AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

PERSPECTIVE

New Perspectives on Antimicrobial Agents: Isavuconazole

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ABSTRACT Isavuconazole is the newest of the clinically available advanced generation triazole antifungals and is active against a variety of yeasts, molds, and dimorphic fungi. Its current FDA-approved indications include the management of invasive aspergillosis as well as mucormycosis, though the latter indication is supported by limited clinical data. Isavuconazole did not achieve noninferiority to caspofungin for the treatment of invasive candidiasis and therefore lacks an FDA-approved indication for this invasive disease. Significant advantages of isavuconazole, primarily over voriconazole but in some circumstances posaconazole as well, make it an appealing option for the management of complex patients with invasive fungal infections. These potential advantages include lack of QTc interval prolongation, more predictable pharmacokinetics, a less complicated drug interaction profile, and improved tolerability, particularly when compared to voriconazole. This review discusses these topics in addition to addressing the *in vitro* activity of the compound against a variety of fungi and provides insight into other distinguishing factors among isavuconazole, voriconazole, and posaconazole. The review concludes with an opinion section in which the authors provide the reader with a framework for the current role of isavuconazole in the antifungal armamentarium and where further data are required.

KEYWORDS isavuconazole, isavuconazonium sulfate, spectrum, review, clinical data, drug-drug interactions, posaconazole, prophylaxis, treatment, voriconazole

As an agent with both intravenous and oral formulations, predictable pharmacokinetics, and improved tolerability over voriconazole, isavuconazole has been a welcome addition to the antifungal armamentarium. Despite the availability of this compound since its FDA approval in 2015, questions regarding its optimal use remain. In particular, questions surrounding the necessity of antifungal therapeutic drug monitoring, its role in the prevention of invasive fungal infections in highly immunocompromised patients, the clinical impact of its CYP450 interactions compared to voriconazole and posaconazole, and the significance of its QTc interval shortening properties require additional data. This perspective paper reviews currently available evidence surrounding the use of isavuconazole and addresses areas where further data would be helpful in optimizing the use of the compound.

OVERVIEW AND PHARMACOKINETICS

Isavuconazonium sulfate is the prodrug of the azole antifungal isavuconazole (1). Isavuconazonium is available in both oral and intravenous formulations and upon arrival into the systemic circulation is rapidly converted to the active isavuconazole by plasma esterases. The dose of isavuconazonium sulfate is 372 mg (equivalent to 200 mg isavuconazole) administered either intravenously or orally thrice daily for 2 days as loading doses prior to beginning daily therapy with 372 mg. The dose does not need to be

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The authors declare a conflict of interest. J.S.L. - Consultant: Merck, Cidara. N.P.W. - Research Grants: Astellas, bioMerieux, F2G, Maxwell Biosciences, Sfunga. G.R.T. - Received research support and consultant for: Amplyx, Astellas, Cidara, F2G, Mayne, Pfizer.

Published 15 August 2022

adjusted for renal dysfunction or mild to moderate hepatic impairment. Alterations may be required for significant liver impairment. However, clear guidance for patients with severe liver dysfunction is currently lacking. As with all azole antifungals, hepatotoxicity may occur.

The pharmacokinetics of isavuconazole differ markedly from the other advanced generation azoles (voriconazole and posaconazole), with a substantially longer terminal half-life (184 h) allowing for once daily dosing after the initial loading doses (1). The pharmacokinetics of isavuconazole also appear more predictable than those of voriconazole and may be slightly more predictable than the newer delayed-release tablet and intravenous formulations of posaconazole (2, 3). Oral bioavailability is greater than 97%, and the volume of distribution is large (~400 L), suggesting distribution into a variety of sites (1). Although isavuconazole appears to penetrate well into the cerebral spinal fluid (CSF) in animal models, results are limited and mixed in humans. In one case report, central nervous system (CNS) tissue concentrations as high as 1.46 mg/kg were reported in a patient with cerebral aspergillosis following craniectomy (4). However, in a series of three patients with coccidioidal meningitis, isavuconazole CSF concentrations were dependent upon the site of collection, with detectable levels (CSF range 0.45 μg/mL to 1.72 μg/mL; CSF:plasma ratio ~0.23 to 0.38) present when collected by lumbar puncture, but were less than 0.25 μg/mL when collected from an external ventricular drain or Ommaya reservoir (5). Fortunately, responses have been encouraging when isavuconazole has been used clinically for infections in the central nervous system (6).

In marked contrast to voriconazole, therapeutic drug monitoring (TDM) of isavuconazole is rarely recommended and has not been associated with improvements in clinical outcomes or reduction of toxicity (7), although one study did report more gastrointestinal adverse effects with prolonged administration and higher serum levels (8). It is important to note that information regarding the utility of TDM for isavuconazole in certain populations such as those receiving renal replacement therapy or extracorporeal membrane oxygenation (ECMO) remains limited (9). Further data regarding the utility of TDM are also required for the pediatric population as well as obese patients (10). The intravenous formulation of isavuconazole also lacks the complicating presence of sulfobutyl ether β cyclodextrin (SBECD), which is an issue with both voriconazole and posaconazole intravenous formulations. This is particularly important in patients with impaired renal function where accumulation of the vehicle, but not nephrotoxicity, occurs (11).

Isavuconazole is both a substrate of CYP3A4 and an inhibitor of this enzymatic pathway. This pathway is commonly involved in the metabolism of multiple agents leading to the lengthy list of drug-drug interactions associated with this as well as other members of the azole antifungal family (12). The pharmacokinetic/pharmacodynamic (PK/PD) parameter of isavuconazole most closely associated with efficacy against invasive infections caused by *Candida* and *Aspergillus* is the ratio of the area under the plasma concentration curve (AUC) to MIC of the organism being treated (13–15). However, different animal models have yielded markedly different PK/PD targets for *Aspergillus*. Interestingly, a rabbit model following galactomannan responses, rather than traditional PK/PD endpoints, appeared to best align with available clinical data (14, 15). The AUC/MIC target determined utilizing a neutropenic mouse model of disseminated candidiasis was 33.3 for 4 tested *C. albicans* strains but was markedly lower for the 2 non-*albicans* isolates evaluated (13).

IN VITRO ACTIVITY

Isavuconazole is a broad-spectrum antifungal with an *in vitro* activity profile similar to that of voriconazole against yeasts, dimorphic fungi, and molds (Table 1), but with the advantage of having activity against the members of the order Mucorales, the causative agents of mucormycosis (16).

***Candida* and other yeasts.** Against several different yeasts, including most *Candida* species, members of the *Cryptococcus neoformans/gattii* species complex, and *Trichosporon* species, isavuconazole MIC values indeed are similar to those observed with voriconazole (17–19). This also includes activity against *C. krusei*, which is intrinsically resistant to

TABLE 1 *In vitro* activity of isavuconazole and other azoles against yeasts, hyaline molds, members of the order Mucorales, and endemic and dimorphic fungi[a]

Species	MIC parameter	MIC range	MIC_{50} range	MIC_{90} range
Yeasts				
Candida albicans (16, 27)	Isavuconazole	≤0.03–>16	≤0.03	≤0.03
	Voriconazole	≤0.03–>16	≤0.03	≤0.03–0.06
	Posaconazole	≤0.03–0.5	≤0.03	≤0.03–0.25
Candida auris (22–24)	Isavuconazole	≤0.03–4	0.5–1	1
	Voriconazole	≤0.03–>16	1–2	2
	Posaconazole	0.03–1	0.25	0.5
Candida glabrata (16, 27)	Isavuconazole	≤0.03–16	0.06–2	0.5–8
	Voriconazole	≤0.03–8	0.06– 1	0.5–4
	Posaconazole	≤0.03–>16	0.525– 1	2–4
Candida krusei (16, 27)	Isavuconazole	≤0.03–2	0.125–0.5	0.25–1
	Voriconazole	0.06–16	0.25–0.5	0.5–4
	Posaconazole	≤0.03–2	0.25–0.5	0.5–1
Candida parapsilosis (16, 27)	Isavuconazole	≤0.03–0.25	≤0.03	≤0.03–0.125
	Voriconazole	≤0.03–0.5	≤0.03–0.06	0.06–0.125
	Posaconazole	≤0.03–0.25	≤0.03–0.06	0.125
Candida tropicalis (16, 27)	Isavuconazole	≤0.03–>16	≤0.03	≤0.03–0.125
	Voriconazole	≤0.03–>16	≤0.03–0.125	0.06–2
	Posaconazole	≤0.03–>16	≤0.03–0.06	0.06–1
Cryptococcus gattii (16–18, 100)	Isavuconazole	≤0.03–0.25	≤0.03–0.125	0.06–0.125
	Voriconazole	≤0.03–0.5	0.125	0.25
	Posaconazole	≤0.03–0.5	≤0.03	0.125
Cryptococcus neoformans (16–18, 100)	Isavuconazole	≤0.03–0.5	≤0.03	≤0.03–0.125
	Voriconazole	≤0.03–0.5	≤0.03–0.06	0.06–0.125
	Posaconazole	≤0.03–0.25	≤0.03–0.06	≤0.03–0.125
Rhodotorula spp. (19, 21, 25, 26)	Isavuconazole	0.125–2	0.5–4	0.125–4
	Voriconazole	0.125–>16	0.5–4	2–>16
	Posaconazole	0.25–>16	1–8	4–>16
Trichosporon spp. (16, 19)	Isavuconazole	≤0.03–0.5	0.06–0.125	0.125–0.5
	Voriconazole	0.06–2	0.06–0.125	0.06–0.25
	Posaconazole	≤0.03–0.5	≤0.03–0.25	0.25
Hyaline molds				
Aspergillus fumigatus (16, 27, 28)	Isavuconazole	≤0.03–>16	0.5	1
	Voriconazole	0.125–>16	0.5	0.5
	Posaconazole	≤0.03–>16	0.125–0.25	0.25–0.5
Aspergillus flavus (16, 27)	Isavuconazole	0.25–16	0.5–2	1–16
	Voriconazole	0.125– 4	0.5–1	0.5–2
	Posaconazole	0.125–2	0.125–0.25	0.5
Aspergillus niger (16, 27)	Isavuconazole	0.25–>16	0.5–2	2–4
	Voriconazole	0.125–4	0.25–2	1–2
	Posaconazole	0.125–2	0.25–0.5	0.5–1
Aspergillus terreus (16, 27)	Isavuconazole	0.125–>16	0.5–1	0.5–4
	Voriconazole	0.125–4	0.25–1	0.5–2
	Posaconazole	0.06–1	0.125–0.25	0.5
Aspergillus lentulus (28, 37, 38)	Isavuconazole	0.25–8	2	4
	Voriconazole	0.25–>16	2	4
	Posaconazole	0.06–1	0.125	1
Aspergillus udagawae (28, 37, 38)	Isavuconazole	1–8		
	Voriconazole	2–>16		
	Posaconazole	0.125–>16		
Aspergillus calidoustus (39)	Isavuconazole	0.5–>16	2	4
	Voriconazole	2–16	4	8
	Posaconazole	4–>16	≥16	≥16
Fusarium oxysporum (27, 41, 101)	Isavuconazole	0.5–>16	>16	>16
	Voriconazole	4–16	8	16
	Posaconazole	1–>16	4	>16
Fusarium solani (27, 41, 101)	Isavuconazole	≥16	>16	>16
	Voriconazole	2–>16	>16	>16
	Posaconazole	4–>16	>16	>16

(Continued on next page)

TABLE 1 (Continued)

Species	MIC parameter	MIC range	MIC_{50} range	MIC_{90} range
Scedosporium spp. (excluding *L. prolificans*) (27, 32, 41, 42)	Isavuconazole	0.5–>16	8–>16	≥16
	Voriconazole	0.25–>16	0.5–1	1–8
	Posaconazole	0.125–>16	1	4–>16
Mucorales				
Rhizopus spp. (45, 47, 49)	Isavuconazole	0.125–>16	1–2	8–>16
	Posaconazole	≤0.03–>16	0.06–0.5	1–8
Rhizopus arrhizus (45, 47, 49)	Isavuconazole	0.125–>16	1–4	2–>16
	Posaconazole	≤0.03–>16	0.25–1	0.5–>16
Mucor spp. (45, 47, 49)	Isavuconazole	1–>16	8–>16	≥16
	Posaconazole	≤0.03–>16	0.5–2	2–>16
Mucor circinelloides (45, 47)	Isavuconazole	1–>16	8	>16
	Posaconazole	0.125–>16	1	2
Endemic and dimorphic fungi				
Blastomyces dermatitidis (16, 51, 52)	Isavuconazole	0.125–4		
	Voriconazole	≤0.03–2		
	Posaconazole	≤0.03–1		
	Itraconazole	≤0.03–4		
Coccidioides spp. (16, 51)	Isavuconazole	0.125–1	0.25	0.5
	Voriconazole	0.06–1	0.125	0.5
	Posaconazole	0.06–1	0.125	0.5
	Itraconazole	≤0.03–0.5	0.125	0.5
Histoplasma capsulatum (16, 51)	Isavuconazole	0.125–2	0.5	2
	Voriconazole	0.06–2	0.25	1
	Posaconazole	0.03–2	0.25	2
	Itraconazole	0.25–2	0.5	1

[a]All values reported as mg/mL.

fluconazole (16, 20, 21). However, against the emerging pathogen *C. auris*, the MICs of isavuconazole have been reported to be somewhat higher than those observed against other *Candida* species. These values are similar to those reported for voriconazole (22–24), which highlights the reduced susceptibility of this species to these triazoles. Similarly, and in agreement with what has been observed for both voriconazole and posaconazole, the *in vitro* potency of isavuconazole against *Rhodotorula* species is reduced (19, 21, 25, 26).

***Aspergillus*.** Isavuconazole also has excellent *in vitro* activity against most *Aspergillus* species, including those that are common causes of infections in humans (i.e., *A. fumigatus*, *A. flavus*, *A. niger*, and *A. terreus*) (16, 27, 28). Several studies have noted the *in vitro* potency of isavuconazole appears to closely parallel that of voriconazole against *Aspergillus*, against both wild-type isolates and those that have reduced susceptibility or are resistant to voriconazole (27–32). Nearly parallel MIC values are also observed between isavuconazole and voriconazole against voriconazole-resistant *A. fumigatus* isolates, which the Clinical and Laboratory Standards Institute CLSI and European Committee on Antimicro-bial Susceptibility Testing (EUCAST) have defined as resistant when the MIC values are 2 μg/mL or higher (28, 33, 34). It is now known that specific mutations with the *CYP51A* gene, which encodes the lanosterol 14α-demethylase enzyme in *Aspergillus*, can lead to voriconazole and isavuconazole resistance, but affect posaconazole to a lesser degree. These include mutations that result in a G448 codon change, which has been reported to occur with prolonged clinical exposure to these antifungals, and the TR_{46}/Y121F/T289A mutation that has been associated with environmental exposure to azoles and azole-like compounds. Both mutations often lead to high-level isavuconazole and voriconazole resistance (i.e., MIC ≥8 μg/mL) (35, 36). In contrast, other codon changes, such as G138, M220, and TR34/L98H, can lead to reduced susceptibility/pan-azole resistance in *A. fumigatus*, while others will primarily affect posaconazole (e.g., G54). The *in vitro* activity of isavuconazole and other extended spectrum triazoles also appears to be species specific, as certain species, including cryptic species such as *A. lentulus*, *A. udagawae* (both members of section *Fumigati*), and *A. calidoustus* (member of section *Usti*), among others, have reduced susceptibility to isavuconazole,

posaconazole, and voriconazole (37–39). Although clinical data linking *in vitro* susceptibility with clinical outcomes are scarce, one pooled analysis of clinical responses in relation to isavuconazole MIC values against *Aspergillus* spp. from the SECURE and VITAL clinical trials reported a lack of correlation between patient outcomes and MICs when values were <16 μg/mL (40). Overall, successful outcomes were observed in ~45% when the isavuconazole MICs were ≤ 1 μg/mL and ~44% when the values were >1 μg/mL. However, two patients for which the isavuconazole MICs were ≥ 16 μg/mL against the cultured *Aspergilllus* spp. died by the day-42 time point. For voriconazole, the overall clinical success was markedly reduced against infections caused by isolates with MIC values >1 μg/mL (20% to 25%) compared to when the MIC values were ≤ 1 μg/mL (44.4% to 47.1%).

***Scedosporium* and *Fusarium*.** Interestingly, despite similar *in vitro* activity between isavuconazole and voriconazole against *Aspergillus* spp., isavuconazole appears to show little to no *in vitro* activity against *Scedosporium* species. (27, 32, 41, 42) Some studies reported values of ≥ 16 μg/mL against *Scedosporium* isolates in general (27, 41). In contrast, the MICs of voriconazole are generally lower, but can be variable, with higher values reported against certain species (e.g., *S. aurantiacum*) (42, 43). This difference may be relevant as scedosporiosis may be difficult to differentiate from aspergillosis clinically. However, neither isavuconazole nor any other of the clinically available antifungals demonstrates *in vitro* activity against *Lomentospora* (formerly *Scedosporium*) *prolificans* (42). Similarly, isavuconazole lacks *in vitro* activity against most *Fusarium* isolates (27, 41).

Mucorales. Isavuconazole demonstrates good *in vitro* activity against certain members of the order Mucorales, which are responsible for mucormycosis. Specifically, several studies have reported that isavuconazole demonstrates favorable *in vitro* activity against *Lichtheimia*, *Rhizopus*, and *Rhizomucor* spp. The activity against *Rhizopus arrhizus* (*oryzae*) is especially important given that this species has been reported in several studies to be the most commonly cultured member of the Mucorales in patients with mucormycosis (44–46). However, the *in vitro* activity of isavuconazole against the Mucorales, as well as posaconazole and itraconazole, appears to be species-specific. Of note, reduced *in vitro* activity against *Mucor* species for isavuconazole has been reported in several studies (45, 47–49). This may be of clinical relevance as *Mucor* spp. are often the second most commonly cultured Mucorales in patients with mucormycosis (44–46). This reduced *in vitro* potency is especially evident against *Mucor circinelloides* (45, 47, 49). Recently, the reduced susceptibility of *M. circinelloides* to posaconazole and isavuconazole has been attributed to the presence of pleiotropic drug resistance (PDR) transporters, *PDR1* and *PDR2* (50), which are members of the ATP binding cassette transporter superfamily that are known to cause resistance to azole in other fungal species.

Endemic and dimorphic fungi. Good *in vitro* activity has also been observed against endemic and dimorphic fungi. *In vitro* susceptibility testing against *Blastomyces* has shown low MICs for isavuconazole with MIC_{90} values similar to those of itraconazole, posaconazole, and voriconazole (16, 51, 52). Testing of *Coccidioides* isolates has similarly shown low isavuconazole MICs (51). These *in vitro* results have translated into *in vivo* efficacy in a murine model of disseminated coccidioidomycosis where improved survival and reduced fungal burden were observed with isavuconazole treatment (53). Numerous *Emergomyces* spp. have been recently identified, with susceptibility results showing comparatively higher isavuconazole MICs than those observed for itraconazole, voriconazole, or posaconazole; however, few isolates have been tested to date (52, 54). Against *Histoplasma*, *in vitro* testing has shown low MICs for most mold-active triazoles, including isavuconazole (51). Interestingly, *Histoplasma* isolates from patients who failed fluconazole therapy demonstrated reduced susceptibility to both fluconazole and voriconazole, but no reduction in isavuconazole activity was observed (55). Data from *in vitro* testing of isavuconazole against *Paracoccidioides* are limited, with only a single isolate reported (MIC of 0.001 μg/mL) (56). *In vitro* testing against *Sporothrix* spp. has revealed reduced activity for isavuconazole, similar to that observed with voriconazole (16, 57). Isavuconazole also has low MICs against *Talaromyces marneffei*, the agent of talaromycosis endemic to Southeastern Asia, although few isolates have been tested (58).

CLINICAL USE: TREATMENT

Invasive *Candida* infections. Isavuconazole failed to demonstrate noninferiority in a randomized double blinded head-to-head comparison with caspofungin in 450 patients (ACTIVE clinical trial), and therefore lacks an FDA indication for invasive candidiasis (candidemia-only form of the disease in >80% of patients) (59). Analysis of the primary endpoint of successful outcome at the end of intravenous therapy revealed a 10.8% difference in favor of caspofungin (95% CI −19.9 to −1.8), which exceeded the allowable bound for meeting the noninferiority criteria. Of note, this is the second time that an azole has failed to achieve noninferiority in a randomized blinded registration trial when compared directly to an echinocandin, the first being a trial comparing fluconazole and anidulafungin over a decade ago (60). It was thought that perhaps the improved *in vitro* activity of isavuconazole might yield different results from fluconazole, yet once again the echinocandin appeared superior. Secondary endpoints such as overall response at 2 weeks after the end of therapy and survival at days 14 and 56 were similar between treatment arms. This negative finding has relegated the use of this compound for *Candida* spp. to situations where mold activity is required in conjunction with activity against *Candida* spp. Such settings include prophylaxis for high-risk patients with hematological malignancies or for use as step-down therapy for infections due to *Candida* spp. from an echinocandin when limitations of other azoles, such as QTc interval prolongation, prevent their use.

Invasive aspergillosis. Isavuconazole is currently FDA approved for the treatment of invasive aspergillosis based on a global, multicenter, randomized double-blind trial that directly compared isavuconazole to voriconazole for the treatment of 527 adult patients with suspected invasive mold infections due to *Aspergillus* or other filamentous fungi (SECURE clinical trial) (61). In excess of 80% of patients in both arms had an underlying hematological malignancy. No significant differences existed between the two agents in any of the microbiologic endpoints or in overall survival. Isavuconazole was better tolerated that voriconazole, specifically with regard to adverse events related to the hepatobiliary system, eye, or skin or subcutaneous tissues. The overall difference in drug-related adverse events was 18% in favor of isavuconazole ($P < 0.001$). Subsequent to the publication of these data, isavuconazole was placed on level footing with voriconazole for the management of invasive aspergillosis in the European guidelines for the management of invasive aspergillosis (62). The Infectious Diseases Society of America (IDSA) aspergillosis guidelines, last updated in 2016, include mention of isavuconazole as an alternative to voriconazole but retain voriconazole as the preferred agent. This was due to the fact that publication of the aforementioned randomized trial had not occurred prior to the deadline for data collection during the synthesis of the guideline recommendations. We expect that isavuconazole will be placed on the same tier as voriconazole for the management of invasive aspergillosis in the next iteration of the IDSA guidance (63). This is also in line with the MSGERG COVID-19 associated pulmonary aspergillosis care step pathway, which includes isavuconazole, voriconazole, and posaconazole all as first-line agents (https://covidandfungus.org/care-step-pathways/).

Mucormycosis. The second of the current FDA-approved indications for isavuconazole is the treatment of invasive mucormycosis in adults (64). This indication is supported by considerably less clinical data than the *Aspergillus* indication due to the infrequency of these infections and the difficulties of enrolling these patients into clinical trials. The VITAL study was of a single arm design from 34 international sites that enrolled 37 patients with mucormycosis between the years of 2008 and 2013 (of note, only 21 of these patients received isavuconazole as primary therapy, with the remainder being converted to isavuconazole from other therapies). The 21 patients receiving isavuconazole as primary therapy were matched to 33 historical controls who received treatment, with standard of care amphotericin B based therapies. Of note, 12 of the historical controls were converted to posaconazole therapy during treatment. Patients received isavuconazole for a median of 84 days (IQR 19–179, range 2–882), and at day 42, four patients (11%) had a partial response, 16 (43%) had stable invasive disease, and 13 (35%) had died. As would be expected in a study of this disease state, 95% of patients had at least one adverse event and three quarters of these were considered serious. Death due to all causes occurred in 7/21 (33%) of isavuconazole-treated patients at 6 weeks compared to 13/33 (39%) in the standard of care matched controls.

Weighted all-cause mortality was 33% versus 41%; $P = 0.595$. No correlation between isavuconazole serum concentrations and clinical outcomes was observed. The 2019 European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium guidelines for the management of mucormycosis recommend isavuconazole and posaconazole as primary therapy for mucormycosis only in situations of pre-existing renal compromise and continue to give preference to liposomal amphotericin B at a dose of 5–10 mg/kg/d as initial therapy (65).

Endemic and dimorphic mycoses. Agents of blastomycosis, coccidioidomycosis, emergomycosis, histoplasmosis, paracoccidioidomycosis, sporotrichosis, and talaromycosis represent a diverse group of fungal pathogens, and many reside within a specific environmental location/niche allowing for exposure and development of disease (66). Against blastomycosis, clinical reports have demonstrated favorable efficacy, although experience is limited (56). In the VITAL study, three patients with blastomycosis received treatment with isavuconazole, with a complete clinical and radiographic response observed in one patient with disseminated infection, while the other two patients received short courses of therapy, which limited efficacy assessments (56).

Isavuconazole was also evaluated for the treatment of primary pulmonary coccidioidomycosis in 9 patients in that study. All nine patients exhibited a response to treatment at the end of treatment as assessed by the data review committee (56). A retrospective review identified nine patients with coccidioidal meningitis treated with isavuconazole, with successful therapy seen in three patients and stable disease observed in the other six patients (67). Successful salvage therapy with isavuconazole in a pediatric case of refractory coccidioidal meningitis has also been reported (68).

Isavuconazole has also demonstrated efficacy against histoplasmosis. Seven patients in the VITAL study were treated for histoplasmosis with isavuconazole as primary therapy (56). One patient with CNS histoplasmosis exhibited a complete clinical and radiographic success. Partial success was seen in three patients, while stable disease was reported in a heart transplant recipient, and treatment failure occurred in two patients with disseminated infection. All patients were alive at the end of study therapy (6, 56). Isavuconazole was also efficacious in a case of endocarditis following valve replacement and amphotericin B therapy (69).

Ten patients with paracoccidioidomycosis were also evaluated in the VITAL study, with all receiving isavuconazole as primary therapy. Complete response occurred in one patient with disseminated infection, while partial responses were seen in seven and progressive infection occurred in two patients, both of whom died (56). Case reports have demonstrated the efficacy of isavuconazole in disseminated *Talaromyces* infections following improvement in amphotericin B formulations (70, 71). No reports of clinical efficacy against sporotrichosis exist, to our knowledge, and other agents are preferred based on results of *in vitro* susceptibility testing. Similarly, other agents are preferred for the treatment of emergomycosis.

CLINICAL USE: PROPHYLAXIS

The use of mold-active prophylaxis, specifically posaconazole, is recommended in patients at high risk for invasive fungal infections (IFIs). Patients for whom this is recommended include those with prolonged neutropenia due to chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), and hematopoietic cell transplant (HCT) recipients requiring augmented immunosuppression for graft-versus-host disease (GVHD). This recommendation is based on studies demonstrating reduced IFIs, mostly invasive aspergillosis, and improved all-cause mortality with posaconazole compared to previous standard of care prophylactic agents fluconazole and itraconazole (72–75).

Isavuconazole represents an attractive alternative to posaconazole for primary prophylaxis due to its similar spectrum of anti-fungal activity and proven efficacy in treating invasive aspergillosis and mucormycosis in similar patient populations. In addition, the tolerability, reliability of absorption with oral administration, favorable drug–drug

interaction profile, and lack of QTc interval prolongation make the compound appealing in this setting (61, 64).

Though not FDA approved for prophylaxis, clinical data have begun to emerge. In a phase 2 study of isavuconazole primary prophylaxis in 20 patients with AML receiving chemotherapy, no proven or probable breakthrough IFIs (bIFIs) were reported (2). A retrospective report published soon after the release of isavuconazole described 5 bIFIs among 27 patients with leukemia and prolonged neutropenia receiving isavuconazole as primary prophylaxis. These bIFIs included 2 cases of *Candida glabrata* fungemia, 1 pulmonary mucormycosis, 1 disseminated *Rhizopus* sp. infection, and 1 *Trichosporon asahii* fungemia (76). A subsequent single-center retrospective study documented proven or probable IFIs in 8.3% (12 out of 145) of patients who received isavuconazole primary prophylaxis. All breakthrough IFIs occurred during periods of prolonged neutropenia (77). Invasive pulmonary aspergillosis (IPA) accounted for 58.3% of IFIs. Disturbingly, breakthrough IPA in patients receiving isavuconazole was significantly higher compared to voriconazole prophylaxis during induction chemotherapy for *de novo* AML.

Several prospective studies followed, aimed at further defining the efficacy and safety of isavuconazole as primary prophylaxis. Bose et al. reported the results of a single-center, open-label prospective, phase 2 study using isavuconazole primary prophylaxis in treatment-naive adult patients with AML or MDS, many of whom received venetoclax and FMS-like tyrosine kinase (FLT) 3 inhibitors (78). Sixty-five patients, 95% of whom had AML, received isavuconazole prophylaxis. The incidence of possible and probable IFI during receipt of isavuconazole prophylaxis was 15% ($n = 10$), with 2 cases of probable IPA and 8 cases of possible IFI. All IFIs occurred during periods of severe neutropenia. Isavuconazole was well tolerated, and, importantly, no QTc interval prolongation was observed.

Another single-center, open-label, prospective study assessed the safety and efficacy of isavuconazole primary prophylaxis through maximum day +98 after allogeneic HCT (79). Among 95 patients who received isavuconazole, there were only 3 IFIs (3.1%), all candidemia, and no invasive mold infections. Notably, 33% underwent T-cell depleted HCT, and 57% patients developed acute GVHD, the majority being grade 2. Consistent with other studies, isavuconazole was very well tolerated. Thus, isavuconazole appears to be a safe and efficacious alternate to other azoles for primary prophylaxis after HCT. Whether isavuconazole compares favorably to posaconazole for the specific high-risk subgroup of HCT recipients with acute GVHD is unknown.

The most recent European Conference on Infections in Leukemia (ECIL) prevention guidelines, published prior to many of the studies cited above, acknowledge the appeal of isavuconazole in terms of toxicities and drug–drug interactions but make no recommendation as to the role of isavuconazole in primary prophylaxis (73). More recently, the American Society for Transplantation and Cellular Therapy (ASTCT) guidelines for the prevention and treatment of aspergillosis in HCT recipients highlighted the fact that isavuconazole is approved only for treatment, not prophylaxis, of this mycosis. The authors also state that while prophylaxis data are limited, it may be a reasonable alternative for patients with prolonged QTc interval or receiving QTc interval-prolonging medications, or to minimize drug–drug interactions or toxicity (level of evidence CIII, "optional," evidence from opinions of respected authorities based on clinical experience) (80).

Experience with isavuconazole prophylaxis in solid organ transplant is more limited. A recent single-center study retrospectively compared 156 lung transplant patients who received voriconazole prophylaxis to 144 similar patients who received isavuconazole (81). The incidence of bIFIs was similar between both groups, occurring in 5 (3.5%) patients who received isavuconazole and 5 (1.9%) who received voriconazole. Again, isavuconazole was found to be better tolerated, with discontinuation of prophylaxis due to adverse events significantly less likely in the isavuconazole arm (11% versus 36%, $P = 0.0001$).

EXPERT OPINION

The clinical appeal of isavuconazole is based around several findings from the early development phase of the compound as well as clinical trials and extensive clinical

use: first, the lack of QTc interval prolongation associated with this compound; second, the improved tolerability of isavuconazole compared to voriconazole and in some instances posaconazole; and finally, the predictable pharmacokinetics.

The lack of QTc interval prolongation associated with the use of isavuconazole marks an improvement in the safety profile of mold-active azoles. This is particularly true when comparing isavuconazole to voriconazole. Early studies evaluating the QTc interval impact of isavuconazole found that it resulted in no increase in the QTc interval of study patients and was associated with a shortening of the QTc interval by 5 msec (1, 82, 83). This shortening of the QTc interval has resulted in considerable interest among clinicians managing invasive fungal infections requiring mold-active therapy, as patients at highest risk for invasive mold infections are frequently receiving numerous QTc interval-prolonging agents or have other comorbidities that may prolong the QTc interval. In particular, this QTc interval shortening, combined with a lack of data surrounding the combination of isavuconazole and amiodarone, has led many clinicians to conclude that the combination of these two agents is safe. This is appealing because it enables the use of the preferred therapy of an anti-*Aspergillus* azole in several clinically important scenarios and avoids the use of lipid formulations of amphotericin B. However, it is important to reiterate that, to the best of our knowledge, it is unknown if this drug combination is safe, as data demonstrating safety are lacking.

Second, the improved tolerability of isavuconazole compared to voriconazole has been a finding in multiple clinical trials, starting with the initial phase 3 aspergillosis trial and continuing into the recent publication of a study examining isavuconazole versus voriconazole for prophylaxis in lung transplant patients (61, 81). Many patients receiving mold-active triazoles for prophylaxis or treatment require long durations of therapy, and thus cumulative drug toxicity is of significant concern. The photosensitizing effects of voriconazole may be particularly troublesome for patients residing at certain latitudes, and fluorosis is also observed in some patients during prolonged therapy (84, 85). Isavuconazole uncommonly causes phototoxicity, and as a difluorinated triazole has not been associated with fluorosis. Furthermore, the increasing reports and recognition of posaconazole-induced hypertension and pseudohyperaldosteronism make isavuconazole increasingly appealing from a tolerability perspective when compared to posaconazole (86–89).

Finally, the predictability of the pharmacokinetics of isavuconazole is a welcome departure from the complicated nonlinear pharmacokinetics and multiple P450 isoenzyme involvement that make therapeutic drug monitoring a requirement with voriconazole (90). While posaconazole, particularly in its current tablet and intravenous formulations, provides a marked improvement in the predictability of posaconazole pharmacokinetics, multiple studies continue to show that approximately 10% of patients receiving posaconazole tablets may not achieve desired serum levels (91–94). This ongoing concern with newer posaconazole formulations, while certainly much less than seen with voriconazole, makes the predictable pharmacokinetics of isavuconazole appealing. These pharmacokinetic properties often lead to isavuconazole being preferred when all three agents are available; however, insurance coverage or patient cash pay price often ultimately decide which therapy is utilized.

The lack of an oral liquid formulation, as well as a warning in the United States prescribing information against opening, dissolving, or crushing the isavuconazonium sulfate capsules, has represented a challenge in the clinical use of isavuconazole since its arrival on the market. Recently, publications have demonstrated that administration of opened isavuconazonium sulfate capsules via enteral feeding tubes yielded therapeutic serum levels (95). In addition, a recent update of the FDA prescribing information allows for utilization of the intravenous formulation through enteral routes, minimizing these clinical difficulties (1). Compared to voriconazole and posaconazole, isavuconazole is associated with fewer drug interactions, and the interactions listed in the

prescribing information and literature appear less clinically challenging and requiring less modification of either isavuconazole or the interacting agent (12, 96–99).

The lack of *Scedosporium* activity is surprising given the activity of voriconazole and posaconazole against these organisms. This is a blind spot for many clinicians and is problematic given the similar spectrum of disease caused by this pathogen and *Aspergillus* spp. and the belief among many clinicians that the newer generation broad spectrum azoles are largely interchangeable (32, 42, 43). Furthermore, the species-specific activity within the Mucorales group of not only isavuconazole but also posaconazole is important for clinicians to recognize. These differences have the potential to create clinical challenges when a microbiological diagnosis has not been confirmed.

There is a clear need for direct, head-to-head comparisons of isavuconazole with posaconazole and/or voriconazole in order to conclusively determine the relative efficacy and safety of isavuconazole as a primary prophylactic agent, particularly in patients with prolonged neutropenia. Until those studies are performed, it appears that isavuconazole is an acceptable substitute for existing extended-spectrum azoles in selected at-risk patients when drug–drug interactions or QTc interval prolongation are barriers to their use.

At this point, isavuconazole appears to be the best tolerated of the 3 currently available newer generation mold active azoles. Admittedly, there is considerably less clinical experience with it than either voriconazole or posaconazole, and it has taken years of accumulated clinical experience for several important toxicities of voriconazole and posaconazole to make themselves apparent. It is clear, however, that isavuconazole possesses the least complex drug interaction profile of the 3 agents. Shortening of the QTc interval with isavuconazole is a unique characteristic of the compound, but more information regarding its clinical significance is clearly needed. The failure of isavuconazole to achieve noninferiority against caspofungin for the management of invasive candidiasis likely represents the superiority of the echinocandins over the azole class for this disease state and is not reflective of a unique problem with isavuconazole. Prospective randomized head-to-head data against posaconazole for prophylaxis in high-risk hematologic malignancy patients would be a welcome addition to the literature; however, the majority of the data available at this point suggests that the two agents are likely comparable for this indication. In summary, isavuconazole is an important option in the management of patients with or at high risk for invasive fungal disease, particularly in patients where toxicities, pharmacokinetics, or drug interactions preclude the use of either voriconazole or posaconazole.

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