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Isavuconazole: A New Broad-Spectrum Triazole Antifungal Agent

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Isavuconazole is a new extended-spectrum triazole with activity against yeasts, molds, and dimorphic fungi. It is approved for the treatment of invasive aspergillosis and mucormycosis. Advantages of this triazole include the availability of a water-soluble intravenous formulation, excellent bioavailability of the oral formulation, and predictable pharmacokinetics in adults. A randomized, double-blind comparison clinical trial for treatment of invasive aspergillosis found that the efficacy of isavuconazole was noninferior to that of voriconazole. An open-label trial that studied primary as well as salvage therapy of invasive mucormycosis showed efficacy with isavuconazole that was similar to that reported for amphotericin B and posaconazole. In patients in these studies, as well as in normal volunteers, isavuconazole was well tolerated, appeared to have few serious adverse effects, and had fewer drug–drug interactions than those noted with voriconazole. As clinical experience increases, the role of this new triazole in the treatment of invasive fungal infections will be better defined.

Keywords. isavuconazole; isavuconazonium sulfate; aspergillosis; mucormycosis; triazoles.

Currently available antifungal agents for the treatment of invasive fungal infections in humans include polyenes, azoles, echinocandins, and pyrimidine analogues. All of these drug classes have disadvantages that can limit their use in clinical practice. Major advantages of the second-generation triazoles, posaconazole and voriconazole, include their extended antifungal spectrum and their availability in both oral and intravenous formulations. However, the use of these agents is often limited by their variable bioavailability, severe adverse events, significant drug–drug interactions, and the emergence of resistance. Isavuconazole is a new extended-spectrum triazole with activity against yeasts, molds, and dimorphic fungi. The safety profile of this agent and its excellent pharmacokinetic characteristics make isavuconazole an attractive option for treatment of invasive fungal infections. The aim of this review is to summarize the in vitro activity, pharmacological attributes, and clinical efficacy that led to the recent US Food and Drug Administration (FDA) approval of isavuconazole for the treatment of invasive aspergillosis and mucormycosis.

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IN VITRO ACTIVITY

Mechanism of Action

Similar to other azoles, isavuconazole inhibits cytochrome P450 (CYP)–dependent 14α-lanosterol demethylation, which is essential for fungal cell membrane ergosterol synthesis. This blockade produces methylated sterols in the fungal membrane, altering its function and allowing the accumulation of ergosterol toxic precursors in the cytoplasm, which leads to cell death [1]. The side arm of the active isavuconazole molecule allows greater avidity of isavuconazole for the binding pocket in the fungal CYP51 protein, conferring broader antifungal spectrum even to pathogens resistant to other azoles [1]. In vitro, isavuconazole has broad antifungal activity against yeasts, molds, and dimorphic fungi [2]. The data that follow give a general idea of the activity of isavuconazole with the caveat that to date, no breakpoints have been established.

Yeasts

Isavuconazole appears to be active against all *Candida* species (Table 1). In general, isavuconazole activity against most *Candida* species is comparable to that of voriconazole and posaconazole [2–4]. The minimum inhibitory concentration (MIC) values for 90% (MIC_{90}) of almost 3000 unique *Candida* isolates collected from 2011 and 2012 by the global SENTRY Antimicrobial Surveillance Program were ≤1 μg/mL for all *Candida* species, with the exception of *C. glabrata* [3, 4]. For most *Candida* species, the MIC_{90} values were ≤0.12 μg/mL; the MIC_{90} for *C. krusei* and *C. guilliermondii* was 1 μg/mL, and for *C. glabrata*, 2 μg/mL. Isavuconazole MIC values for those isolates of *C. glabrata* that were resistant to fluconazole and/or voriconazole ranged from 1 μg/mL to ≥8 μg/mL [4]. It appears that for *C. glabrata* especially, isavuconazole is similar to other azoles in regard to the development of resistance.

Isavuconazole shows in vitro activity against *Cryptococcus neoformans* and *Cryptococcus gattii*; most isolates are susceptible to <0.25 μg/mL [5, 7]. Low MIC values against less common yeasts, including *Trichosporon* species, *Geotrichum capitatum*, *Saccharomyces cerevisiae*, *Rhodotorula* species, and *Pichia* species have been reported [3, 6, 8] (Table 1).

Molds

Isavuconazole appears to have potent in vitro activity against the most common *Aspergillus* species, *A. fumigatus* and *A. flavus* [2, 3, 9–12] (Table 2). The MIC_{90} for these *Aspergillus* species was 1 μg/mL. Higher MIC values have been observed with *A. niger* (MIC_{90} 2 μg/mL) [3, 10–12]. In one study, isavuconazole retained activity against preselected *A. fumigatus* isolates that were resistant to other azoles [9], but cross-resistance was shown in another study of azole-resistant isolates [12]. These resistant isolates were shown to have mutations of the *CYP51* gene, leading to azole cross-resistance, an emerging problem mostly in Europe, but also described in India [12, 15, 16].

The spectrum of activity of isavuconazole includes some other hyaline molds, such as *Paecilomyces lilacinus* and *Scedosporium apiospermum*, but the drug has limited in vitro activity against *Fusarium* species [2, 11]. *Scedosporium prolificans* appears to be resistant to isavuconazole, as it is to most antifungal agents [11]. Dematiaceous molds, including *Bioplaris spicifera*, *Alternaria* species, *Curvularia lunata*, and *Exophiala* species, have MICs that vary from 0.25 μg/mL to 16 μg/mL to isavuconazole [13, 17, 18] (Table 3). MIC_{90} values for most pigmented molds range from 1 μg/mL to 4 μg/mL. Additionally, isavuconazole has activity against many dermatophytes [19].

Genera in the family Mucoraceae (order Mucorales) are resistant to most azoles, with the exception of posaconazole. In vitro studies with isavuconazole show that this drug is active against many genera of Mucoraceae [10, 11, 13, 14] (Table 2). However, the MICs vary widely within a given genera. For example, some isolates in the genus *Rhizopus* have MIC

Table 1. In Vitro Susceptibilities of Isavuconazole Against *Candida* Species, *Cryptococcus* Species, and Less Common Yeasts

Organism	No.	MIC_{50}, μg/mL	MIC_{90}, μg/mL	MIC Range, μg/mL	Reference
Candida spp					
C. albicans	1249	0.015	0.03	≤0.008–1	[3, 4]
C. glabrata	557	0.5	2	0.015–8	[3, 4]
C. parapsilosis	498	0.06	0.12	≤0.008–1	[3, 4]
C. tropicalis	252	0.06	0.12	≤0.008–4	[3, 4]
C. krusei	77	0.5	1	0.06–2	[3, 4]
C. lusitaniae	52	0.03	0.06	≤0.008–0.12	[3, 4]
C. dubliniensis	35	0.015	0.03	≤0.008–0.06	[3, 4]
C. kefyr	29	0.015	0.03	≤0.008–0.03	[3, 4]
C. guilliermondii	22	0.5	1	0.12–4	[3, 4]
Cryptococcus spp					
C. neoformans	1308	0.03	0.06	<0.008–0.5	[5]
C. gattii	406	0.03	0.12	<0.008–0.5	[5]
Uncommon yeasts					
Trichosporon asahii	40	0.12	0.12	0.03–0.25	[6]
Trichosporon mucoides	10	0.06	0.25	0.03–0.25	[6]
Trichosporon inkin	4	. . .	. . .	0.03–0.12	[6]
Geotrichum capitatum	7	. . .	. . .	0.03–0.5	[6]
Saccharomyces cerevisiae	20	0.06	0.25	0.03–1	[6]
Rhodotorula spp	14	0.03	0.03	0.03–0.12	[6]
Pichia spp	11	0.03	0.03	0.03–0.25	[6]

Abbreviation: MIC, minimum inhibitory concentration.

Table 2. In Vitro Susceptibilities of Isavuconazole Against Hyaline Molds and Mucorales

Organism	No.	MIC_{50}, μg/mL	MIC_{90}, μg/mL	MIC Range, μg/mL	Reference
Aspergillus spp					
A. fumigatus	855	0.5	1	0.06–≥8	[12]
A. flavus	444	0.5	1	0.12–4	[12]
A. nidulans	106	0.125	1	0.06–1	[12]
A. niger	207	1	2	0.06–≥8	[12]
A. versicolor	75	0.25	0.5	0.03–≥8	[12]
A. terreus	384	0.25	0.5	0.06–2	[12]
Fusarium spp	50	16	>16	1–>16	[11, 13]
Paecilomyces lilacinus	22	1	2	0.2–2	[13]
Scedosporium apiospermum	44	2	4	0.5–8	[11, 13]
Scedosporium prolificans	6	. . .	. . .	>16	[11]
Mucorales					
Absidia spp	80	1	8	0.03–16	[14]
Cunninghamella spp	18	2	16	0.12–16	[14]
Mucor spp	79	4	16	<0.015–>128	[14, 15]
Rhizomucor spp	29	2	16	0.015–64	[14]
Rhizopus spp	199	1	4	0.12–32	[14, 15]

Abbreviation: MIC, minimum inhibitory concentration.

values as low as 0.12 μg/mL, but others have MIC values as high as 32 μg/mL.

Dimorphic Fungi

The MICs of isavuconazole for *Histoplasma capsulatum* and *Coccidioides* species range from 0.12 μg/mL to 2 μg/mL [13] (Table 3). Only 6 isolates of *Blastomyces dermatitidis* have been studied, and MIC values ranged from 0.5 μg/mL to 4 μg/mL. MICs against a small number of isolates of *Sporothrix* species were reported to be high for isavuconazole and similar to those noted with voriconazole [2].

PHARMACOLOGY

Isavuconazonium sulfate, the prodrug of isavuconazole, is available in both intravenous and oral formulations. The dosage strength of 372 mg isavuconazonium sulfate corresponds to 200 mg of isavuconazole, the active component, in both formulations. The capsules each contain 186 mg isavuconazonium sulfate (100 mg isavuconazole). The recommended dosing regimen for both oral and intravenous formulations is a loading dose of 600 mg, given as 200 mg every 8 hours, for 2 days followed by 200 mg daily thereafter [20].

Unlike voriconazole and posaconazole, the prodrug, isavuconazonium sulfate, is highly water soluble, and therefore the intravenous formulation does not require solubilization by a cyclodextrin vehicle. This is an advantage as this eliminates the concerns of nephrotoxicity from the cyclodextrin vehicle, which is used in the intravenous formulations of voriconazole and posaconazole [21].

After intravenous infusion, the prodrug is broken down quickly to the active component, isavuconazole, and an inactive cleavage product. In healthy adults, plasma concentrations of the prodrug and the inactive cleavage product are detectable only during the intravenous infusion and are not detectable 30 minutes later. Following oral administration, plasma concentrations of the active compound reach maximum concentrations (C_{max}) by 2–3 hours; the prodrug and cleavage product are not measurable in plasma after oral administration.

In healthy adult volunteers, isavuconazole exhibits linear and dose-proportional pharmacokinetics. The oral bioavailability of isavuconazole is 98% [22, 23]. Absorption of isavuconazole is not affected by food intake. In addition to excellent bioavailability, isavuconazole serum concentrations show low intersubject variability. In healthy volunteers, the C_{max} at steady state was 2.5 ± 1.0 μg/mL [23]. In a small number of patients with acute myeloid leukemia and neutropenia, similar pharmacokinetic profiles for intravenous isavuconazole were found [24].

Isavuconazole has a large volume of distribution, is >99% protein bound, and has a long terminal half-life of 100–130 hours [22, 23]. Consistent with this long terminal elimination half-life, tissue levels persist long after plasma levels become undetectable [25]. The route of elimination in humans has not been established, but animal studies have shown that excretion occurs primarily via feces. Urine elimination of isavuconazole is negligible, and thus this agent is unlikely to be useful for the treatment of urinary tract infections.

Table 3. In Vitro Activity of Isavuconazole Against Dematiaceous Molds and Dimorphic Fungi

Organism	No.	MIC_{50}, μg/mL	MIC_{90}, μg/mL	MIC Range, μg/mL	Reference
Dematiaceous molds					
Exophiala spp	106	2	4	0.25–16	[18]
Alternaria alternata	30	1	1	0.5–2	[13]
Alternaria infectoria	50	4	4	2–4	[17]
Bipolaris spicifera	30	2	4	0.5–4	[13]
Curvularia lunata	24	2	4	1–4	[13]
Dimorphic fungi					
Blastomyces dermatitidis	6	. . .	. . .	0.5–4	[13]
Histoplasma capsulatum	28	0.5	2	0.12–2	[13]
Coccidioides posadasii	30	0.25	0.5	0.12–1	[13]

Abbreviation: MIC, minimum inhibitory concentration.

Metabolism of isavuconazole takes place in the liver via the CYP enzyme family, specifically CYP3A4 and CYP3A5 isoenzymes. The metabolites do not have antifungal activity. Data suggest that patients with liver disease have higher exposure to isavuconazole. The clearance of isavuconazole in patients with mild to moderate hepatic impairment (Child-Pugh class A and B) is impaired [26], but no dosage adjustment is recommended for these patients. There are no data for patients who have Child-Pugh class C liver disease.

Area under the curve (AUC) values and C_{max} are not significantly affected in patients with renal impairment; no dose adjustment is necessary in this patient group [20]. Isavuconazole is likely not dialyzable by either hemodialysis or continuous hemofiltration; however, no pharmacokinetic studies have been reported in patients undergoing renal replacement therapy.

Similar to observations with voriconazole, the metabolism of isavuconazole may be affected by race. Compared with healthy white subjects, Chinese subjects were found to have a lower clearance of isavuconazole (2.6 L/h vs 1.6 L/h, respectively) and a 50% higher AUC [21]. However, at this point, no dosage adjustment has been recommended based on race. Age and sex minimally affect the pharmacokinetics of isavuconazole. No pharmacokinetic studies of isavuconazole have been reported in children.

Isavuconazole is considered a pregnancy class C drug and should not be given to pregnant women. Because the drug was found in breast milk of lactating rats, it should not be used in women who are breastfeeding.

DRUG–DRUG INTERACTIONS

Isavuconazole is a substrate for CYP3A4, so inhibitors of this enzyme lead to increased levels of isavuconazole and should be used with caution (Table 4).

Potent inducers of CYP3A4, such as rifampin, carbamazepine, and long-acting barbiturates, significantly decrease isavuconazole serum levels and should not be used with this antifungal [21].

Isavuconazole is a moderate inhibitor of CYP3A4 and inhibits to a variable extent the metabolism of sirolimus, tacrolimus, and cyclosporine, which can lead to higher levels of these drugs. Serum levels need to be monitored if these drugs are given with isavuconazole. The effects on other CYP3A4 substrates, such as midazolam and atorvastatin, appear to be mild and dosage

Table 4. Drug–Drug Interactions With Isavuconazole

Type of Interaction, Drug	Recommendation
Increases isavuconazole level	
Lopinavir/ritonavir	Use with caution
Decreases isavuconazole level	
Rifampin Carbamazepine Long-acting barbiturates St John's wort	Contraindicated
Levels increased by isavuconazole	
Sirolimus Tacrolimus Cyclosporine Mycophenolate mofetil Digoxin	Use with caution. Monitor serum levels of these drugs and adjust dose when given with isavuconazole
Colchicine Dagibatran	Use with caution. May require dose adjustment
Atorvastatin Midazolam	No dose adjustment recommended when given with isavuconazole; monitor patient
Levels decreased by isavuconazole	
Bupropion	Use with caution. Dose increase of bupropion may be necessary.
Lopinavir/ritonavir	Use with caution

Source: Adapted from [21].

adjustment is not recommended [27]. However, patients should be monitored for adverse effects if these drugs are used concomitantly with isavuconazole.

Isavuconazole has a minimal effect on CYP2C9 and CYP2C19, and thus can be used with warfarin and omeprazole without dosage adjustment of these drugs [28]. Isavuconazole is a weak inhibitor of P-glycoprotein, and if given with digoxin may lead to higher serum digoxin levels [21]. Overall, when compared with voriconazole and posaconazole, isavuconazole seems to have fewer drug–drug interactions.

SIDE EFFECTS

Isavuconazole appears to be relatively safe and well tolerated. The most common side effects reported are gastrointestinal, including nausea, vomiting, and diarrhea, but these rarely have led to discontinuation of the drug [23, 29–31] (Table 5). Other common side effects reported to be associated with isavuconazole in <15% of volunteers and patients include headache, rash, and peripheral edema [23, 29–31]. Commonly noted side effects with voriconazole, such as visual disturbances, hallucinations, and photosensitivity, have not been described with isavuconazole.

Elevations in hepatic enzyme levels can occur with isavuconazole therapy, as with other azoles. The usual pattern is elevation of alanine aminotransferase and aspartate aminotransferase, but elevations in alkaline phosphatase levels also have been noted. There are reports of a few patients who had severe hepatotoxicity, but whether this was caused solely by isavuconazole or was related to other underlying illness is not clear [20]. Liver enzymes should be monitored in patients taking isavuconazole, as is recommended for all other azole drugs.

Table 5. Adverse Effects Associated With Isavuconazole

Most frequent side effects or other abnormalities
Gastrointestinal
Nausea
Vomiting
Diarrhea
Headache
Rash
Elevation of liver enzymes
QTc shortening
Less common side effects or other abnormalities
Peripheral edema
Hypokalemia
Infusion reactions
Acute respiratory distress
Chills
Dyspnea
Hypotension

Differing from other triazoles that cause QTc segment prolongation, isavuconazole has been noted to cause dose-dependent QTc shortening by as much as 13 msec with 200 mg daily and 24.6 msec with 600 mg daily in healthy volunteers [20]. Among 257 patients treated with isavuconazole in a clinical trial of invasive mold infections, 17 (7.5%) had QTc shortening >60 msec from baseline [21]. At this point, the clinical significance of QTc shortening is unclear, except for patients who have the rare disease familial short QT syndrome, who should not receive isavuconazole.

Infusion reactions that include acute respiratory distress, chills, dyspnea, and hypotension have been noted in a few patients [21]. Whether these reactions are related to particulates in the intravenous formulation, which are composed of isavuconazole that has been cleaved from the prodrug while being infused, is not clear [21]. It is recommended that an in-line filter (0.2–1.2 μm) be used for the infusion of isavuconazole [20].

CLINICAL USES

Aspergillosis

Isavuconazole has been approved for the treatment of invasive aspergillosis based on the results of a randomized, double-blind, noninferiority clinical trial that compared isavuconazole with voriconazole for primary treatment of invasive aspergillosis and other invasive mold infections [21, 32–34]. A total of 516 adult patients with proven, probable, or possible invasive fungal disease, as defined by European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria [35], were randomized 1:1 to receive isavuconazole or voriconazole. The primary endpoint of the study was all-cause mortality at day 42 for this entire population.

The analysis of efficacy for treating invasive aspergillosis focused on the subset of 272 patients who had proven (65 patients) or probable (207 patients) invasive fungal infection [21]. Probable infection was based on a positive galactomannan assay in half of the patients in both treatment arms. Efficacy was defined as success at the end of treatment by EORTC/MSG criteria [36] and was adjudicated by a blinded data review committee.

It should be noted that the actual number of patients who had proven or probable aspergillosis was 231; the other 41 patients included in the analysis of efficacy at the end of treatment had other invasive mold infections. Of the 231 patients who had invasive aspergillosis, 123 received isavuconazole and 108 received voriconazole, and 16% had proven infection and 84% had probable infection.

Hematological malignancies were the most common underlying condition (84%); 65% were neutropenic and 20% had received an allogeneic hematopoietic cell transplant. The median

duration of intravenous therapy was 5 days in both arms, and the total duration of antifungal treatment was 45 and 46.5 days for isavuconazole and voriconazole, respectively.

Day 42 all-cause mortality for all patients who received study drug did not differ significantly (18.6% for the isavuconazole arm and 20.2% for the voriconazole arm). Similarly, the overall success (complete and partial response) at the end of treatment was not different (35% and 36.4% for the isavuconazole and voriconazole arms, respectively). For the 231 patients who had proven or probable invasive aspergillosis, both the 42-day mortality (18.7% and 22.2%) and success at the end of treatment (35% vs 38.9%) were not different between the isavuconazole and voriconazole arms, respectively.

Mucormycosis

The data on which the approval for the treatment of invasive mucormycosis is based are not as strong as those for aspergillosis. In large measure this is because of the rarity of mucormycosis and resultant inability to enroll enough cases into a randomized controlled treatment trial. The study that was used for licensing was an open-label, noncomparative trial that evaluated isavuconazole for treatment of invasive aspergillosis in patients with renal impairment and for treatment of invasive fungal infections caused by rare molds, including members of the order Mucorales [21, 30]. This study allowed both primary treatment of invasive mold infections and salvage treatment of patients who were intolerant of or failing prior antifungal therapy. Of 149 patients enrolled in this study, 37 had proven (86%) or probable (14%) invasive mucormycosis by EORCT/MSG criteria [35]. Twenty-one of the 37 had not received prior antifungal therapy, 11 had refractory disease, and 5 were intolerant of prior therapy. A hematologic malignancy was present in 59%; 35% had received a hematopoietic cell transplant, and 27% were neutropenic. Diabetes was a risk factor in only 4 patients. Pulmonary involvement was present in 22 patients (59%), and half of those patients also had another site of infection, mainly sinus, ocular, and central nervous system. The median duration of treatment was 84 days (range, 2–882 days).

The endpoints of this study were all-cause mortality at day 42 and overall response at day 42 as assessed by an independent data review committee. The mortality at day 42 was 38%; mortality was higher among patients who had refractory disease or were intolerant of prior therapy (43.7%) compared with those who were treated for primary mucormycosis (33.3%). The overall response rate at day 42, as judged by the data review committee, was 31.4%.

A matched case-control analysis was performed comparing the 21 patients who had primary treatment with isavuconazole with the cases of 33 patients who were treated with amphotericin B and whose data had been entered into the global Fungiscope Registry, an ongoing observational database. Matching was done by severity of infection, hematologic malignancy, and whether surgical debridement was performed. In this analysis, isavuconazole-treated and amphotericin B–treated patients had similar mortality (33.3% vs 41.3%, respectively). These mortality rates are consistent with historical data showing mortality rates of 35%–45% in patients who were treated with amphotericin B [37, 38] and in those who were entered into several posaconazole salvage studies [39, 40].

Other Fungal Infections

The data on the role of isavuconazole for the treatment of patients with invasive mold infection caused by *Fusarium* and *Scedosporium* species are limited to 9 and 3 patients, respectively [41]. Only 3 patients with fusariosis and 1 with scedosporiosis had a complete or partial response at the end of therapy [41].

Twenty-nine patients with endemic mycoses—paracoccidioidomycosis (10), coccidioidomycosis (9), histoplasmosis (7), and blastomycosis (3)—were entered into the rare molds treatment trial [31]. Disseminated infection was present in 70% and 57% of patients with paracoccidioidomycoses and histoplasmosis, respectively. Successful response at the end of therapy was 64%, but 3 patients died from progression of disease (2 with paracoccidioidomycosis and 1 with blastomycosis). These data suggest that isavuconazole could be an alternative for the treatment of dimorphic fungi infections, but the number of patients treated is too small to recommend the use of this agent at this time.

A phase 2, randomized, double-blind, multicenter trial that evaluated 3 dosing regimens of isavuconazole compared with fluconazole in 160 immunocompromised patients with esophageal candidiasis noted an overall 96% clinical and microbiological success rate [29]. However, given the efficacy of fluconazole, it seems unlikely that isavuconazole will assume a major role in the treatment of mucosal candidiasis.

SUMMARY

Isavuconazole has been approved by the FDA for the treatment of invasive aspergillosis and mucormycosis. Advantages of this triazole are the availability of a water-soluble intravenous formulation, excellent bioavailability of the oral formulation, predictable pharmacokinetics, and, to date, few adverse effects. However, clinical experience is limited for the treatment of invasive fungal infections when compared with voriconazole and posaconazole. Voriconazole remains the drug of choice for the treatment of invasive aspergillosis, but isavuconazole could be considered an attractive alternative for patients who cannot tolerate voriconazole. Lipid formulations of amphotericin B remain the treatment of choice for mucormycosis. Posaconazole is typically used for step-down therapy and for those patients who cannot tolerate amphotericin B. Isavuconazole is an

acceptable alternative to posaconazole in those patients. The role of isavuconazole in treating endemic mycoses and other fungal infections should be clarified by further studies.

Note

Potential conflict of interest. Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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