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In Vitro Activities of Posaconazole, Fluconazole, Itraconazole, Voriconazole, and Amphotericin B against a Large Collection of Clinically Important Molds and Yeasts

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The in vitro activity of the novel triazole antifungal agent posaconazole (Noxafil; SCH 56592) was assessed in 45 laboratories against approximately 19,000 clinically important strains of yeasts and molds. The activity of posaconazole was compared with those of itraconazole, fluconazole, voriconazole, and amphotericin B against subsets of the isolates. Strains were tested utilizing Clinical and Laboratory Standards Institute broth microdilution methods using RPMI 1640 medium (except for amphotericin B, which was frequently tested in antibiotic medium 3). MICs were determined at the recommended endpoints and time intervals. Against all fungi in the database (22,850 MICs), the MIC_{50} and MIC_{90} values for posaconazole were 0.063 μg/ml and 1 μg/ml, respectively. MIC_{90} values against all yeasts (18,351 MICs) and molds (4,499 MICs) were both 1 μg/ml. In comparative studies against subsets of the isolates, posaconazole was more active than, or within 1 dilution of, the comparator drugs itraconazole, fluconazole, voriconazole, and amphotericin B against approximately 7,000 isolates of *Candida* and *Cryptococcus* spp. Against all molds (1,702 MICs, including 1,423 MICs for *Aspergillus* isolates), posaconazole was more active than or equal to the comparator drugs in almost every category. Posaconazole was active against isolates of *Candida* and *Aspergillus* spp. that exhibit resistance to fluconazole, voriconazole, and amphotericin B and was much more active than the other triazoles against zygomycetes. Posaconazole exhibited potent antifungal activity against a wide variety of clinically important fungal pathogens and was frequently more active than other azoles and amphotericin B.

Over the past 2 decades, the incidence of systemic mycoses has increased dramatically. This is primarily due to the increase in the number of at-risk individuals, principally those with impaired immunity, such as transplant recipients, cancer patients receiving chemotherapy, and human immunodeficiency virus-infected patients (2, 17, 24, 32, 37). The most common fungal pathogens are species of *Candida*, *Cryptococcus*, *Coccidioides*, *Aspergillus*, and *Histoplasma*; less common pathogens include agents of zygomycosis (primarily species of *Rhizopus*, *Mucor*, *Cunninghamella*, *Apophysomyces*, *Absidia*, and *Rhizomucor*), hyalohyphomycosis, and phaeohyphomycosis (32).

Mortality rates associated with systemic mycoses, particularly those involving members of the zygomycetes, remain unacceptably high. Effective treatment requires both an early diagnosis, to facilitate prompt initiation of therapy, and broad-spectrum therapeutic agents with activity against both common and "emerging" pathogens. Until recently, the drugs available to treat invasive fungal infections were limited by their spectrum of activity, the development of resistance, and less than optimal tolerability and drug interaction profiles (15). To address these issues, a new generation of triazoles, including posaconazole (POS), voriconazole (VRC), and ravuconazole (RAV), has been developed. These agents possess potent broad-spectrum activity and favorable pharmacokinetic profiles (3, 12, 15). Among these extended-spectrum triazoles, POS has proven to be a potent inhibitor of ergosterol synthesis in both yeasts and molds (19) and to be active against a wide range of pathogens (1, 4, 28, 29), including *Aspergillus* spp. (16, 29) and the zygomycetes (7, 34).

This report summarizes in vitro data for 19,000 clinically important strains of yeasts and molds collected from 200 medical centers worldwide over a 10-year time span. Where available, data are also provided on the comparator drugs itraconazole (ITC), fluconazole (FLC), VRC, and amphotericin B (AMB). Overall, POS exhibited potent broad-spectrum antifungal activity; it was frequently more active than the other azoles, and its spectrum of activity was comparable to that of AMB and superior to those of all other marketed antifungals.

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MATERIALS AND METHODS

Antifungal agents. POS was prepared at Schering-Plough Research Institute, Kenilworth, NJ. ITC and AMB were obtained from Janssen Pharmaceutica N.V., Beerse, Belgium, and Sigma Chemical Co., St. Louis, MO, respectively. VRC and FLC were obtained from Pfizer Inc., New York, NY.

Susceptibility testing. MIC testing was performed as described in the Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) documents M27-A2 and M38-A and versions thereof (20, 21). For slower-growing organisms, such as the dermatophytes, *Cryptococcus* and *Histoplasma* spp., if insufficient growth was observed at 48 h then the plates were incubated for longer periods (typically 72 h). Test panels were either prepared in the individual laboratories using drug powders or obtained as frozen panels from Trek Diagnostics Systems Inc. (Cleveland, OH).

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TABLE 1. In vitro activities of posaconazole, itraconazole, fluconazole, voriconazole, and amphotericin B against all fungi, molds, and yeasts tested

Antifungal agent	In vitro activity against[a]: All fungi			All molds			All yeasts		
	n	MIC (μg/ml) 50%	MIC (μg/ml) 90%	n	MIC (μg/ml) 50%	MIC (μg/ml) 90%	n	MIC (μg/ml) 50%	MIC (μg/ml) 90%
POS	22,850	0.063	1.0	4,499	0.125	1.0	18,351	0.063	1.0
ITC	18,877	0.125	1.0	3,204	0.5	4.0	15,673	0.125	1.0
FLC	17,884	0.5	128.0	1,779	256.0	256.0	16,105	0.5	16.0
VRC	9,598	0.031	0.5	1,826	0.25	2.0	7,772	0.031	0.5
AMB	16,567	1.0	1.0	3,013	1.0	2.0	13,554	1.0	1.0

[a] n is the number of MICs determined. 50% and 90%, MIC_{50} and MIC_{90}, respectively.

Data analysis. Susceptibility data were collected from individual investigators and entered into a global database. Not all strains were tested against all of the comparator drugs; however, all strains in this study were tested against POS. All data relating to control/quality control isolates were excluded from the analysis. In a few instances, an investigator may have tested an isolate more than once; consequently, in the tables, "n" refers to the number of MICs not the number of isolates.

RESULTS

All isolates. Overall, POS exhibited potent in vitro activity against approximately 19,000 fungal microorganisms. MIC_{50} and MIC_{90} values for POS were as follows: 0.063 μg/ml and 1.0 μg/ml, respectively, for all fungi (22,850 MICs); 0.125 μg/ml and 1.0 μg/ml for all molds (4,499 MICs); and 0.063 μg/ml and 1.0 μg/ml for all yeasts (18,351 MICs).

For the subsets of these 19,000 isolates that were also tested against other antifungal agents, POS was more active than, or within 1 dilution of, ITC, FLC, VRC, and AMB (Table 1). Although VRC exhibited a lower mean MIC_{50} than did POS against yeasts, POS was more active than VRC against molds.

Mold isolates. For subsets of mold isolates tested against each antifungal agent, POS was either more potent than or equivalent to ITC, AMB, and VRC (Table 2). Against hyaline molds, including *Aspergillus* spp., *Fusarium* spp., and a miscellaneous group comprising other species, such as *Acremonium*, *Basidiomycetes*, *Bjerkandera*, *Coprinus*, *Paecilomyces*, *Pseudallescheria*, and *Schizophyllum*, POS was equivalent to VRC, AMB, and ITC.

POS showed good activity against *Aspergillus* spp. (including *A. fumigatus*, *A. flavus*, and *A. niger*) and against the majority of zygomycetes (including *Rhizopus*, *Mucor*, *Absidia*, and *Cunninghamella* spp.). For all strains of *Aspergillus* spp. tested, the MIC_{50} and MIC_{90} values were 0.125 μg/ml and 0.5 μg/ml, respectively, whereas for all zygomycetes tested, the MIC_{50} and MIC_{90} values were 0.5 μg/ml and 4.0 μg/ml, respectively. In comparisons with other antifungal agents against *Aspergillus* spp. (1,423 MICs), POS was either more potent than or equivalent to ITC, VRC, and AMB (Table 2). However, POS was the only triazole that provided consistent activity against the zygomycetes (86 MICs) (Table 2).

Against dimorphic fungi (including *Penicillium*, *Histoplasma*, *Blastomyces*, and *Coccidioides* spp.), POS was generally more potent than, or equivalent to, ITC and AMB (Table 2). All drugs had limited activity against *Fusarium* spp. (Table 2). The *Fusarium* strains most susceptible to POS were *F. moniliforme* and *F. oxysporum*.

POS also showed good activity against agents that cause chromoblastomycosis, mycetoma, and phaeohyphomycosis, including *Scedosporium apiospermum* (though not *Scedosporium prolificans*) and *Exophiala*, *Alternaria*, and *Bipolaris* spp. (Table 2), and POS was generally more active than ITC and AMB against these organisms. Against dermatophytes, including *Trichophyton rubrum*, *T. mentagrophytes*, and *T. tonsurans*, POS was more potent than FLC and comparable to ITC (Table 3).

Yeast isolates. POS showed good activity against *Candida* spp. (Table 4), including those species that are inherently less susceptible to FLC (e.g., *Candida* spp. *C. glabrata*, *C. krusei*, *C. guilliermondii*, and *C. dubliniensis*). The strains most susceptible to POS were *C. albicans* and *C. dubliniensis*, whereas *C. glabrata* was the least susceptible. Although POS was slightly less active than VRC against *Candida* spp., it was more active than either ITC or AMB. Against *Cryptococcus* spp., POS was more active than FLC and comparable to ITC, VRC, and AMB (Table 4).

Azole-resistant *Candida* isolates. *Candida* isolates with MICs of >32 μg/ml, >0.5 μg/ml, and >2 μg/ml for FLC, ITC, and VRC, respectively, are considered resistant (21). Of the 6,595 isolates tested against all four azoles, 6.4%, 16.5%, and 3.3% were resistant to FLC, ITC, and VRC, respectively (Table 5). The frequency of isolates with MICs for POS that were >2 μg/ml was 3%. Resistance to one azole significantly impacted susceptibility to the other azoles.

DISCUSSION

The present study has extended the findings of earlier in vitro investigations of the antifungal activity of POS in demonstrating its wide spectrum of activity against more than 19,000 strains of yeasts and molds encountered in infectious disease practice at more than 200 medical centers throughout the world. As well as having good activity against most *Candida* spp. (including *C. glabrata* and *C. krusei*), POS exhibited good activity against the majority of organisms responsible for causing aspergillosis, cryptococcosis, zygomycosis, chromoblastomycosis, mycetoma, and phaeohyphomycosis. In comparison with the other antifungal agents tested (FLC, ITC, VRC, and AMB), POS was generally more potent than FLC and either equipotent to or more potent than ITC,

TABLE 2. Comparative in vitro activities of posaconazole, itraconazole, voriconazole, and amphotericin B against mold isolates

Organism	No. of MICs	MIC (μg/ml)[a]							
		POS		ITC		VRC		AMB	
		50%	90%	50%	90%	50%	90%	50%	90%
All molds	1,702	0.25	1.0	0.5	2.0	0.25	2.0	0.5	2.0
All hyaline molds[b]	1,636	0.25	1.0	0.5[c]	2.0[c]	0.25	1.0	0.5	2.0
All *Aspergillus* spp.	1,423	0.125	0.5	0.5	2.0	0.25	0.5	0.5	1.0
A. flavus	89	0.25	0.5	0.5	1.0	0.5	1.0	1.0	2.0
A. fumigatus	1,119	0.125	0.5	0.5	1.0	0.25	0.5	0.5	1.0
A. niger	101	0.25	0.5	1.0	2.0	0.5	2.0	0.125	1.0
A. terreus	22	0.25	0.25	0.5	0.5	0.25	0.5	2.0	2.0
Other *Aspergillus* spp.[d]	92	0.125	1.0	0.5	2.0	0.25	1.0	1.0	2.0
All zygomycetes	86	0.5	4.0	1.0	32.0	16.0	128.0	0.25	2.0
Rhizopus spp.	32	1.0	8.0	4.0	32.0	16.0	128.0	1.0	2.0
Mucor spp.	18	1.0	16.0	2.0	32.0	64.0	128.0	0.25	1.0
Absidia spp.	16	0.125	0.25	0.125	0.5	16.0	128.0	0.25	0.5
Cunninghamella spp.	6	0.031–1.0	0.031–1.0	0.125–2.0	0.125–2.0	8.0–128.0	8.0–128.0	0.125–2.0	0.125–2.0
Apophysomyces spp.	5	0.031–4.0	0.031–4.0	0.031–8.0	0.031–8.0	16.0–128.0	16.0–128.0	0.031–4.0	0.031–4.0
Saksenaea spp.	4	0.016–2.0	0.016–2.0	0.016–0.125	0.016–0.125	0.5–4.0	0.5–4.0	0.063–0.5	0.063–0.5
Rhizomucor spp.	3	0.016–0.25	0.016–0.25	0.016–0.25	0.016–0.25	2.0–16.0	2.0–16.0	0.063–0.125	0.063–0.125
Cokeromyces spp.	2	0.25–4.0	0.25–4.0	0.25–8.0	0.25–8.0	16.0–64.0	16.0–64.0	0.125–0.5	0.125–0.5
All dimorphic fungi	151	0.063	0.25	0.031	0.25	ND	ND	0.25	0.5
Histoplasma spp.	53	0.019	0.25	0.019	0.063	ND	ND	0.25	0.5
Blastomyces spp.	38	0.063	0.125	0.031	2.0	ND	ND	0.125	0.5
Coccidioides spp.	25	0.125	0.25	0.125	0.25	ND	ND	0.5	0.5
Paracoccidioides spp.	13	0.063	0.125	0.016	0.063	ND	ND	0.125	0.25
Penicillium marneffei	12	0.016	0.016	0.008	0.063	ND	ND	0.5	4.0
Sporothrix spp.	10	0.5	1.0	0.25	0.5	ND	ND	0.5	1.0
All *Fusarium* spp.	67	16.0	32.0	16.0[e]	32.0[e]	16.0	32.0	8.0	32.0
F. solani	39	32.0	32.0	ND	ND	16.0	32.0	16.0	32.0
F. oxysporum	12	2.0	4.0	ND	ND	4.0	32.0	8.0	16.0
F. moniliforme	2	1.0	1.0	ND	ND	1.0	1.0	1.0–4.0	1.0–4.0
Other *Fusarium* spp.[f]	14	16.0	16.0	ND	ND	4.0	16.0	1.0	2.0
Agents of chromoblastomycosis, mycetoma, and phaeohyphomycosis	241	0.25	16.0	1.0	64.0	ND	ND	2.0	32.0
Scedosporium prolificans	80	16.0	32.0	64.0	64.0	ND	ND	16.0	32.0
Scedosporium apiospermum	26	0.25	1.0	1.0	32.0	ND	ND	2.0	8.0
Pseudallescheria spp.	41	0.25	1.0	0.5	1.0	ND	ND	2.0	4.0
Aspergillus nidulans	20	0.063	0.25	0.25	0.5	ND	ND	1.0	2.0
Exophiala spp.	14	0.25	0.5	0.5	1.0	ND	ND	0.5	1.0
Alternaria spp.	13	0.125	0.25	0.5	1.0	ND	ND	0.5	4.0
Cladosporium spp.	11	0.063	16.0	0.125	16.0	ND	ND	1.0	4.0
Bipolaris spp.	10	0.063	0.125	0.063	0.25	ND	ND	0.25	0.25
Other[g]	26	0.125	0.25	0.25	1.0	ND	ND	0.5	1.0
Other molds[h]	58	0.25	0.5	0.063	1.0	0.25	0.5	0.25	2.0

[a] 50% and 90%, MIC_{50} and MIC_{90}, respectively. When *n* is <10, the MICs shown are ranges. ND, not determined.
[b] Includes *Aspergillus* spp. and *Fusarium* spp. (MIC data for which are shown below), and other various species, including strains of *Acremonium*, *Basidiomycetes*, *Bjerkandera*, *Coprinus*, *Paecilomyces*, *Pseudallescheria*, and *Schizophyllum*.
[c] Fewer isolates (n = 1,501) were tested against ITC; therefore, the values for ITC cannot be compared directly.
[d] Includes strains of *A. glaucus*, *A. nidulans*, *A. oryzae*, *Aspergillus* spp., *A. sydowii*, *A. ustus*, and *A. versicolor*.
[e] Fewer isolates (n = 23) were tested against ITC; therefore, the values for ITC cannot be compared directly.
[f] Unspeciated *Fusarium*.
[g] Includes strains of *Cladophialophora*, *Curvularia*, *Exserohilum*, *Fonsecaea*, *Pithomyces*, *Ramichloridium*, *Ulocladium*, and *Wangiella*.
[h] Includes strains of *Acremonium*, *Basidiomycetes*, *Bjerkandera*, *Coprinus*, *Paecilomyces*, *Pseudallescheria*, *Schizophyllum*, and *Trichophyton*.

VRC, and AMB. Although POS exhibited slightly higher mean MIC_{50} values compared with VRC against *Candida* spp., including the inherently less susceptible strains *C. glabrata* and *C. krusei*, and against *Cryptococcus* spp., it was generally more active than VRC against molds. Against the zygomycetes, POS was the only triazole that exhibited consistent activity, but it was generally less active against these organisms than AMB. All drugs had limited activity against *Fusarium* spp. However, successful outcomes have been reported in patients with fusariosis who were treated with

TABLE 3. Comparative in vitro activities of posaconazole, itraconazole, and fluconazole against isolates of dermatophytes

Organism	No. of MICs	MIC (μg/ml)[a] POS 50%	POS 90%	ITC 50%	ITC 90%	FLC 50%	FLC 90%
All dermatophytes	180	0.031	0.25	0.063	0.25	4.0	64.0
Trichophyton rubrum	91	0.063	0.125	0.063	0.25	2.0	32.0
T. mentagrophytes	29	0.016	0.125	0.031	0.25	8.0	64.0
T. tonsurans	23	0.031	0.25	0.031	0.063	4.0	32.0
Other *Trichophyton* spp.[b]	5	0.063–0.5	0.063–0.5	0.031–4.0	0.031–4.0	1.0–128.0	1.0–128.0
Microsporum spp.[c]	16	0.016	0.125	0.016	0.5	2.0	128.0
Epidermophyton floccosum	15	0.016	0.25	0.016	0.25	2.0	2.0
Arthroderma benhamiae	1	0.031	0.031	0.031	0.031	1.0	1.0

[a] 50% and 90%, MIC_{50} and MIC_{90}, respectively. When *n* is <10, the MICs shown are ranges.
[b] Includes strains of *T. krajdeneii*, *T. raubitschekii*, *T. soudanense*, and *T. terrestre*.
[c] Includes strains of *M. canis*, *M. gypseum*, and *M. persicolor*.

POS, suggesting that in vitro testing might not accurately predict the clinical outcome (11, 31).

Previous studies comparing the in vitro activity of POS with that of other antifungal agents have described similar findings. In comparison with other triazole agents, POS has generally been reported to have greater activity than FLC and ITC against yeasts such as *Candida* spp., *Cryptococcus* spp., and *Saccharomyces cerevisiae* (1, 4, 13, 23, 27, 28, 30), although in some studies, it was no more active than ITC against *Candida* spp. (26) or *Cryptococcus neoformans* (25). POS has also proved more active than AMB and flucytosine against most *Candida* spp. (26) and has been found to have similar activity to VRC against the majority of *Candida* spp. (23, 30). However, against *C. glabrata*, which has proved the least-susceptible *Candida* species to POS (28, 30), it was slightly less active than VRC, both in the present study and in an earlier investigation by Pfaller et al. (30).

Consistent with previous reports (22, 28), isolates with elevated MICs to one azole were generally less susceptible to all azoles. *C. albicans* and *C. glabrata*, in approximately equal numbers, were the species most frequently characterized as being resistant to FLC and VRC. In contrast, the majority of ITC-resistant isolates were *C. glabrata*. Comparing POS and VRC, the numbers of *C. glabrata* MICs that were >2 μg/ml (the VRC-resistant breakpoint) were nearly identical for both drugs. However, for both *C. albicans* and other species of *Candida*, the number of POS MICs that were >2 μg/ml was nearly twofold lower than for VRC.

In studies focusing on *Aspergillus* spp., POS has proved more active than both ITC (4, 22) and AMB (22). In a comparison of POS with RAV, VRC, ITC, and AMB against 239 isolates of *Aspergillus* spp. and other filamentous fungi (including *Fusarium*, *Rhizopus*, and *Mucor* spp.), POS was the most active agent (94% of isolates inhibited at a MIC of ≤1 μg/ml) (29). In the case of zygomycetes, POS exhibited good activity against 36 zygomycetes belonging to six genera; AMB also showed good activity, VRC was significantly less active, and ITC and terbinafine showed variable activity (7). Two additional studies compared the activity of POS with those of AMB, VRC, FLC, and ITC or with VRC and caspofungin (CSP) against collections of 37 and 59 zygomycetes, respectively (8, 34). In both studies, POS was significantly more active than VRC; in the individual

TABLE 4. Comparative in vitro activities of posaconazole, itraconazole, fluconazole, voriconazole, and amphotericin B against isolates of *Candida* spp. and *Cryptococcus* spp.

Organism	No. of MICs	MIC (μg/ml)[a] POS 50%	POS 90%	ITC 50%	ITC 90%	FLC 50%	FLC 90%	VRC 50%	VRC 90%	AMB 50%	AMB 90%
All *Candida* spp.	6,965	0.063	1.0	0.125	1.0	0.5	16.0	0.031	0.5	1.0[b]	1.0[b]
C. albicans	3,535	0.031	0.063	0.063	0.25	0.25	2.0	0.008	0.063	1.0[b]	1.0[b]
C. glabrata	1,218	1.0	2.0	1.0	4.0	8.0	64.0	0.25	2.0	1.0[b]	1.0[b]
C. parapsilosis	970	0.063	0.25	0.25	0.5	1.0	4.0	0.031	0.125	1.0	1.0
C. tropicalis	719	0.063	0.25	0.125	0.5	1.0	4.0	0.063	0.5	1.0	1.0
C. krusei	189	0.5	1.0	1.0	1.0	32.0	64.0	0.25	0.5	1.0	2.0
C. lusitaniae	84	0.063	0.25	0.25	2.0	1.0	4.0	0.031	0.063	1.0	2.0
C. guilliermondii	26	0.25	1.0	0.5	4.0	4.0	32.0	0.063	8.0	0.5	1.0
C. dubliniensis	164	0.031	0.125	0.063	0.5	0.25	32.0	0.016	0.125	0.5	1.0
Other *Candida* spp.[c]	60	0.25	2.0	0.5	1.0	4.0	16.0	0.063	0.25	1.0	1.0
Cryptococcus spp.[d]	271	0.125	0.25	0.125	0.5	4.0	8.0	0.063	0.125	1.0	1.0

[a] 50% and 90%, MIC_{50} and MIC_{90}, respectively.
[b] The number of strains of *C. albicans* and *C. glabrata* tested against AMB was slightly less (for all *Candida* spp., *n* = 6,921; for *C. albicans*, *n* = 3,517; and for *C. glabrata*, *n* = 1,192).
[c] Includes strains of *C. famata*, *C. kefyr*, *C. lipolytica*, *C. pelliculosa*, *C. pseudotropicalis*, *C. rugosa*, *C. sphaerica*, *C. stellatoidea*, and *C. zeylanoides*.
[d] Includes strains of *C. laurentii* and *C. neoformans*.

TABLE 5. Comparative in vitro activities of posaconazole, itraconazole, fluconazole, and voriconazole, against isolates of *Candida* spp. exhibiting resistance to itraconazole, fluconazole, and voriconazole

Isolates (resistance level)	No. of MICs[a]	MIC (μg/ml)[b]							
		POS		ITC		FLC		VRC	
		50%	90%	50%	90%	50%	90%	50%	90%
FLC resistant (MIC, >32 μg/ml)									
All *Candida*	446	1.0	16.0	2.0	32.0	128.0	256.0	2.0	32.0
C. albicans	167	0.5	16.0	2.0	32.0	128.0	256.0	2.0	32.0
C. glabrata	149	2.0	16.0	4.0	16.0	256.0	256.0	4.0	8.0
Other *Candida* spp.	130	0.5	4.0	1.0	32.0	128.0	128.0	0.5	32.0
ITC resistant (MIC, >0.5 μg/ml)									
All *Candida*	1,151	1.0	4.0	1.0	16.0	16.0	128.0	0.5	4.0
C. albicans	176	1.0	16.0	4.0	32.0	64.0	256.0	2.0	32.0
C. glabrata	719	1.0	4.0	1.0	8.0	16.0	128.0	0.5	4.0
Other *Candida* spp.	256	0.5	2.0	1.0	8.0	32.0	128.0	0.5	16.0
VRC resistant (MIC, >2 μg/ml)									
All *Candida*	234	4.0	16.0	8.0	32.0	128.0	256.0	8.0	32.0
C. albicans	101	2.0	16.0	8.0	32.0	128.0	256.0	8.0	32.0
C. glabrata	88	4.0	16.0	16.0	32.0	128.0	256.0	4.0	16.0
Other *Candida* spp.	45	2.0	32.0	2.0	32.0	128.0	128.0	32.0	32.0
With POS MIC of >2 μg/ml									
All *Candida*	176	8.0	32.0	16.0	32.0	128.0	256.0	4.0	32.0
C. albicans	62	8.0	32.0	16.0	32.0	128.0	256.0	16.0	64.0
C. glabrata	86	8.0	16.0	16.0	32.0	128.0	256.0	4.0	8.0
Other *Candida* spp.	28	16.0	32.0	8.0	32.0	128.0	128.0	32.0	32.0

[a] The data set is the same as that used in Table 4. There were a total of 6,595 MICs for all four drugs.
[b] 50% and 90%, MIC_{50} and MIC_{90}, respectively.

studies, POS was far more active than either FLC (34) or CSP (8) and slightly more active than ITC (34). In the clinic, POS has been used as salvage therapy to treat over 100 patients with zygomycosis; the rate of success (i.e., either complete or partial response) was at least 60% (10, 35).

In agreement with our findings, good activity against *Coccidioides immitis* has been reported in other studies, although POS proved slightly less active than ITC in one study (9). Both this and previous studies demonstrated that POS is less active against *Scedosporium prolificans* than against *S. apiospermum* (5). Similarly, although POS was not compared with VRC against these organisms in the data presented above, other investigators have shown that POS is significantly less active than VRC against *S. prolificans* and slightly less active than VRC against *S. apiospermum* (5, 18).

The molecular basis for the enhanced in vitro activity of POS over the other azoles remains to be determined. At a first approximation, the in vitro activity of a drug is governed by its ability to accumulate within the cell coupled with its affinity for its target site. Several lines of evidence suggest that decreased susceptibility to azoles results from both changes in intracellular accumulation and changes in the target site (6, 14, 33). The azole target site is 14α-demethylase (CYP51), which is located predominantly in the endoplasmic reticulum. None of the fungal CYP51 enzymes have been crystallized; therefore, information on the way in which the azoles bind to the protein has come primarily from homology modeling studies. One recent study suggested that the long side chain of POS and ITC, a side chain that is absent in VRC and FLC, helps stabilize binding of these azoles to CYP51; this appears to be particularly true for CYP51 proteins with mutations close to the active site (36). This model also suggested that mutations that interfered with binding of the long side chain negatively impacted POS and ITC more than they impacted FLC and VRC. It is conceivable that an increased affinity for CYP51 is responsible for the unique activity of POS against the zygomycetes. In this regard, expression of the CYP51 from *Rhizopus oryzae* in an azole-susceptible *Saccharomyces cerevisiae* strain resulted in a 4-fold decrease in susceptibility to POS and a >250-fold decrease in susceptibility to VRC; there were no changes in susceptibility to either AMB or CSP (unpublished data). These data suggest that for *R. oryzae*, and possibly for other zygomycetes, the nature of the interaction between drug and target protein is a major determinant of susceptibility. With regard to drug accumulation, the level of efflux pump expression can strongly influence the susceptibility of a cell to azoles (33). Studies, primarily using yeasts, demonstrated that whereas all azoles appear to be substrates for the ATP-dependent pumps, POS and ITC are not substrates for the major facilitator encoded by *MDR1* (D. Sanglard, F. Ischer, and J. Bille, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. M-221, p. 379, 2002); again, the molecular basis for these differences remains to be established.

In summary, the differences between POS and the other triazoles described above may account for the unusually broad spectrum of activity of POS and may also be important in combating the increase in triazole resistance currently being observed among some fungal pathogens, notably *Candida* spp., for which multiple molecular mechanisms may be responsible for the decrease in susceptibility.

Conclusion. Overall, POS exhibited potent antifungal activity and had a broad spectrum of activity. POS was more potent than FLC against all organisms tested and was frequently more potent than ITC, VRC, and AMB. Among the triazoles, POS was the only agent that exhibited consistent activity against the zygomycetes. POS also showed good activity against the vast majority of organisms that cause aspergillosis, candidiasis, cryptococcosis, chromoblastomycosis, mycetoma, and phaeohyphomycosis, confirming its potential as a useful agent for patients with serious systemic mycoses.

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