconazole in IA.[21] Fifty percent survival was attained with an AUC/MIC ratio of 24.73 (95% confidence interval [CI], 22.50 to 27.18). As expected, isavuconazole was ineffective at improving survival in isolates harboring azole resistance genes and elevated MIC values.

Pharmacokinetics

Isavuconazole is commercially available as the prodrug isavuconazonium sulfate.[12] The active moiety (isavuconazole) is rapidly produced through hydrolysis by plasma esterases. Animal model and human studies have described a high oral bioavailability of isavuconazole (98%) (see Table 2). The oral absorption is not significantly affected by food, enabling isavuconazole to be taken without regard to meals. Single dose studies of IV (50, 100, or 200 mg) and oral (100, 200, 400 mg) isavuconazole demonstrated peak plasma concentrations (Cmax) of 2–2.5 mcg/mL achieved at the end of the 1-hour infusion and 1.5 to 3 hours after oral administration.[24] While disproportionate increases in plasma AUC and Cmax concentrations raised the possibility of non-linear drug exposure and saturable metabolism, this was not observed in subsequent pharmacokinetic studies.[24,25] In multidose studies, isavuconazole steady-state concentrations were not reached until approximately 2 weeks of once-daily dosing. There was significant (3–5-fold) drug accumulation from study day 1 to study day 14. However, the Cmax and AUC values were proportional for the 50 mg and 100 mg daily doses (indicating that isavuconazole follows nonsaturable linear elimination).[25] Isavuconazole is extensively protein bound (99%) similar to posaconazole and widely distributed (volume of distribution 155–494 L) which is consistent with

other azole antifungals.[24] Isavuconazole primarily undergoes hepatic metabolism through CYP3A4 and subsequently UGTs, with only 0.02%–0.38% of unchanged drug being recovered in urine.[12] Elimination is biphasic, with a half-life of 0.42–2 hours and 56–104 hours in the distribution and terminal elimination phases, respectively.[24] The prolonged half-life of isavuconazole compared to other azole antifungals allows for once-daily maintenance dosing.

The pharmacokinetic profile of isavuconazole has been reported in special populations, including hepatic impairment, renal impairment, and geriatrics. The increased water solubility of the isavuconazole prodrug (isavuconazonium sulfate) facilitates formation of a solution without addition of a cyclodextrin which limits the use of IV voriconazole and posaconazole due to the risk of renal toxicity in patients with a CrCl <50 mL/min. Due to the lack of cyclodextrin and minimal renal excretion, isavuconazole can be given to patients with mild, moderate, and severe renal impairment without need for dose adjustment. Patients with mild to moderate hepatic impairment (Child-Pugh Class A or B) exhibit decreases in clearance (40% and 48%, respectively), but such reductions do not warrant dose reduction in these patients.[26,27] Currently, there are no data in patients with severe hepatic impairment (Child-Pugh Class C).[12] No published data exist which report the pharmacokinetics of isavuconazole in pediatric patients. AUC does not change significantly in elderly males (>65 years of age); however there are slight increases for elderly females when compared to elderly males and younger females (AUC increase 38% and 47%, respectively). Nevertheless, these increases were not considered significant enough to warrant dose modification.[12] Finally, the pharmacokinetics of isavuconazole were assessed in a pharmacokinetic model between healthy Western and Chinese subjects.[12]

Table 2 Comparison of pharmacokinetic parameters of selected triazoles

Parameter	Fluconazole[48]	Voriconazole[49,50]	Posaconazole[50,51]	Isavuconazole[12,50]
Available	Oral tablets	Oral tablets	Oral suspension	Oral capsules
Formulations	Oral suspension	Oral suspension	Oral tablets	Intravenous
	Intravenous	Intravenous	Intravenous	
Oral bioavailability, %	>90	>90[a]	Range 8–47[b]	98
Volume of distribution, (L/kg)	0.6	4.6	Range 5–25	Range 4.4–7.7
Protein binding, %	Range 11–12	58	>99	99
CSF penetration (relative)	Good	Good	Poor	Poor
Urine concentration - active drug	Good	Poor	Poor	Poor
Metabolism (primary route)	Minor hepatic (predominately renally eliminated)	Hepatic	Hepatic	Hepatic
Elimination (primary route)	Renal	Renal	Fecal	Fecal
Half-life, hours	31	6	Range 25–35	Range 56–104

Notes: [a]Decreased when administered with food; [b]oral tablets have higher bioavailability than oral suspension.
Abbreviation: CSF, cerebrospinal fluid.

Compared to Western subjects, Chinese subjects had a 40% lower clearance of isavuconazole. Despite the reduction in clearance, there is no formal dose adjustments for Chinese patients.

Clinical studies
Candidiasis

The safety and efficacy of oral isavuconazole for the treatment of uncomplicated esophageal candidiasis was evaluated in a Phase 2, randomized, double-blind, parallel group, noninferiority study at eight sites in South Africa.[28] Adults 18–65 years of age were randomized (1:1:1:1) to receive one of the following once-daily oral regimens for a minimum of 14 days: isavuconazole 200 mg on day 1 followed by 50 mg from day 2 to the end-of-therapy (EOT); isavuconazole 400 mg on days 1, 7, 14, and 21; isavuconazole 400 mg on day 1, followed by 100 mg from day 2 to the EOT; or fluconazole 200 mg on day 1, followed by 100 mg from day 2 to the EOT. Approximately one third of study patients had HIV infection. *C. albicans* was isolated in 96.6% of cases, followed by *C. glabrata* (2.8%) and *C. tropicalis* (0.7%). Endoscopically-confirmed clinical response at the EOT was observed in 146 (95.4%) patients, and was similar between treatment groups. Overall, each dosing regimen of isavuconazole demonstrated noninferiority (within a margin of 15%) to fluconazole. Of note, the dose of fluconazole used in this study is lower than the dose currently recommended by the Infectious Diseases Society of America for this indication.[4] In addition, patients with recurrent or refractory disease and those having failed prior antifungal therapy were excluded from this trial, which represent a large portion of patients in need of well-tolerated alternatives with oral dosage formulations.

The ACTIVE trial was a Phase 3, randomized, double-blind, parallel-group study evaluating the safety and efficacy of isavuconazole (200 mg IV every 8 hours for six doses, followed by 200 mg IV daily) compared to caspofungin 70 mg IV daily in the treatment of candidemia and invasive candidiasis.[29] After day 10, isavuconazole-treated patients had the option to step down to oral isavuconazole 200 mg daily, and caspofungin-treated patients had the option to step down to oral voriconazole 400 mg every 12 hours until EOT (maximum of 56 days). Overall treatment response at the end of IV therapy, as assessed by the Data Review Committee, occurred in 60.3% and 71.1% of patients treated with isavuconazole and caspofungin, respectively (adjusted treatment difference of −10.8%; 95% CI, −19.9 to −1.8%).[30] The study failed to meet criteria for noninferiority of isavuconazole in

overall treatment response at the end of IV therapy. These results are consistent with another published study indicating superiority of anidulafungin over fluconazole for primary therapy in patients with invasive candidiasis.[31]

Aspergillosis

Isavuconazole has been FDA-approved for the treatment of IA based on results from the SECURE study, a Phase 3, randomized, double-blind, multicenter, active-controlled, non-inferiority study.[32] This study evaluated the safety and efficacy of isavuconazole vs voriconazole for the primary treatment of IFIs in 516 patients. Adults with proven, probable, or possible IFIs (as defined by the European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria) caused by *Aspergillus* spp. or other filamentous fungi were randomized 1:1 to receive isavuconazole (200 mg IV every 8 hours for six doses followed by 200 mg IV or oral daily thereafter) or voriconazole (6 mg/kg IV every 12 hours for two doses followed by 4 mg/kg IV every 12 hours or 200 mg orally every 12 hours thereafter). Included patients received treatment for at least 7 days following resolution of clinical signs or symptoms, up to a maximum duration of 84 days. Patients with moderate to severe renal dysfunction (defined as a calculated CrCl <50 mL/min) and patients treated with systemic mold-active antifungals for at least 4 days within the 7 days prior to receipt of first dose of study drug were excluded. The primary outcome was all-cause mortality through day 42 in the intention-to-treat population with a noninferiority margin of 10%. More than 80% of patients in each group had an underlying hematological malignancy at baseline, and 63% (isavuconazole) and 68% (voriconazole) were neutropenic. Of note, 36% of patients in the isavuconazole group and 35% of patients in the voriconazole group were diagnosed by serum galactomannan assay. The all-cause mortality of 18.6% and 20.2% in isavuconazole and voriconazole-treated patients (respectively) met criteria for noninferiority (adjusted treatment difference −1.0%; 95% CI, −7.8 to 5.7). All-cause mortality through day 84 was 29% and 31%, respectively. For the subset of patients with proven or probable IA (n=231), both all-cause mortality (18.7% and 22.2%, respectively) and overall clinical, mycological, and radiologic response at EOT (35% and 38.9%, respectively) were comparable. This study has important limitations worth discussing. First, patients undergoing treatment for hematological malignancies were not eligible for inclusion if they were receiving mold-active prophylaxis, which is common clinical practice. Thus, the efficacy of isavuconazole for

breakthrough infections remains uncertain.[33] Additionally, *Aspergillus* spp. was the most common causative pathogen for patients with culture-confirmed IFIs, and most patients were treated for lower respiratory tract disease, which limits these data in the generalizability of isavuconazole treatment for other molds or for extrapulmonary infections.[33] Third, over one third of patients in each group were diagnosed with serum galactomannan testing. Finally, serum concentration monitoring of voriconazole was not allowed during the study. Studies have linked voriconazole serum concentrations to improved treatment responses in patients with IFIs.[34]

Mucormycosis

The safety and efficacy of isavuconazole for primary or salvage treatment of IA in patients with renal impairment and for rare IFIs, including mucormycosis was evaluated in a Phase 3, single-arm, open-label, multicenter, noncomparative trial.[35] Adult patients with renal impairment and proven, probable, or possible IA were included. Additionally, patients with culture-confirmed IFIs caused by rare molds, including Mucormycetes were eligible. Included patients received isavuconazole 200 mg IV or orally every 8 hours for six doses, followed by 200 mg daily for up to 180 days or longer in patients with clinical benefit. Of the 149 patients enrolled, 37 had proven (86%) or probable (14%) mucormycosis only; the majority of which were lower respiratory tract infections (59.4%) with or without other organ involvement. Pathogens causing mucormycosis included Mucorales not otherwise specified (35%), *Rhizopus oryzae* (19%), *Mucor* spp. (16%), and *Rhizomucor* spp. (14%). The median duration of treatment was 84 days (interquartile range 19–179, range 2–882). Overall, eleven (31.4%) patients had a successful response at EOT. All-cause mortality at days 42 and 84 were 38% and 43%, respectively, which is similar to published data on amphotericin B and posaconazole oral solution in immunocompromised hosts.[36–38] Patients receiving isavuconazole for primary treatment had a lower mortality through day 42 compared with those receiving salvage therapy for refractory disease or those intolerant to other antifungals (33.3%, 45.5%, and 40%, respectively).

To further define the clinical efficacy of isavuconazole, a case-control analysis was reported in which patients with mucormycosis who received primary treatment with isavuconazole were compared to contemporary controls from the FungiScope registry who received amphotericin B followed by posaconazole.[35] The crude (33% vs 39%, *P*=0.775) and weighted all-cause mortality at day 42 (33% vs 41%, *P*=0.595) and survival at day 84 (57% vs 50%, *P*=0.653)

did not differ for patients treated with either isavuconazole or amphotericin B formulations, respectively.

Safety and tolerability

Clinically significant or commonly associated adverse effects with triazoles include gastrointestinal (nausea, vomiting, hepatic enzyme elevations) and cardiovascular (QTc prolongation) effects.[9] However, the severity and incidence to which these occur vary between the different triazoles. In general, isavuconazole is well-tolerated and appears to have a similar safety profile to that of fluconazole.[39] In Phase 1 and 2 studies, no serious adverse effects occurred due to isavuconazole.[24,25,28] Furthermore, in Phase 3 clinical trials, isavuconazole appears to have a more favorable safety profile compared to that of voriconazole and a comparable safety profile to that of caspofungin.[30,32,35] The most frequently reported adverse events were gastrointestinal disorders (nausea [26%], vomiting [25%], diarrhea [22%], constipation [13%], elevated liver enzymes [16%]), headache (17%), hypokalemia (14%), dyspnea (12%), cough (12%), peripheral edema (11%), and back pain (10%). In the SECURE study, isavuconazole-treated patients had significantly fewer hepatobiliary disorders (9% vs 16%; *P*=0.016), skin and subcutaneous tissue disorders (33% vs 42%; *P*=0.037), and eye disorders (15% vs 27%; *P*=0.002) compared to voriconazole-treated patients.[32] In addition, significantly fewer patients reported treatment-emergent adverse events considered drug-related by investigators with isavuconazole compared to voriconazole (42% vs 60%; *P*<0.001). Drug discontinuation due to either treatment-emergent or drug-related adverse events was less common with isavuconazole compared to voriconazole (14% vs 23% and 8% vs 14%, respectively).[32] However, the increased number of adverse events and drug discontinuations in the voriconazole group may be attributable (at least in part) to the inability to monitor voriconazole serum concentrations. The frequency of treatment-emergent (94.6%) and study-drug related (35.1%) adverse events in patients treated for invasive mucormycosis in the VITAL study were similar to the SECURE study.[35] The most common treatment-emergent adverse events were nausea, vomiting, diarrhea, and pyrexia.

Cardiovascular adverse events (most notably QTc prolongation) are a significant concern with the available triazoles. This concern may be enhanced with drug interactions that affect the metabolism of many QT-prolonging medications.[40] However, unlike current triazoles, most studies have not shown an association with isavuconazole and QTc prolongation with the exception of the VITAL study.[25,26,35]

In the VITAL study, 25% of patients had an increase in QTc of more than 30 msec.[35] This finding will need to be evaluated in future studies to better delineate its potential clinical significance. On the other hand, isavuconazole was noted to cause a dose- and concentration-related QTc interval shortening in other studies. When isavuconazole is administered at the maintenance dose of 200 mg daily, the least squares mean difference in the QTc from placebo was −13.1 msec (90% CI: −17.1, −9.1).[12] In clinical studies, all occurrences of QTc shortening were temporary and did not require intervention. The clinical significance of isavuconazole-induced QTc shortening is unknown; however, patients with familial short-QT syndrome should not receive therapy with isavuconazole.[12,41,42] Furthermore, caution is warranted during the coadministration of isavuconazole with medications known to shorten the QT interval (ie, lamotrigine, primidone, rufinamide).[12,41,42]

Drug interactions

The triazoles have a significant number of drug–drug interactions, especially with itraconazole and voriconazole.[9] These interactions are facilitated primarily through their variable inhibition of the cytochrome P450 system (most notably CYP3A4).[43] Isavuconazole's interaction profile most closely resembles that of posaconazole, and appears to have less drug interactions than voriconazole.[39,40] Specifically, in vitro studies have shown isavuconazole to be a substrate of both CYP3A4 and CYP3A5, inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2D6, P-gp, BCRP, and human OCT2. Isavuconazole is also a weak inducer of CYP3A4, CYP2B6, CYP2C8, and CYP2C9.[12] However, in vivo drug–drug interaction studies have demonstrated isavuconazole to be a mild–moderate inhibitor of CYP3A4, a mild inducer of CYP2B6, a mild inhibitor of P-gp and UGT, and did not affect the pharmacokinetics of substrates of CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 (see Table 3).[12] Consequently, isavuconazole is contraindicated with concomitant administration of strong inducers

Table 3 Comparative inhibition of selected CYP450 isoenzymes by triazoles

Azole	CYP2C8	CYP2C9	CYP2C19	CYP3A4
Fluconazole	++	++	+	++
Itraconazole	+	+	−	+++
Voriconazole	++	++	+++	++
Posaconazole	−	−	−	+++
Isavuconazole	−	−	−	+/++

Notes: −, no inhibition; +, mild inhibition; ++, moderate inhibition; +++, strong inhibition. Data from references.[12,52,53]

and inhibitors of CYP3A4 such as ketoconazole, rifampin, carbamazepine, and St John's wort (see Table 4). Similar to other triazoles, concomitant administration of isavuconazole with immunosuppressive agents (cyclosporine, tacrolimus, and sirolimus) requires potential dose reduction and more frequent monitoring of the immunosuppressive agents. Currently, there are no formal dose reduction recommendations. However, authors of a recent case report recommend an initial 50% reduction in tacrolimus dose when used in combination with isavuconazole.[44] Furthermore, medications that have a narrow therapeutic window that are substrates of P-gp (eg, digoxin) require therapeutic drug monitoring (TDM) and possible dosage adjustments.[12] Of note, isavuconazole is not affected by medications which alter the gastric pH, unlike itraconazole and the suspension formulation of posaconazole.

Dosing and administration

Isavuconazole is administered orally and intravenously as the prodrug isavuconazonium sulfate. Isavuconazole capsules contain 186 mg of isavuconazonium sulfate, which is equivalent to 100 mg of isavuconazole.[12] The capsules can be administered without regard to food, unlike voriconazole and the oral formulations of posaconazole.[9] Isavuconazole injection is supplied as a single-dose vial containing 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole). The reconstituted injection should be added to a compatible diluent (0.9% sodium chloride or 5% dextrose) and administered through an in-line filter over at least 1 hour.[12]

The recommended dosing of isavuconazole is to give a loading dose of 372 mg isavuconazonium sulfate (200 mg of isavuconazole) every 8 hours for six doses, followed by a maintenance dose of 372 mg isavuconazonium sulfate (200 mg of isavuconazole) once daily.[12] The maintenance dose can be started 12–24 hours after the last loading dose. As discussed previously, dosage adjustments are not warranted in patients with renal disease, mild to moderate liver disease, or advanced age. Isavuconazole has not adequately been studied in patients <18 years of age, thus its use should be avoided in these patients due to lack of available data. In addition, animal studies have shown that isavuconazole is excreted in breast milk; therefore, nursing mothers should not receive therapy with this agent. Lastly, isavuconazole should only be utilized in pregnant patients or patients with severe hepatic impairment (Child-Pugh Class C) if the potential benefits outweigh the risks associated with therapy.[12]

Table 4 Selected drug–drug interactions with isavuconazole

Medication	Clinical significance
Ketoconazole	• Isavuconazole's AUC increases by ~5-fold when administered with concomitant ketoconazole • Use with strong CYP3A4 inhibitors is contraindicated
Rifampin	• Isavuconazole's AUC decreases by ~2-fold with concomitant rifampin • Use with strong CYP3A4 inducers is contraindicated
Lopinavir/ritonavir	• Isavuconazole's AUC increases by ~2-fold with concomitant lopinavir/ritonavir • Use with caution
Sirolimus, tacrolimus, cyclosporine, and mycophenolate mofetil	• Isavuconazole increases the AUC of sirolimus and tacrolimus by ~2-fold, cyclosporine by ~1.25-fold, and mycophenolate mofetil by ~1.5-fold with concomitant administration • Use with caution, TDM of sirolimus, tacrolimus, and cyclosporine is recommended • 50% dose reduction of tacrolimus has been recommended
Atorvastatin, and digoxin	• Isavuconazole increases the AUC of these agents by ~1.25-fold with concomitant administration • Use with caution, TDM should be performed with digoxin
Midazolam	• Isavuconazole increases the AUC of midazolam by ~2-fold with concomitant administration • Use with caution

Note: Data from references.[12,44]
Abbreviations: AUC, area under the time-concentration curve; TDM, therapeutic drug monitoring.

Serum concentration monitoring

Due to significant inter-patient and intra-patient variability in serum concentrations, serum concentration monitoring is often utilized for most triazoles (itraconazole, voriconazole, and posaconazole) for select indications.[9,34,45] Similar to fluconazole, routine serum concentration monitoring is not currently required with isavuconazole. However, pharmacokinetic studies have shown that Chinese patients have a 40% lower clearance of isavuconazole compared to Western patients suggesting that CYP polymorphisms may play an important role in the metabolism of the drug.[12] In addition, isavuconazole is a substrate of CYP3A4, thus inhibitors and inducers of this isoenzyme can affect the serum concentrations of isavuconazole. Considering the possibility of inter- and intra-patient variability with isavuconazole, case reports and clinical trials have reported TDM with isavuconazole.[32,35,44,46,47] However, correlation between serum concentrations and adverse effects and efficacy have not been fully assessed at this time.[40] Since the need for isavuconazole TDM remains unclear, further investigation is warranted.

Potential place in therapy for IFIs

Features of isavuconazole include a broad spectrum of antifungal activity, availability of both oral and IV formulations, favorable safety profile (notably the absence of QTc prolongation), reduced drug–drug interactions (relative to voriconazole), and favorable pharmacokinetic profile. To date, isavuconazole has been evaluated for treatment of IA, mucormycosis, and candidiasis.

Isavuconazole has been shown to be non-inferior to voriconazole in patients with IA.[32] In addition, isavuconazole was associated with fewer adverse events and drug discontinuations. Therefore, isavuconazole can be used as alternative therapy in patients with IA who cannot tolerate voriconazole therapy due to severe adverse effects (hepatotoxicity, skin reactions, and visual disturbances) or have prolonged QTc prior to therapy or while on voriconazole therapy. Isavuconazole may also be utilized in those patients with IA who have CrCl <50 mL/min and require IV therapy since its formulation does not contain cyclodextrin.

Currently, the mainstays of therapies for mucormycosis are amphotericin B formulations and posaconazole. Amphotericin B is often utilized as primary therapy for mucormycosis, while posaconazole is often used in sequence after amphotericin B therapy or as primary therapy in those patients unable to tolerate amphotericin B therapy. Isavuconazole is as effective as current primary and salvage therapy for patients with mucormycosis even though the evidence comes from a small number of patients (n=37).[35] Outcomes are similar to those of amphotericin B formulations when used as primary therapy. Considering the significant adverse effects of amphotericin B formulations (most notably nephrotoxicity), the limited evidence to support posaconazole as primary therapy and the inability to use IV posaconazole in patients with reduced renal function, isavuconazole may be an invaluable option for the primary therapy of mucormycosis. In addition, isavuconazole can serve as an alternative to oral formulations of posaconazole for sequence therapy.

Finally, the current evidence of isavuconazole in other IFIs, notably candidiasis, is not as robust as compared to IA and mucormycosis. The ACTIVE study did not show non-inferiority of isavuconazole to caspofungin in patients with candidemia and invasive candidiasis.[30] Based on these data,

it appears that echinocandins will remain as preferred initial therapy for invasive candidiasis. However, isavuconazole may be a reasonable step-down oral option in those patients who cannot receive other azoles due to tolerability or spectrum of activity limitations.

Conclusion

IFIs, notably IA and mucormycosis, are associated with significant morbidity and mortality, especially in immunocompromised patients. Current treatment options for these dreaded infections are plagued with shortcomings. Isavuconazole is a broad-spectrum triazole with a good pharmacokinetic profile and favorable safety and drug–drug interaction profiles. Based on the current data, isavuconazole appears to be a viable alternative treatment option for patients with IA who are intolerant of voriconazole as well as those patients with mucormycosis who are not able to tolerate or fail amphotericin B or posaconazole therapy. Given the lack of "real world" clinical experience with isavuconazole, post-marketing surveillance will be important to understand the true degree of safety of this agent as well as the role of serum concentration monitoring.

Disclosure

The authors report no conflicts of interest relevant to this work.

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