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In Vitro Activity of the New Triazole Voriconazole (UK-109,496) against Opportunistic Filamentous and Dimorphic Fungi and Common and Emerging Yeast Pathogens

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The in vitro antifungal activity of a new triazole derivative, voriconazole, was compared with those of itraconazole and amphotericin B against 67 isolates of *Aspergillus flavus*, *Aspergillus fumigatus*, *Bipolaris* spp., *Fusarium oxysporum*, *Fusarium solani*, *Pseudallescheria boydii*, *Rhizopus arrhizus*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Sporothrix schenckii*. The in vitro activities of voriconazole were also compared with those of amphotericin B, fluconazole, and itraconazole against 189 isolates of emerging and common yeast pathogens of *Blastoschizomyces capitatus*, *Candida* (13 species), *Cryptococcus neoformans*, *Hansenula anomala*, *Rhodotorula rubra*, *Saccharomyces cerevisiae*, *Sporobolomyces salmonicolor*, and *Trichosporon beigelii*. MICs were determined according to a procedure under evaluation by the National Committee for Clinical Laboratory Standards (NCCLS) for broth microdilution testing of filamentous fungi and by the NCCLS M27-A broth microdilution method for yeasts. The in vitro activities of voriconazole were similar to or better than those of itraconazole and amphotericin B against *Aspergillus* spp., *Fusarium* spp., and *P. boydii* as well as against *B. dermatitidis* and *H. capsulatum*. The activities of voriconazole were also comparable to or better than those of amphotericin B, fluconazole, and itraconazole against most species of yeasts tested. Exceptions were certain isolates of *R. rubra* and *S. salmonicolor*. These results suggest that voriconazole has a wide spectrum of activity in vitro; its effectiveness in the treatment of human mycoses is under evaluation in clinical trials.

The risk of opportunistic infections is markedly increased in patients who are severely immunocompromised due to cancer chemotherapy (1), organ or bone marrow transplantation (14, 23), or human immunodeficiency virus (HIV) infection (20, 32). Although *Candida albicans* is the organism most often associated with serious fungal infections (19), other *Candida* species and yeast-like pathogens as well as filamentous fungi such as *Aspergillus*, *Fusarium*, and *Bipolaris* species and *Pseudallescheria boydii* have emerged as clinically important pathogens associated with opportunistic infections (12, 14, 16, 23, 26, 27, 32). Dimorphic fungi such as *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Sporothrix schenckii* (6, 7) have also been associated with serious fungal infections in the immunocompromised host.

The increase in the variety of pathogens associated with serious fungal infections has not been matched by a corresponding increase in the number of antifungal agents available for their treatment. Amphotericin B and azole derivatives, most notably fluconazole and itraconazole, are the primary drugs used for treatment of serious fungal infections (13, 15). However, limitations in the efficacy and/or tolerability of these agents have prompted a search for new drugs that may be effective in the management of patients with mycoses due to a wide range of filamentous fungi and yeast pathogens. Much of this search has centered on azole derivatives (13, 15).

Voriconazole is a new triazole derivative similar to fluconazole and itraconazole (2) that acts by inhibiting fungal cytochrome P-450-dependent, 14-alpha-sterol demethylase-mediated synthesis of ergosterol (18, 31). However, its chemical structure is modified from that of fluconazole by replacement of one triazole moiety by a fluoropyrimidine grouping and alpha methylation (31). Recent in vitro (3, 4, 22, 28, 30) and in vivo (5, 8, 17, 24) studies have demonstrated the effectiveness of voriconazole against certain opportunistic filamentous and dimorphic fungi (molds) (3, 22, 28) and yeasts (3, 4, 30). Some of these previous in vitro studies have evaluated a limited number of isolates and species.

The National Committee for Clinical Laboratory Standards (NCCLS) method M27-A (approved standard [25]) describes reproducible macro- and microdilution methods for testing *Candida* spp. and *Cryptococcus neoformans* against the established antifungal agents. A standard method is not available for testing the wide variety of filamentous fungi. However, the NCCLS Subcommittee for Antifungal Susceptibility Tests is currently evaluating the clinical relevance of the microdilution procedure (9, 10) that was used to test for the susceptibility of the molds in this study. The present study was undertaken to determine voriconazole's in vitro activity against a wide spectrum of opportunistic filamentous and dimorphic fungi as well as against common and emerging yeast pathogens by following the M27-A microdilution method for yeasts (25) and the testing conditions that are under evaluation for molds (9, 10).

MATERIALS AND METHODS

Antifungal agents. Voriconazole and fluconazole (Pfizer, Inc., New York, N.Y.), itraconazole (Janssen Pharmaceutica, Titusville, N.J.), and amphotericin B (E.R. Squibb & Sons, Princeton, N.J.) were provided as standard powders by the manufacturers.

Filamentous fungal isolates. A total of 5 to 12 isolates each of the opportunistic filamentous fungi *Aspergillus flavus*, *Aspergillus fumigatus*, *Bipolaris* spp., *Fusarium oxysporum*, *Fusarium solani*, *P. boydii*, and *Rhizopus arrhizus* and the dimorphic fungi *B. dermatitidis*, *H. capsulatum* var. *capsulatum*, and *S. schenckii* were evaluated. These isolates were recovered from the clinical specimens of 67 individual patients with severe fungal infections. These cultures were received at the Medical College of Virginia, Virginia Commonwealth University from different medical centers in the United States during the last 3 years. Identification of each strain was done by using routine mycological techniques. Twenty of the opportunistic mold isolates were evaluated in two previous collaborative studies conducted by the NCCLS Subcommittee for Antifungal Susceptibility Tests (9,

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TABLE 1. Optical densities and stock inoculum sizes of the filamentous and dimorphic fungi[a]

Fungus (no. tested)	Optical density at 530 nm (range)	Inoculum size (10^6)[a]
A. flavus (11)	0.09–0.11	0.8–1.6
A. fumigatus (12)	0.09–0.11	1.3–1.8
Bipolaris spp.[b] (6)	0.2	0.3–1.0
F. oxysporum (6)	0.15–0.17	1.0–2.7
F. solani (6)	0.15–0.17	0.5–1.2
P. boydii (6)	0.15–0.17	0.3–0.8
R. arrhizus (5)	0.15–0.17	0.4–1.6
S. schenckii (5)	0.09–0.11	3–4.5
B. dermatitidis (5)	0.2	0.3–0.5
H. capsulatum (5)	0.2	0.3–0.5

[a] Stock inoculum sizes are given in ranges of CFU per milliliter.
[b] Species tested included *Bipolaris hawaiiensis* and *Bipolaris spicifera.*

10) to identify the optimal testing conditions for this group of fungi. The mold isolates were maintained in sterile water, as previously described (21), and subcultured on antimicrobial agent-free potato dextrose agar (PDA) to ensure viability and purity.

Yeast isolates. The 189 clinical yeast-like isolates from the Medical College of Virginia, Virginia Commonwealth University culture collection included 14 common and emerging *Candida* species and *C. neoformans* (see Table 4) and the following six emerging yeast-like pathogens, *Blastoschizomyces capitatus*, *Hansenula anomala*, *Rhodotorula rubra*, *Saccharomyces cerevisiae*, *Sporobolomyces salmonicolor*, and *Trichosporon beigelii* (see Table 5). The common pathogens were recovered during the last 3 years from either oral cavities, urine samples, or blood and other sterile body fluids. Each strain represented a unique isolate from a patient managed in several medical centers in the United States and Europe. In order to evaluate isolates with different susceptibility patterns, the set included strains for which either the MICs of amphotericin B and itraconazole were high (see Table 4) or *Candida* spp. strains from AIDS patients with recurrent thrush which were resistant to fluconazole (MICs, ≥64 μg/ml) (29). The emerging yeast pathogens encompassed colonizing or infective human isolates as well as environmental strains. The species selected have been associated in the last few years with human infections in the immunocompromised host (16). Yeast isolates were also maintained in sterile water (21) and subcultured on antimicrobial agent-free medium to ensure viability and purity.

Microdilution methods. The broth microdilution method currently being evaluated for the antifungal susceptibility testing of conidia-forming filamentous fungi by the NCCLS Subcommittee (9, 10) was performed for the molds. The NCCLS M27-A broth microdilution method (25) was used when the yeast isolates were tested.

Inoculum preparation. (i) Stock inoculum suspensions of the molds were prepared from 7-day (*Aspergillus* spp., *Bipolaris* spp., *P. boydii*, *R. arrhizus*, and *S. schenckii*) or 7- to 10-day (*B. dermatitidis* and *H. capsulatum*) cultures grown on PDA at 35°C (cultures for *Fusarium* spp. were grown at 35°C for 48 to 72 h and then at 25 to 28°C until day 7). Mature colonies were covered with approximately 2 ml of sterile saline (0.85%). The resulting stock suspensions were adjusted spectrophotometrically to the optical densities summarized in Table 1. These suspensions contained conidia or sporangiospores and hyphal fragments and were diluted to 1:50 in RPMI-1640 (RPMI) medium (pH 7.0 with 0.165 M morpholinepropanesulfonic acid) to obtain 2× inoculum sizes of 0.9×10^4 to 4.7×10^4 CFU/ml as demonstrated by quantitative colony counts on Sabouraud dextrose agar (SDA). (ii) Stock inoculum suspensions of the yeasts were obtained from 24-h cultures (48 h for *C. neoformans*) on SDA at 35°C. The turbidities of the yeast suspensions were adjusted by the spectrophotometric method, and then the suspensions were diluted 1:1,000 in RPMI medium, resulting in 2× concentrations of 0.8×10^3 to 4.2×10^3 CFU/ml (11, 25) as demonstrated by quantitative colony counts on SDA.

Drug dilutions. Voriconazole, itraconazole, and amphotericin B stock solutions (1,600 μg/ml) were prepared in 100% dimethyl sulfoxide (DMSO). Additive twofold drug dilutions of these agents were prepared at 100× the final concentrations in 100% DMSO, followed by further dilutions (1:50) in RPMI medium to yield 2× the final strength required for the test. Fluconazole (1,280 μg/ml) was prepared in sterile water and diluted in RPMI medium instead of DMSO. Final drug concentrations were 0.03 to 16 μg/ml for voriconazole, itraconazole, and amphotericin B and 0.12 to 64 μg/ml for fluconazole. Serial dilutions were frozen at −40°C until needed.

Test procedure. On the day of the test, each microdilution well containing 100 μl of the 2× drug concentrations was inoculated with 100 μl of the diluted (2×) inoculum suspension (final volume in each well was 200 μl). Growth and sterility control wells were included for each isolate tested. The NCCLS M27-A quality control (QC) isolates *Candida parapsilosis* (ATCC 22019) and *Candida krusei* (ATCC 6258) were tested as described above each time a set of isolates was evaluated. In addition, when antifungal susceptibility testing of the filamentous fungi was performed, MICs for the reference isolate, *Paecilomyces variotii* (ATCC 22319), which has served as a control of drug activity in previous collaborative studies of the NCCLS Subcommittee (9, 10), were determined. Microdilution trays were incubated at 35°C and examined at 24 or 48 h or until

TABLE 2. MICs of voriconazole, fluconazole, itraconazole, and amphotericin B against quality control and reference isolates

Isolate	Antifungal agent	MIC range (μg/ml)	
		Present study	Reference[a]
C. parapsilosis (ATCC 22019)	Voriconazole	0.06–0.12	NA
	Fluconazole	2–4	2–8
	Itraconazole	0.12–0.25	0.06–0.25
	Amphotericin B	0.5–2	0.25–1.0
C. krusei (ATCC 6258)	Voriconazole	0.25	NA
	Fluconazole	32–64	16–64
	Itraconazole	0.25–0.5	0.12–0.5
	Amphotericin B	2	0.5–2
P. variotii (ATCC 22319)	Voriconazole	0.06–0.12	NA
	Itraconazole	0.06–0.5	0.03–1
	Amphotericin B	0.25–0.5	0.25–1

[a] Established reference MIC ranges for the two NCCLS QC *Candida* strains (25). The MIC range for *P. variotii* was obtained in two previous collaborative studies by the NCCLS Subcommittee (9, 10). NA, not available.

TABLE 3. Susceptibilities of 67 opportunistic filamentous and dimorphic fungi to voriconazole, itraconazole, and amphotericin B[a]

Fungus (no. tested)	Antifungal agent	MIC range (μg/ml)	G mean (μg/ml)
Opportunistic filamentous fungi			
A. flavus (11)	Voriconazole	0.5–1.0	0.57
	Itraconazole	0.06–0.12	0.1
	Amphotericin B	1.0–2	1.07
A. fumigatus (12)	Voriconazole	0.06–0.5	0.29
	Itraconazole	0.12–>16	0.24
	Amphotericin B	1.0	1.0
Bipolaris spp.[b] (6)	Voriconazole	0.12–1.0	0.33
	Itraconazole	<0.03–0.12	0.06
	Amphotericin B	0.5–1.0	0.65
F. oxysporum (6)	Voriconazole	4	4
	Itraconazole	1.0–>16	8
	Amphotericin B	2	2
F. solani (6)	Voriconazole	8–16	10.5
	Itraconazole	1.0–>16	8
	Amphotericin B	1.0–2	1.31
P. boydii (6)	Voriconazole	0.25–0.5	0.33
	Itraconazole	0.5–1.0	0.76
	Amphotericin B	1.0–4	2.6
R. arrhizus (5)	Voriconazole	8–>16	18.37
	Itraconazole	0.25–1.0	0.43
	Amphotericin B	0.5–1.0	0.57
Dimorphic fungi			
B. dermatitidis (5)	Voriconazole	0.06–0.12	0.1
	Itraconazole	0.06	0.06
	Amphotericin B	0.12–0.25	0.14
H. capsulatum (5)	Voriconazole	0.06	0.06
	Itraconazole	0.06	0.06
	Amphotericin B	0.25–0.5	0.42
S. schenckii (5)	Voriconazole	8–>16	16
	Itraconazole	0.25–1.0	0.5
	Amphotericin B	0.5–2	1.5

[a] The MICs of voriconazole and amphotericin B correspond to complete (100%) growth inhibition, and the MICs of itraconazole correspond to prominent growth inhibition (approximately ≤50% of the growth control).
[b] Species tested included *Bipolaris hawaiiensis* and *Bipolaris spicifera.*

TABLE 4. Susceptibilities of 129 selected common pathogenic yeasts to voriconazole, fluconazole, itraconazole, and amphotericin B

Fungus (no. tested)	Antimicrobial agent	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
C. albicans (32)	Voriconazole	<0.03–4	0.06	0.5
	Fluconazole	0.12–>64	0.5	32
	Itraconazole	<0.03–1.0	0.06	0.5
	Amphotericin B	0.5–4	1.0	2
C. glabrata (14)	Voriconazole	0.06–4	0.5	4
	Fluconazole	4–64	16	64
	Itraconazole	0.5–>16	1.0	2
	Amphotericin B	1.0–2	1.0	2
Candida guilliermondii (8)	Voriconazole	<0.03–0.06	0.06	ND
	Fluconazole	0.5–8	2	ND
	Itraconazole	0.12–0.5	0.25	ND
	Amphotericin B	0.5–1.0	1.0	ND
C. krusei (12)	Voriconazole	0.12–0.5	0.25	0.5
	Fluconazole	16–32	32	16
	Itraconazole	0.12–1.0	0.5	1.0
	Amphotericin B	0.25–1.0	1.0	1.0
C. lusitaniae (17)	Voriconazole	<0.03–0.06	<0.03	0.06
	Fluconazole	0.12–4	0.5	2
	Itraconazole	<0.03–0.5	0.12	0.25
	Amphotericin B	0.25–2	1.0	2
C. parapsilosis (18)	Voriconazole	<0.03–0.5	0.06	0.25
	Fluconazole	0.25–8	2	2
	Itraconazole	0.03–0.5	0.12	0.25
	Amphotericin B	1.0–2	1.0	1.0
C. tropicalis (16)	Voriconazole	<0.03–>16	0.06	0.25
	Fluconazole	0.25–>64	1.0	32
	Itraconazole	0.06–>16	0.5	0.5
	Amphotericin B	0.5–8	1.0	1.0
Cryptococcus neoformans (12)	Voriconazole	<0.03–0.25	0.06	0.12
	Fluconazole	2–16	4	16
	Itraconazole	0.06–1.0	0.25	1.0
	Amphotericin B	1.0–2	1.0	1.0

[a] The MICs of voriconazole, fluconazole, and itraconazole correspond to prominent growth inhibition (approximately ≤50% of the growth control), and the MIC of amphotericin B corresponds to complete (100%) growth inhibition.

growth was sufficient (heavy growth) for MIC determination (24 to 72 h for yeasts and opportunistic molds and up to 5 to 7 days for the dimorphic fungi). With the aid of a reading mirror, growth in the control well (drug-free medium) was compared with that in each well. For fluconazole and itraconazole, the MIC was the lowest concentration showing prominent growth inhibition (approximately ≤50%); for amphotericin B, the MIC was the lowest concentration showing 100% growth inhibition (25). Both criteria were used for voriconazole.

Data analysis. MIC ranges were obtained for each species-drug combination tested. MICs for 50 and 90% of the isolates of each species tested (MIC_{50} and MIC_{90}, respectively) were determined for the common yeast species (≥10 isolates). Since the MIC ranges for the molds were generally narrow, geometric (G) mean MICs were determined to facilitate comparisons of the activity of the drugs.

RESULTS

With the exception of *B. dermatitidis* and *H. capsulatum*, all other isolates produced sufficient growth to determine MICs between 48 and 72 h. The MICs for *B. dermatitidis* and for *H. capsulatum* were determined on days 5 and 7, respectively.

QC and reference isolates. The MICs of voriconazole, fluconazole, itraconazole, and amphotericin B for the two NCCLS QC isolates *C. krusei* (ATCC 6258) and *C. parapsilosis* (ATCC 22019) and the control isolate *P. variotii* (ATCC 22319) are listed in Table 2. The MIC ranges for fluconazole, itraconazole, and amphotericin B were comparable to the expected ranges for the QC (25) and reference (9, 10) strains.

Susceptibility of the molds. Complete growth inhibition MIC ranges and G mean MICs of voriconazole and amphotericin B and prominent growth inhibition MIC ranges and G mean MICs of itraconazole for the 67 molds are summarized in Table 3. Based on these in vitro data, the activity of voriconazole was comparable to those of the other two agents against most of the species tested. The MICs of voriconazole were slightly less than those of itraconazole for *A. fumigatus* and *F. oxysporum*, and the MICs of itraconazole and amphotericin B were less than those of voriconazole for *R. arrhizus* and *S. schenckii*. By the less-stringent criterion (prominent growth inhibition; not shown in Table 3), the G mean MICs of voriconazole and itraconazole were ≤0.25 μg/ml for *Aspergillus* and *Bipolaris* species. Similarly, for *Fusarium* spp. and *P. boydii*, the G mean MIC of voriconazole was ≤0.35 μg/ml. In contrast, the G mean MICs of itraconazole were 0.76 μg/ml for *P. boydii* and >5 μg/ml for *Fusarium* spp. For *R. arrhizus* and *S. schenckii*, amphotericin B G mean MICs were ≤1.52 μg/ml, while voriconazole G mean MICs were ≥5 μg/ml.

Susceptibility of the yeast pathogens. Based on prominent growth inhibition MIC ranges and MIC_{50}s for the three azoles, the in vitro activities of voriconazole against common pathogenic yeasts were comparable to those of itraconazole and were superior to those of the other two antifungal drugs tested. For voriconazole, the MIC_{50}s ranged from <0.03 μg/ml for *Candida lusitaniae* to 0.5 μg/ml for *Candida glabrata*. In contrast, the MIC_{50}s of fluconazole and amphotericin B were 0.5 to 32 μg/ml and 1.0 μg/ml, respectively, for all of these pathogens. Examination of MIC_{90}s corroborated these comparisons (Table 4). Partial inhibition or trailing was observed when voriconazole was tested against *C. albicans* and *C. tropicalis*, and complete-inhibition MICs could not be determined for these two species. Otherwise, complete inhibition MICs (not shown in Table 4) for the other species were similar to the prominent growth inhibition endpoints.

Voriconazole in vitro results were also less than those of

TABLE 5. Susceptibilities of 60 emerging yeast pathogens to voriconazole, fluconazole, itraconazole, and amphotericin B[a]

Fungus (no. tested)	Antimicrobial agent	MIC range (μg/ml)	MIC_{50} (μg/ml)
B. capitatus (5)	Voriconazole	0.06–0.25	0.12
	Fluconazole	16–64	32
	Itraconazole	0.25–0.5	0.5
	Amphotericin B	1.0–2	1.0
Candida ciferrii (6)	Voriconazole	0.12–0.5	0.25
	Fluconazole	32–>64	64
	Itraconazole	0.5–2	1.0
	Amphotericin B	1.0–2	1.0
Candida famata (5)	Voriconazole	<0.03–1.0	<0.03
	Fluconazole	0.5–>64	2
	Itraconazole	0.06–0.5	0.12
	Amphotericin B	1.0–2	1.0
Candida kefyr (5)	Voriconazole	<0.03–0.06	<0.03
	Fluconazole	0.5–4	2
	Itraconazole	0.06–0.25	0.25
	Amphotericin B	0.5–2	1.0
Candida lambica (6)	Voriconazole	<0.03	<0.03
	Fluconazole	16–>64	32
	Itraconazole	0.06–0.25	0.12
	Amphotericin B	0.06–0.25	0.12
Candida lipolytica (5)	Voriconazole	<0.03–0.25	0.06
	Fluconazole	4–32	8
	Itraconazole	0.12–1.0	0.25
	Amphotericin B	1.0	1.0
Candida rugosa (5)	Voriconazole	<0.03–0.06	0.06
	Fluconazole	4–16	8
	Itraconazole	0.06–0.5	0.25
	Amphotericin B	1.0–2	1.0
H. anomala (5)	Voriconazole	0.12–0.25	0.25
	Fluconazole	2–4	2
	Itraconazole	0.25–1.0	0.5
	Amphotericin B	0.25–1.0	1.0
R. rubra (5)	Voriconazole	0.25–4	4
	Fluconazole	0.5–>64	>64
	Itraconazole	0.25–4	2
	Amphotericin B	0.5–1.0	0.5
S. cerevisiae (5)	Voriconazole	0.06–0.25	0.12
	Fluconazole	1–4	2
	Itraconazole	0.5–1.0	0.5
	Amphotericin B	0.5–2	1.0
S. salmonicolor (3)	Voriconazole	0.25–4	ND
	Fluconazole	8–>64	ND
	Itraconazole	1.0–2	ND
	Amphotericin B	0.5–1.0	ND
T. beigelii (5)	Voriconazole	<0.03–0.12	<0.03
	Fluconazole	1.0–2	2
	Itraconazole	0.06–0.25	0.25
	Amphotericin B	0.5–2	2

[a] The MICs of voriconazole, fluconazole, and itraconazole correspond to prominent growth inhibition (approximately ≤50% of the growth control), and the MIC of amphotericin B corresponds to complete (100%) growth inhibition. ND, not determined.

fluconazole, itraconazole, and amphotericin B for most of the emerging yeast pathogens tested. The MIC ranges for voriconazole were ≤0.03 to 1.0 μg/ml, with the exception of those for *R. rubra* and *S. salmonicolor* (MIC ranges of 0.25 to 4 μg/ml) (Table 5).

DISCUSSION

Voriconazole in vitro activities were higher than or similar to those of itraconazole and amphotericin B for most of the molds tested, with the exceptions of *R. arrhizus* and *S. schenckii* (Table 3). Despite differences in testing conditions, these results are generally consistent with the few previous comparisons of the in vitro activities of voriconazole to those of established agents against a similar spectrum of filamentous fungi. Mean MICs of voriconazole of 0.04, 0.25, and 2.18 μg/ml have been reported for *B. dermatitidis*, *Aspergillus* spp. and *P. boydii*, and *S. schenckii*, respectively (3, 22, 24). In the same studies, the respective MICs of itraconazole against these fungi were 0.15, 0.25, 1.09, and 0.70 μg/ml and those for amphotericin B were 0.07, 2, 16, and 0.92 μg/ml. The MICs of voriconazole for *Fusarium* spp. have been more variable in the different studies, with MIC ranges of 0.5 to 4 μg/ml (22, 28) and of 4 to 16 μg/ml in this report as well as in another study (3). When the species tested were reported, voriconazole in vitro results for *F. oxysporum* were slightly less than those for *F. solani* (28), as is also shown in Table 3. While the MICs of voriconazole for *Bipolaris* spp. (Table 3) are in agreement with a previous evaluation (28) with three strains of *Bipolaris australiensis* (MIC range of 0.25 to 2 μg/ml), the corresponding MICs of itraconazole were higher (MIC range of 0.06 to >64 μg/ml) than those for the species evaluated in this study. The activities of this agent against *H. capsulatum* and *R. arrhizus* have not been previously evaluated. Since there is very little information regarding the clinical relevance of in vitro data for the molds, these in vitro results should be validated in vivo.

This study also demonstrated that MIC endpoints for voriconazole were comparable to or less than those of the established agents for the common yeast pathogens, including some isolates for which the amphotericin B and itraconazole MICs were high (>2 μg/ml), as well as fluconazole-resistant (MICs of >64 μg/ml) and susceptible-dose-dependent (MICs of 16 to 32 μg/ml) *Candida* spp. strains (Table 4). Moreover, with the exception of *R. rubra* and *S. salmonicolor*, voriconazole in vitro activities were also higher than those of the established agents for the emerging yeast pathogens. Similar data have been reported for the common yeasts, but *C. lusitaniae* was not included in one study (4), and the other study evaluated only *C. albicans* (30). In the latter study, proportionally higher MICs of voriconazole were reported for fluconazole-resistant strains (MICs of >100 μg/ml) than for susceptible strains (MICs of <25 μg/ml) (30). This may suggest possible cross-resistance. Only three to six isolates per species of the emerging yeast-like pathogens were available for testing, because their association with human disease is rare. The antifungal activity of voriconazole has not been previously determined for these species (Table 5), with the exception of *Candida kefyr* (4). In addition, very little data regarding the activities of the established agents against these pathogens have been reported. Again, the suggested potential use of voriconazole against these yeast species needs to be elucidated.

The in vitro data obtained in this and other studies (3, 4, 22, 28, 30) suggest that voriconazole may be effective in the treatment of opportunistic fungal infections. Preliminary results from both preclinical and clinical studies support this suggestion. In a neutropenic guinea pig model of systemic aspergillosis, oral voriconazole (10 mg/kg of body weight per day) was significantly more effective than either itraconazole (10 mg/kg per day) or intravenous amphotericin B (4 mg/kg) on alternate days (18). These investigators also noted that voriconazole was significantly more effective than itraconazole in reducing *Aspergillus* content in the lungs of immunocompromised animals with pulmonary aspergillosis. In neutropenic guinea pigs with systemic candidiasis, voriconazole has been shown to be as effective as itraconazole and fluconazole and more effective than amphotericin B (31). Voriconazole also has been shown to be effective in guinea pigs with experimental pulmonary or intracranial infections caused by *C. neoformans* (17).

It has been shown that oral voriconazole (50 mg, administered once daily, or 200 mg, administered once or twice daily for 7 days) was clinically effective in 80 to 100% of HIV-positive patients with oropharyngeal candidiasis (31). Denning et al. (5) reported interim results from a clinical trial in which 71 patients with acute invasive aspergillosis were treated with intravenously administered voriconazole (6 mg/kg every 12 h [q12h] for two doses, followed by 3 mg/kg q12h for 6 to 27 days and by oral administration of 200 mg q12h for 4 to 24 weeks). Of 36 patients evaluated at the time of the report, 75% experienced satisfactory responses to voriconazole therapy and 25% failed treatment. Dupont et al. (8) evaluated the efficacy of orally administered voriconazole (200 mg q12h for 4 to 24 weeks) in 25 nonneutropenic patients with chronic invasive aspergillosis. Of the 13 patients evaluated at the time of the report, 69% had favorable responses to treatment. In contrast, 50% of the patients included in this trial had failed prior treatment with either itraconazole or amphotericin B.

The present results, animal studies, and limited clinical data suggest that voriconazole may be a potent agent for treatment of fungal infections due to both established and emerging yeast and mold pathogens. Further clinical trials will determine its efficacy in the treatment of human mycoses.

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