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REVIEW

Isavuconazole in the treatment of invasive aspergillosis and mucormycosis infections

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Abstract: We have a limited arsenal with which to treat invasive fungal infections caused by *Aspergillus* and Mucorales. The morbidity and mortality for both pathogens remains high. A triazole antifungal, isavuconazole, was recently granted approval by the US Food and Drug Administration and the European Medicines Agency for the treatment of invasive aspergillosis and mucormycosis. A randomized double-blind comparison trial for the treatment of invasive aspergillosis found isavuconazole noninferior to voriconazole. A separate, open-label study evaluating the efficacy of isavuconazole in the treatment of mucormycosis found comparable response rates to amphotericin B and posaconazole treated historical controls. The prodrug isavuconazonium sulfate is commercially available in both an oral and intravenous formulation and is generally well tolerated. Isavuconazole's broad spectrum of activity, limited side effect profile, and favorable pharmacokinetics will likely solidify its place in therapy.

Keywords: isavuconazonium, antifungal, zygomycosis, mucor, mold infection, pharmacokinetics, pharmacodynamics, clinical efficacy, therapy, new agent

Introduction

Invasive fungal infections are responsible for significant morbidity and mortality, particularly in immunocompromised hosts. Although mortality from invasive candidiasis has decreased in recent years, an overall increase in the number of deaths from invasive fungal infections has been noted, largely due to invasive aspergillosis and other molds.[1–4] The number of patients at risk has also increased as a greater number of patients are exposed to immunosuppressive therapy and more intensive chemotherapy regimens.

Currently available antifungal agents are useful for the management of the majority of the mycoses encountered in routine practice, however, significant differences exist between the triazoles in regard to efficacy, pharmacokinetics and pharmacodynamics, drug–drug interactions, the need for therapeutic drug monitoring (TDM), and toxicity.[5] The use of amphotericin B is problematic given the incidence of nephrotoxicity and requirement for intravenous (IV) administration, and flucytosine is not useful as monotherapy for most infections and lacks meaningful activity against a multitude of others (including *Aspergillus* spp. and the Mucorales). The echinocandins are excellent agents in the fight against invasive candidal infections,[6] however, their use in the treatment of aspergillosis is limited to combination or salvage therapy, and they are used solely in combination with polyenes in the treatment of mucormycosis.

The water-soluble prodrug isavuconazonium sulfate was developed specifically to facilitate IV administration without the need for potentially nephrotoxic excipients such

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as β-cyclodextrin, and displays excellent oral bioavailability (~98%).[7] This review will summarize the role of this new triazole in the treatment of *Aspergillus* and Mucorales infections.

In vitro activity and animal models

The triazoles, including isavuconazole, exert their effects within the fungal cell membrane. The inhibition of cytochrome P450 (CYP)-dependent 14-α-demethylase by azoles prevents the conversion of lanosterol to ergosterol. This mechanism results in the accumulation of toxic methyl sterols and resultant inhibition of fungal cell growth and replication. The side arm of the active isavuconazole molecule allows for greater affinity of isavuconazole for the binding pocket in the fungal CYP51 protein increasing the antifungal spectrum and conferring activity against some isolates resistant to other triazoles.[8]

The in vitro activity of isavuconazole has been demonstrated against molds, yeasts, and dimorphic fungi using standardized methodologies as suggested by the Clinical and Laboratory Standards Institute.[9–16] Activity is seen against most *Aspergillus* spp. including *A. fumigatus*, *A. flavus*, *A. terreus*, and *A. niger*[16] with minimum inhibitory concentration to inhibit 50% of the organism growth (MIC_{50}s) of 0.25–1 μg/mL. In recent years, the emergence of azole resistant *Aspergillus* spp. has become a threat to patients with the majority of clinical cases to date reported from western Europe.[17] In these resistant isolates, mutations within the *CYP51A* gene (which encodes the enzyme targeted by azoles) or within the gene promoter, have been identified that reduce drug affinity or increase target quantity conferring azole resistance. *Aspergillus* isolates with elevated minimal inhibitory concentrations (MICs) to posaconazole and voriconazole have been evaluated for isavuconazole susceptibility and cross-resistance between azoles has been found inconsistent.[18,19] For example, *Aspergillus* isolates with the alterations L98, G138, Y431C, or G434C show elevated MICs to all triazoles including isavuconazole, however, the MICs of posaconazole are much lower than those of voriconazole and isavuconazole. In contrast, isolates with the G54 mutation show lower voriconazole and isavuconazole MICs compared to posaconazole, and MICs are variable among azoles in isolates with the M220 alteration.[18] These results suggest a potential role for routine susceptibility testing now that multiple azoles are available for clinical use. Further work will need to be performed to guide the clinician and to ensure these in vitro findings are indicative of in vivo efficacy.

Genera in the family Mucoraceae (order Mucorales) include *Rhizopus*, *Cunninghamella*, *Lictheimia* (formerly *Absidia*), *Mucor*, and *Rhizomucor*. Prior to the availability of isavuconazole, these organisms were resistant to all azoles with the exception of posaconazole.[9] The in vitro activity of isavuconazole against the Mucorales is more variable with MIC_{50} values ranging from 1 to 4 μg/mL depending on the specific species and isolate tested.[20] For example, *Rhizopus* isolates have MIC values to isavuconazole as low as 0.12 μg/mL with others as high as 32 μg/mL; findings suggesting susceptibility testing should be performed on all Mucorales isolates in attempts to maximize pharmacokinetic/pharmacodynamic parameters during treatment.

Isavuconazole has fungistatic activity against yeasts such as *Candida* and *Cryptococcus*; however, appears to be fungicidal against *Aspergillus* spp. The area under the curve to MIC ratio (AUC/MIC) is the primary predictor of drug efficacy in animal models of aspergillosis.[21–23] Animal models have thus far consisted primarily of dose-finding experiments given the differences in metabolism between murine models and humans, and assessments of efficacy using a number of different fungal species and strains. This work has thus far focused on *Candida*, *Cryptococcus*, *Aspergillus*, and the Mucorales, with other invasive molds, yeasts, and endemic mycoses to be examined in the near future.[21,23–29]

Pharmacology

Isavuconazonium is a prodrug of isavuconazole and is a water-soluble molecule consisting of a N-(3-acetoxypropyl)-N-methylamino-carboxymethyl group attached to isavuconazole via an ester moiety (Figure 1).[30] Isavuconazonium sulfate is the commercially available prodrug formulation and is available in both an oral capsule and IV lyophilized powder.[9,31] The IV formulation of isavuconazonium sulfate is 372 mg, which is equivalent to 200 mg of isavuconazole. The oral capsule has 186 mg of isavuconazonium sulfate leading to 100 mg of isavuconazole.[31] Special attention should be paid to initiation of this agent as dosing isavuconazonium sulfate involves a loading dose followed by once daily administration. The loading dose is 372 mg of isavuconazonium sulfate (200 mg of isavuconazole) every 8 hours for 2 days, then 372 mg of isavuconazonium sulfate (200 mg of isavuconazole) once daily. When transitioning from an IV to an oral formulation, a repeat loading dose is not necessary.[32] Dosing in the pediatric population has not been determined (trial is ongoing) and no recommendations can be given for this population.

Isavuconazonium's oral formulation is well absorbed and has excellent bioavailability (98%). In preclinical studies

isavuconazole exhibited linear and dose-proportional pharmacokinetics with low interpatient variability (2.5±1.0 μg/mL).[33] Food has no effect on the pharmacokinetics of isavuconazonium and is not a limitation during its administration.[31] The volume of distribution for isavuconazonium is large at 450 L and the drug half-life is 130 hours. Thus tissue levels persist long after plasma levels are undetectable.[29]

The IV prodrug formulation is water soluble, unlike voriconazole or posaconazole, and does not require cyclodextrin for solubilization. Following IV infusion, the prodrug and inactive cleavage product are undetectable after 30 minutes. With oral administration, the maximum concentration (C_{max}) is reached within 2–3 hours; the prodrug and cleavage products are undetectable with oral administration. Elimination occurs primarily via the fecal route while renal excretion is <1% of the dose administered suggesting little utility in the treatment of fungal urinary tract infections.[32,34]

The metabolism of isavuconazonium is through rapid hydrolyzation, mainly by serum butylcholinesterase, to isavuconazole; CYP3A4, CYP3A5, and uridine diphosphate-glucuronosyl transferase are substrates of isavuconazole.[32] The metabolites do not possess antifungal activity. In those with mild-to-moderate hepatic impairment (Child–Pugh class A or B) dosage adjustment is not needed. No data are available for dosing in those with Child–Pugh class C liver disease.

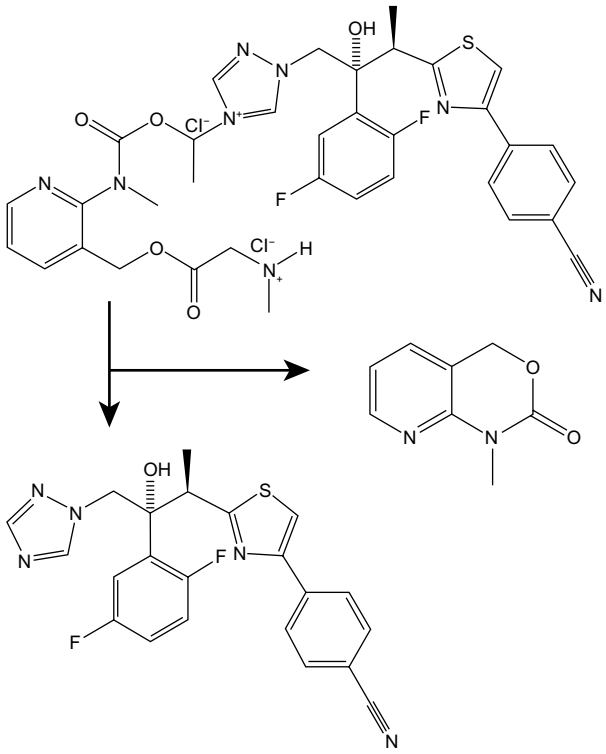

Figure 1 Metabolism of isavuconazonium by plasma esterases into an inactive byproduct and the active antifungal isavuconazole.

Renal impairment does not result in changes in the C_{max} or AUC of isavuconazole and dosage adjustment is not needed in this group either. Pharmacokinetic studies have not been performed in dialysis patients to date, however, it is likely not cleared by hemodialysis or continuous hemofiltration.[8]

Isavuconazole is a pregnancy class C drug and should not be administered to pregnant women. Additionally, it is present in breast milk and should not be given to women who are breastfeeding.

Drug–drug interactions

The triazole antifungal agents demonstrate significant drug–drug interactions that may adversely affect patient outcomes.[35] Each patient's current medications should be reviewed for potentially deleterious drug interactions. As a class, these include altered serum levels of the azoles and of coadministered agents including calcineurin inhibitors and mammalian target of rapamycin inhibitor immunosuppressive agents, psychiatric and neurotropic medications, some benzodiazepines, digoxin, and antiretroviral agents among others.[36–52] All of the azoles have important interactions via the CYP450 enzymes, notably CYP3A4.

Inhibitors of CYP3A4 lead to increased levels of isavuconazole and should be used with caution (Table 1). Inducers of CYP3A4 include rifampin, carbamazepine, barbiturates among others and significantly reduce serum levels of isavuconazole and concurrent administration should be avoided.

Isavuconazole is a moderate inhibitor of CYP3A4 and impairs the metabolism of sirolimus, tacrolimus, and cyclosporine causing higher levels of these immunosuppressive medications and warranting drug monitoring.[53]

TDM is routinely used for voriconazole, and in selected cases is used for fluconazole, itraconazole, and posaconazole.[54]

Table 1 Effect of isavuconazole compared to voriconazole on CYP substrates

CYP	Substrate	Isavuconazole	Voriconazole
3A4	Midazolam	↑2.05-fold	↑10.3-fold
	Sirolimus	↑1.84-fold	↑11.0-fold
1A2	Caffeine	NCS	NCS
2C8	Repaglinide	NCS	NCS
2C9	Warfarin	NCS	↑2-fold (PT)
2C19	Omeprazole	NCS	↑4-fold
2B6	Buproprion	↓42%	↑1.3-fold
2D6	Dextromethorphan	NCS	NCS

Abbreviations: CYP, cytochrome; NCS, not clinically significant; PT, prothrombin time.

No recommendation can be made for or against routine isavuconazole TDM, however, in some clinical cases it is clear TDM will be needed (eg, bidirectional drug–drug interactions, during care of the morbidly obese).

Current treatments for invasive aspergillosis and mucormycosis

Both invasive aspergillosis and mucormycosis are devastating infections and improving patient outcomes requires aggressive screening of at-risk populations to ensure early diagnosis and the rapid initiation of appropriate antifungal therapy. The currently recommended first-line therapy in the treatment of invasive aspergillosis is voriconazole,[55] with amphotericin B formulations and echinocandins reserved for those intolerant or refractory to this agent. The Mucorales are treated by amphotericin B with adjunctive surgical intervention when possible, yet mortality remains between 50% and 100%.[56] Due to the aforementioned problems with currently available antifungal agents, isavuconazole was developed specifically to provide advantages over currently available antifungal compounds and has now been studied in three Phase III trials: 1) the SECURE trial – isavuconazole versus voriconazole for primary treatment of invasive mold disease caused by *Aspergillus* and other filamentous fungi; 2) the VITAL trial – an open label study of isavuconazole in the treatment of patients with aspergillosis and renal impairment or of patients with invasive fungal disease caused by rare molds, yeasts, or dimorphic fungi; and 3) Isavuconazole (BAL8557) in the treatment of candidemia and other invasive *Candida* infections. Together these trials provide important information on the efficacy, safety, and clinical use of isavuconazole.

Clinical efficacy

The SECURE study was a Phase III, double-blind, randomized noninferiority study to compare the efficacy and safety of isavuconazole to voriconazole in the primary treatment of *Aspergillus* spp. or other filamentous fungi.[57] The primary endpoint was all-cause mortality at day 42 in the intention-to-treat (ITT) population. The main secondary endpoint was a composite of clinical, mycological, radiological, and overall response, as assessed by a blinded data-review committee (DRC). Patients randomized to isavuconazole were administered 200 mg IV three times a day for days 1 and 2, followed by either IV or oral 200 mg once daily. Those patients receiving voriconazole were administered 6 mg/kg IV twice daily on day 1, followed by 4 mg/kg IV twice daily on day 2, then either 4 mg/kg IV twice daily or 200 mg oral twice daily from day 3 onwards. Overall 516 adult patients were randomized and treated (258 per group) in the ITT population. The baseline demographics were similar between the two treatment groups, although there were fewer males in the isavuconazole group and more acute myeloid leukemia patients in the voriconazole group. All-cause mortality through day 42 for the ITT population was 18.6% (isavuconazole) and 20.2% (voriconazole; adjusted treatment difference: –1.0%; 95% confidence interval: –7.8%, 5.7%). Overall response rates at end of treatment in the modified ITT population were 35.0% (isavuconazole) and 36.4% (voriconazole). The study concluded that isavuconazole was noninferior to voriconazole for the primary treatment of invasive mold disease and the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have since licensed isavuconazole for the treatment of invasive aspergillosis.

The VITAL study was a Phase III, open-label, noncomparative trial evaluating the efficacy and safety of isavuconazole in patients with invasive aspergillosis with renal impairment or as primary or salvage treatment for mucormycosis.[58] Isavuconazole 200 mg (IV or oral) was given three times daily for six doses, followed by 200 mg/day until invasive fungal disease resolution or ≥180 days. Outcomes included mortality at day 42 and overall response as determined by an independent DRC. Of the 149 patients enrolled, 37 had proven (86%) or probable (14%) invasive mucormycosis by European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria.[59] Mortality at day 42 was 37.8%. A matched case-control cohort of 33 patients treated with amphotericin B from the FungiScope registry was compared with 21 patients who received isavuconazole for the primary treatment of mucormycosis. Mortality rates were not significantly different between cases and controls (33.3% and 41.3%, respectively). A relationship between trough isavuconazole levels, fungal isolate MICs, and key outcomes could not be identified, possibly due to the relatively small number of patients with data available. Clinical responses occurred across the range of isavuconazole MICs and trough levels observed. The FDA has licensed isavuconazole for the treatment of mucormycosis, while the EMA has licensed isavuconazole in those for whom amphotericin B formulations are inappropriate. This difference suggests the continued opinion that amphotericin B formulations are first-line therapy for most cases of mucormycosis.

Safety and tolerability

Isavuconazole has been shown to be fairly well tolerated and safe thus far. In the SECURE study, patients on isavuconazole had significantly fewer study drug-related adverse events (AEs), as compared to voriconazole (42.4%

vs 59.8%; $P<0.001$). AEs frequently associated with voriconazole such as visual disturbances, elevation in hepatic enzymes, and photosensitivity were significantly less common with isavuconazole. A few less frequent side effects noted were hypokalemia, peripheral edema, and infusion-related reactions. Acute respiratory distress, chills, dyspnea, and hypotension were among the infusion-related reactions.

Similar AE results were shown in the VITAL study. In total, 35/37 (95%) patients experienced one or more AEs during treatment, and 28 (76%) patients had serious AEs. The most common AEs were gastrointestinal complaints, such as nausea, vomiting, and diarrhea. Twenty-four patients discontinued isavuconazole treatment in the VITAL study, of which, six of these patients stopped due to AEs (relapse or progression of malignancy, two patients; acute liver injury, two patients; *Escherichia coli* bacteremia, one patient; and nausea, one patient). Overall, the AEs reported in the VITAL trial were similar in distribution to those reported in the SECURE invasive aspergillosis trial. There was no organ-specific pattern of serious AEs, however, as with all other azoles, liver enzymes should be monitored in patients receiving isavuconazole.

Isavuconazole differs uniquely from other triazoles in its class, in that it has dose- and concentration-dependent QTc interval shortening.[7] QTc shortening up to 13 ms with 200 mg once daily dosing and 24.6 ms with 600 mg daily have been shown in healthy volunteers. Inhibition of the L-type calcium channel is the proposed mechanism by which QTc shortening occurs.[31] The clinical significance of this effect is unclear, however, those with familial short-QT syndrome should not receive isavuconazole.

Patient-focused perspectives

There are several advantages of isavuconazole, inherent in its pharmacology, which lend itself well to patient convenience and adherence. Unlike posaconazole and itraconazole, isavuconazole absorption is not affected by food and exhibits excellent oral bioavailability, close to 98%.[7] These aspects lend themselves well for easy IV-to-PO conversion once a patient is clinically stable. Additionally, thus far there has been little interpatient variability suggesting routine TDM may not be necessary, however, further study in this area is needed before any recommendation for or against TDM can be made. The dosing of isavuconazole after the 48-hour loading period is once daily, with two capsules of 186 mg isavuconazonium sulfate taken daily adding in patient convenience and potentially compliance. The IV formulation of isavuconazole does not require solubilization from a cyclodextrin vehicle, which eliminates concerns of nephrotoxicity that have arisen from the solubilizing agent including with IV voriconazole.[60,61]

The reduction in side effects in the isavuconazole treated patients compared to voriconazole treated patients in the SECURE study (difference of 17%) does provide a significant advantage. Side effects of therapy may prolong hospital stays, delay additional chemotherapy while medication changes are made or patient symptoms resolve, and/or lead to patient distress (particularly visual hallucinations). The reduction in these untoward events, while maintaining antifungal efficacy, is a welcome additional to the antifungal armamentarium.

Long-term therapy with voriconazole has been linked with cutaneous malignancy,[62–64] and hyperfluorosis with the development of painful exostoses in patients with impaired renal function.[65,66] The side effects of isavuconazole with long-term use have not been fully evaluated, however, several patients in the VITAL study received prolonged therapy without side effects. Cutaneous malignancy has not been recognized to date, and hyperfluorosis with isavuconazole is unlikely given the differences in chemical structure between voriconazole and isavuconazole and that this phenomenon does not appear to be a class-effect.[67]

Conclusion

Isavuconazole has been recently approved by the FDA and EMA for the treatment of invasive aspergillosis and mucormycosis. This new triazole offers several advantages over existing antifungals including comparable efficacy to currently used agents with fewer side effects, advantageous pharmacokinetic parameters, and excellent bioavailability with oral administration. Future studies examining the role of isavuconazole in prophylaxis against invasive fungal infections, use in combination with other agents, and if TDM is necessary on a routine basis will further refine its role in the fight against these highly morbid and often lethal infections.

Disclosure

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