

A Randomized, Double-Blind, Double-Dummy, Multicenter Trial of Voriconazole and Fluconazole in the Treatment of Esophageal Candidiasis in Immunocompromised Patients

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The efficacy, safety, and tolerability of voriconazole and fluconazole were compared in 391 immunocompromised patients with mycology- and biopsy-proven esophageal candidiasis. Primary efficacy analysis (256 patients) of esophageal treatment as assessed by esophagoscopy revealed success rates of 98.3% with voriconazole and 95.1% with fluconazole. The 95% confidence interval for the difference in success rates ranged from -1.0% to 7.5%. The overall safety and tolerability of both antifungals were acceptable. Fewer patients discontinued voriconazole treatment because of insufficient clinical response (4 patients [2.0%] vs. 5 patients [2.6%]). More patients discontinued voriconazole than fluconazole treatment because of laboratory test abnormalities (7 patients [3.5%] vs. 2 patients [1.0%]) or treatment-related adverse events (5 patients [2.5%] vs. 1 patient [0.5%]). The most frequent adverse events (23%) with voriconazole were mild, transient visual disturbances. Voriconazole (200 mg, b.i.d.) was shown to be at least as effective as fluconazole in the treatment of biopsy-proven esophageal candidiasis in immunocompromised patients.

Oropharyngeal candidiasis is a frequent problem in patients receiving cytotoxic chemotherapy for malignancy [1] and is the most common opportunistic infection in individuals with AIDS, occurring in $\leq 90\%$ of pa-

tients at some stage during their illness [2]. *Candida* esophagitis may occur with or without concomitant oropharyngeal involvement and is generally associated with severe immunological impairment. Approximately 10%–15% of patients with HIV infection are reported to suffer from *Candida* esophagitis [3, 4], although some reports have put the incidence as high as 50% [2]. The introduction of highly active antiretroviral therapy (HAART) in the late 1990s has undoubtedly reduced the incidence of *Candida* esophagitis, but it remains a significant cause of morbidity in this population [5–7].

Because esophageal candidiasis is associated with severe morbidity and may be a focus of dissemination in some immunocompromised patients, prompt treatment with a systemic antifungal agent is essential [2].

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The study was conducted according to the revised Declaration of Helsinki (Hong Kong, 1989) and within the local laws and regulations relevant to the use of new therapeutic agents in each country of conduct. The study protocol was approved by the appropriate ethics review committee for the center concerned. Written, informed consent was obtained from all subjects before entry into the study.

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Intravenous amphotericin B is often poorly tolerated, and is reserved for patients with endoscopically proven disease where azole therapy is ineffective or contraindicated [8, 9]. The widespread use of less toxic lipid formulations of amphotericin B has been limited by their relatively high cost [10, 11]. Fluconazole is now an integral part of the clinical management of esophageal candidiasis, because it is well tolerated and is associated with a rapid onset of action and quick resolution of symptoms [12–14]. Recently, however, fluconazole-refractory oral candidiasis has emerged as an increasing problem [10, 15], and therapeutic failures have been reported in ~5% of cases of oropharyngeal or esophageal candidiasis in patients with advanced AIDS [16]. The increasing incidence of therapeutic failure is thought to be due to selection of intrinsically resistant strains, such as *Candida krusei*, and the emergence of fluconazole-resistant *C. albicans* infections [7].

The new triazole antifungal voriconazole has been shown to be 10- to 500-fold more potent than fluconazole against a broad-spectrum of fungal pathogens, including fluconazole-resistant *Candida* species and *Aspergillus* in vitro [17, 18]. It has also demonstrated in vitro activity against a wide range of *Candida* species isolated from immunocompromised patients with HIV infection [19] or hematological malignancy [20]. Moreover, clinical trials and case reports with voriconazole indicate that it has promising activity in the treatment of oropharyngeal candidiasis in AIDS patients [21], fluconazole-refractory infections [22, 23], and other serious fungal infections in immunocompromised patients [24–26].

The aim of this randomized, double-blind, double-dummy, multicenter study was to compare the efficacy, safety, and tolerability of voriconazole (200 mg, b.i.d.) and fluconazole (400 mg on day 1, followed by 200 mg, once daily) in the treatment of esophageal candidiasis in immunocompromised patients.

Table 1. Primary endoscopic outcome assessments analyzed by mycological findings.

Organism	Total ^a	Success ^b		Failure		Not evaluable	
		Vori	Flu	Vori	Flu	Vori	Flu
<i>Candida albicans</i>	354	132	141	5	9	42	25
<i>C. krusei</i>	4	1	2	0	0	1	0
<i>C. glabrata</i>	12	5	14	0	0	1	2
<i>C. parapsilosis</i>	1	0	1	0	0	0	0
<i>C. tropicalis</i>	1	0	1	0	0	0	0
Unspecified <i>Candida</i> species	20	9	4	0	0	5	2

NOTE. Flu, fluconazole; Vori, voriconazole.

^a >1 isolate per sample; *n* = 392.

^b Defined as "cured + improved."

METHODS

Patients

A total of 487 immunocompromised patients from 15 countries were screened for inclusion in this study. Patients were immunocompromised male or nonpregnant females, 18–75 years of age, and had a diagnosis of esophagitis based on clinical symptoms (dysphagia, odynophagia, retrosternal pain, nausea/vomiting) graded as "absent," "mild," "moderate," or "severe" at baseline (before antifungal administration on day 1), with or without concomitant oropharyngeal candidiasis. Esophageal candidiasis was confirmed by esophagoscopy, *plus* positive microscopy *and* mycological culture from a brush biopsy or tissue biopsy of esophageal lesions.

Mycology

Specimens from esophageal lesions were examined for *Candida* hyphae and yeast cells by direct microscopy and cultured on Sabouraud's dextrose agar containing chloramphenicol for 48 h at 30°C. Cultures were considered positive if ≥ 1 cfu was recovered. Microscopy, histopathology, and culture were performed at screening (days –2 to 0) and on day 43 or end of treatment (EOT) if this was earlier. Swabs were also taken from oropharyngeal lesions or from the mouth in the absence of obvious lesions at screening and on day 43/EOT, and microscopy and culture were carried out as described previously.

Biopsy materials were placed onto the surface of a Sabouraud dextrose agar plate containing chloramphenicol and incubated for at ≥ 48 h at 30–37°C. Swabs were wiped over the surface of a Sabouraud dextrose agar plate containing chloramphenicol and incubated for ≥ 48 h at 30–37°C. Cultures were subsequently stored at 4°C on Sabouraud dextrose agar slopes containing chloramphenicol until collected and analyzed for identification and susceptibility testing.

Susceptibility Testing

The methods used for identification and susceptibility testing were consistent with those of the National Committee for Clinical Laboratory Standards (NCCLS) method 27A, with the exception that RPMI was replaced by high-resolution medium [27].

Treatment

Patients who fulfilled the inclusion and exclusion criteria were randomized to treatment with a computer-generated randomization schedule using a 4-per-block design. Patients received either voriconazole (day 1: 400 mg voriconazole [1 × 200 mg tablet, b.i.d.] plus fluconazole placebo [4 × 100 mg capsules, once daily]; day 2 onward: 400 mg voriconazole [1 × 200 mg, b.i.d.] plus fluconazole placebo [2 × 100 mg, once daily]), or

Table 2. Success rates in the primary and secondary outcome efficacy analyses.

Category	Esophagoscopy EOT (per protocol; primary)		Symptoms EOT (ITT; secondary)	
	Voriconazole (n = 115)	Fluconazole (n = 141)	Voriconazole (n = 200)	Fluconazole (n = 191)
Cure	109 (94.8)	127 (90.1)	164 (82.0)	159 (83.2)
Improvement	4 (3.5)	7 (5.0)	12 (6.0)	15 (7.9)
Failure	2 (1.7)	7 (5.0)	12 (6.0)	12 (6.3)
Not evaluable	NA	NA	12 (6.0)	5 (2.6)

NOTE. Data are no. (%) of patients. EOT, end of treatment; ITT, intention-to-treat; NA, not applicable.

fluconazole (day 1:400 mg fluconazole [4 × 100 mg capsules, once daily] plus voriconazole placebo [1 × 200 mg tablet, b.i.d.]; day 2 onward: 200 mg fluconazole [2 × 100 mg, once daily] plus voriconazole placebo [1 × 200 mg, b.i.d.]).

Duration of therapy ranged from 2 to 6 weeks, depending on the severity of esophageal infection and the response to treatment. Treatment was continued for 7 days after resolution of all clinical signs and symptoms but was not allowed to exceed 42 days of therapy.

Efficacy Analysis

Primary efficacy outcome. The primary analysis of efficacy was based on the response to treatment as assessed by esophagoscopy on day 43 or EOT. The grade of esophageal candidiasis (0, no evidence of esophagitis; 1, a few raised white plaques ≤2 mm in size with hyperemia but no edema or ulceration; 2, many raised plaques >2 mm in size with hyperemia and edema but no ulceration; 3, confluent, linear, and nodular elevated plaques with hyperemia and ulceration; 4, as 3, with increased friability of the mucous membranes and occasional narrowing of the lumen) was compared to that at screening and categorized as “cured” (normal endoscopy), “improved” (abnormal endoscopy but improvement of ≥1 grade), or “failed” (no change or ≥1 grade deterioration in endoscopic appearance over screening). The primary efficacy analysis was performed on the per protocol (PP) and intention-to-treat (ITT) populations, where “success” was defined as esophagitis cured + improved as described elsewhere by Mel Cox et al. [28]. The ITT population included all patients who received ≥1 dose of their randomized study treatment. In addition, the PP population had to have no significant deviations to the inclusion/exclusion criteria.

Secondary efficacy outcome. The secondary analysis of efficacy was also determined on day 43 or EOT. These efficacy end points were (1) esophageal candidiasis success determined by symptomatic assessment; (2) oropharyngeal candidiasis suc-

cess determined by assessment of symptoms; and (3) time to clinical cure of esophageal candidiasis determined by symptomatic assessment. Symptoms were assessed relative to those at screening and categorized as cured (resolution of all symptoms), improved (improvement of ≥1 symptoms; no worsening of any symptom), or failed (worsening of any symptom or no change in all symptoms). For all secondary endpoints, success was defined as “symptoms cured + improved” compared with baseline.

Safety Evaluations

Safety assessments (hematology, clinical chemistry, urinalysis) were performed at screening, baseline, and on days 8, 15, 29, and 43/EOT and at follow-up (4 weeks after EOT). All adverse events or serious adverse events that occurred during treatment, or within 30 days of EOT, were recorded using the standard Coding Symbol Thesaurus of Adverse Reaction Terms dictionary. An ophthalmologist performed a full range of investigations, including visual acuity, contrast sensitivity, color perception, and fundoscopy, at baseline, day 43/EOT, and follow-up.

Statistical Analysis

The primary objective of this study was to demonstrate that voriconazole was not inferior to fluconazole. With an expected cure rate of 80% in each group, there was an 80% chance that the 2-sided CI for the observed difference in cure rates between voriconazole and fluconazole would have a lower limit of not less than -15% and an upper limit of >0. Thus, voriconazole was deemed to be not inferior to fluconazole if the lower limit of the approximate 2-sided 95% CI for the difference in success rates (patients cured + improved) between the 2 groups at EOT did not fall below -0.15 (-15%). All statistical analyses were performed using SAS [29]. Time to symptomatic cure in both treatment groups was assessed from Kaplan-Meier survival curves.

Table 3. Differences in success (cure + improvement) rates between treatments in the primary and secondary outcome efficacy analyses.

Analysis	Population	Vori, %	Flu, %	Difference, ^a %	95% CI for difference ^b
Primary					
EC success (esophagoscopy)	Per protocol (n = 256)	98.3	95.1	-3.2	(-1.0 to 7.5)
Secondary					
EC success (symptoms)	ITT (n = 391)	88.0	91.1	-3.1	(-9.2 to 3.0)
OC success (symptoms)	ITT, symptoms at baseline (n = 292)	88.4	93.8	-5.5	(-12.0 to 1.0)

NOTE. EC, esophageal candidiasis; Flu, fluconazole; ITT, intention-to-treat; OC, oropharyngeal candidiasis; Vori, voriconazole.

^a Voriconazole-fluconazole.

^b CI, unadjusted confidence interval. Lower limit to be compared with a noninferiority margin of -15%.

RESULTS

Patients and treatment. A total of 200 of the 487 patients screened were randomized to receive voriconazole, and 191 were given fluconazole. All randomized patients had a diagnosis of esophageal candidiasis, and 325 also had oropharyngeal candidiasis, 168 (84%) in the voriconazole group and 157 (82%) in the fluconazole group. The demographic characteristics of the 2 treatment groups, including esophagitis grade, use of antiretrovirals (including HAART), and the median duration of treatment (14 days for voriconazole vs. 15 days for fluconazole) was similar. In total, 368 patients (94%) had a diagnosis of AIDS. The remaining 23 patients had other underlying diseases, including hematologic malignancies and chronic obstructive pulmonary disease. Baseline CD4 cell counts were comparable between the 2 treatment groups. The majority of patients, 117 (58.5%) in the voriconazole group and 114 (59.7%) in the fluconazole group exhibited a CD4 cell count <50 cells/mm³. In contrast, only 23 (11.5%) patients in the voriconazole group and 25 (13.1%) patients in the fluconazole group had a CD4 cell count >200 cells/mm³.

Mycology. *C. albicans* was the most common pathogen isolated at screening: 179 patients (89.5%) and 175 patients (91.6%) in the voriconazole and fluconazole groups, respectively. *C. glabrata* and *C. krusei* were isolated from 6 and 2 patients in each group, respectively, and unknown *Candida* species were present in 14 (7%) voriconazole-treated patients and 6 (3.1%) fluconazole-treated patients. Most non-*albicans* species were associated with *C. albicans* (table 1).

Susceptibility testing. Susceptibility testing on the isolates from fluconazole-treated patients indicated that voriconazole MICs were 25- to 250-fold lower than those for fluconazole; however, they increased in parallel with the fluconazole MICs when assigned to the 3 NCCLS breakpoints for fluconazole. The voriconazole MIC ranges for fluconazole susceptible (S), susceptible-dose dependent (S-DD), and resistant (R) isolates were 0.006-0.19 µg/mL, 0.098-1.56 µg/mL, and 0.78-3.1 µg/mL, respectively. Three of the 9 isolates from patients treated with fluconazole who were classified as failures exhibited flu-

conazole MICs >50 µg/mL, compared to none in patients treated with voriconazole who failed. There was no correlation between MICs and clinical outcome for the voriconazole-treated patients. Patients successfully treated with voriconazole had MICs ranging from 0.006 to 1.0 µg/mL, whereas those who failed had MICs ranging from 0.012 to 0.098 µg/mL.

Primary efficacy analysis. In the PP analysis, 109 (94.8%) of 115 patients treated with voriconazole exhibited an endoscopically proven cure, compared with 127 (90.1%) of 141 patients in the fluconazole group (table 2).

The success rate (cured + improved) for esophageal candidiasis as assessed by esophagoscopy was 98.3% for voriconazole and 95.1% for fluconazole, with a difference of -3.2% (table 3). There were no significant treatment-by-country interactions, and the limits of the unadjusted (for country) approximate 2-sided 95% CI were -1.0% to 7.5%. Because the lower limit is above the predefined noninferiority margin of -15%, voriconazole can be considered to be not inferior to fluconazole.

There were no endoscopic failures in the patients with non-*C. albicans* infections treated with voriconazole or fluconazole; however, all *C. krusei* and *C. parapsilosis* and 7 of 12 *C. glabrata* isolates were recovered from patients in whom *C. albicans* was also isolated (table 1); it is therefore likely that most, if not all, of these non-*albicans* isolates were nonpathogenic.

In addition, 297 patients with esophagoscopy at EOT had a swab or brushing and underwent a mycological evaluation, regardless of their endoscopic findings. In this analysis, 127 (87.6%) of 145 patients treated with voriconazole demonstrated eradication, compared to 125 (82.2%) of 152 patients in the fluconazole group.

Visual inspection of the primary efficacy outcome data from the large subgroup of patients with advanced AIDS suggests that the efficacy of the 2 treatments is similar in those with a CD4 cell count <50 cells/mm³ (table 4). Similarly, according to primary outcome measures, the efficacy of the 2 drugs was similar regardless of the severity of the patients' esophagitis at baseline (table 5).

Secondary efficacy analysis. In the ITT analysis, 164 (82.0%) of 200 patients treated with voriconazole exhibited symptomatic cures, compared with 159 (83.2%) of 191 patients treated with fluconazole (table 2).

The success rate for the treatment of esophageal candidiasis assessed by symptoms was 88.0% of patients in the voriconazole group and 91.1% of patients given fluconazole. The overall difference in success rates for esophageal candidiasis symptoms was -3.1%, giving unadjusted 2-sided 95% CI limits of -9.2% to 3.0%. The lower limit is again lower than -15%, and voriconazole can be considered to be as effective as fluconazole (table 3).

The success rates for oropharyngeal candidiasis as assessed from resolution of symptoms were similar to those for esophageal candidiasis, with success rates of 88.4% and 93.8% for voriconazole and fluconazole, respectively (table 3). The difference in success rates was -5.5%, and the unadjusted approximate 2-sided 95% CI limits were -12.0% to 1.0%. The noninferiority of voriconazole was confirmed, because the lower limit was greater than -15%.

A follow-up visit was required 4 weeks after EOT. At this examination, response to antifungal therapy was based on symptomatic assessment. In the voriconazole group, 10 (5.7%) of 176 patients considered a success at the end of therapy relapsed, compared to 18 (10.3%) of 174 patients in the fluconazole group. There were no statistically significant differences in the time to symptomatic cure with a median time of 8 days in both groups, which corresponds with the first protocol-mandated visit (figure 1).

Safety evaluation. The analysis of adverse events was carried out on all 391 randomized patients. Although the number of patients who experienced adverse events during treatment was similar in each group (voriconazole, 159 patients [79.5%], vs. fluconazole, 141 patients [74%]), treatment-related adverse events were more frequent in those taking voriconazole (60 patients [30%]) than in those receiving fluconazole (27 patients [14%]). Most adverse events in both groups involved the special senses (e.g., sight, hearing, touch, etc.), digestive, metabolic, and nutritional body systems (table 6). Treatment-related visual adverse events, mainly mild enhancement or alteration of visual perception, were experienced by 36 patients (18%) taking voriconazole compared with 10 patients (5%) taking fluconazole. The visual adverse events observed were transient, disappearing without medical intervention either on continued dosing or after EOT. There was no report of long-term visual sequelae in any subject. In both treatment groups, 10 patients (5%) experienced abnormal vision that was not associated with the study drugs.

Of the 391 patients recruited, 132 patients (66%) in the voriconazole group and 135 patients (71%) in the fluconazole group completed the study. In the voriconazole group, 5 pa-

tients (2.5%) discontinued because of treatment-related adverse events, compared to 1 (0.5%) in the fluconazole group. Four of 5 treatment discontinuations in the voriconazole group were due to mild-to-moderate visual disturbances, and all resolved within a range of 1-10 days of stopping treatment. No treatment-related visual adverse event was assessed as severe. Increases of >3 times the upper limit of the normal range in aspartate transaminase (20% vs. 8%), alanine transaminase (11% vs. 7%), and alkaline phosphatase (10% vs. 8%) were more frequently observed in the voriconazole group than in the fluconazole group. Seven patients (3.5%) in the voriconazole group and 2 patients (1.1%) taking fluconazole discontinued because of laboratory abnormalities. Discontinuations in the voriconazole group involved transient, mild-to-moderate liver function test abnormalities or alkaline phosphatase elevations. Both of the 2 fluconazole-treated patients discontinued because of alkaline phosphatase elevations, which were >5 times the upper limit of the normal range. In the voriconazole group, 4 patients (2.0%) discontinued treatment because of insufficient clinical response compared with 5 (2.6%) in the fluconazole group.

DISCUSSION

In this comparative, noninferiority study, success rates of 98.3% and 95.1% were achieved with voriconazole and fluconazole, respectively, when a primary efficacy endpoint based on esophageal response as assessed by esophagoscopy was considered.

Table 4. Summary of esophageal candidiasis efficacy assessments by CD4 cell count.

Category, baseline ^a	Voriconazole	Fluconazole
Cure		
<50	82 (41.0)	90 (47.1)
50-200	29 (14.5)	33 (17.3)
>200	27 (13.5)	21 (11.0)
Improvement		
<50	6 (3.0)	7 (3.7)
50-200	2 (1.0)	1 (0.5)
>200	1 (0.5)	1 (0.5)
Failure		
<50	4 (2.0)	6 (3.1)
50-200	0 (0)	0 (0)
>200	1 (0.5)	3 (1.6)
Not evaluable		
<50	25 (12.5)	11 (5.8)
50-200	12 (6.0)	9 (4.7)
>200	11 (5.5)	9 (4.7)
Total	200 (100)	191 (100)

NOTE. Data are no. (%) of patients.

^a Baseline CD4 cell count, cells/mm³.

These results show clearly that voriconazole (200 mg, b.i.d.) is at least as effective as fluconazole (200 mg, once daily) in the treatment of microbiologically and histologically proven esophageal candidiasis in immunocompromised patients, including those with severe AIDS having a baseline CD4 count of <50 cells/mm³. These results support those of Troke et al. [21], who reported clinical efficacy of 97%–100% in AIDS patients with oropharyngeal candidiasis treated with voriconazole (200 mg, once daily or b.i.d.).

In the past few years there has been an increase in incidence of infections caused by fluconazole-resistant *C. albicans* strains and non-*albicans* species with high fluconazole MICs, especially in AIDS patients who have received extensive prior azole therapy or prophylaxis [15, 30–32]. In vitro studies indicate that voriconazole may be effective against these non-*albicans* isolates [17, 33]. In our study, the efficacy of voriconazole was not affected by the species distribution at baseline, and fewer patients taking voriconazole discontinued therapy because of an insufficient clinical response. These results support those of Ruhnke et al. [22] and Hegener et al. [23], who reported clinical cure with voriconazole (200 mg, b.i.d.) in 80%–100% of AIDS patients with esophageal candidiasis, even in those with end-stage AIDS and severe CD4 lymphocyte depletion [22, 23]. In our study, the number of non-*albicans* cases is too small to draw meaningful conclusions: most non-*albicans* species were associated with *C. albicans* and likely to be contaminants. The results indicate that voriconazole is similar in efficacy to the current gold standard. Further characterization of the safety profile of voriconazole and its effectiveness in treating esophagitis due to fluconazole-resistant *Candida* species will determine whether it should be considered as an effective alternative therapy.

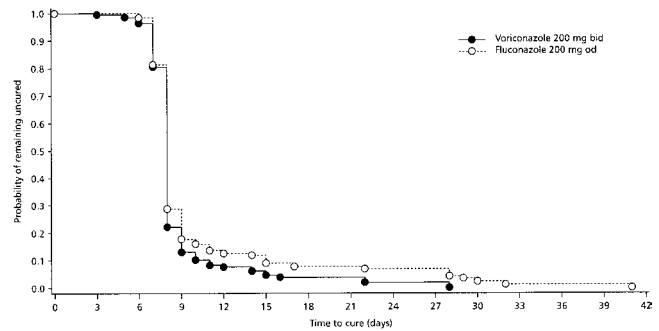


Figure 1. Time-to-clinical cure of esophageal candidiasis

In this trial, both antifungals had acceptable tolerability and safety, although there were more treatment-related adverse events with voriconazole than with fluconazole. Visual adverse events were reported more frequently with voriconazole, and no visual adverse events were assessed as severe. Mild, transient, visual adverse events, in particular enhanced brightness of light or blurred vision, have been reported elsewhere with voriconazole [21, 34, 35]. Similarly, in our study, the visual adverse effects were transient and reversible, often resolving while the patients were still receiving the drug. Comprehensive ophthalmological investigations conducted at the EOT suggest no long-term visual sequelae in any patient.

The higher incidence of liver function test abnormalities with voriconazole is consistent with the azole class. This is not unexpected, because pharmacokinetic studies in healthy volunteers have demonstrated that the main route of elimination of voriconazole is by metabolic clearance, with only 1% of the drug being excreted in the urine as unchanged compound [34].

The data from this study support previous experience with

Table 5. Summary of esophageal candidiasis efficacy assessments by baseline esophagitis severity.

Drug, treatment category	Esophagitis			
	Grade 1	Grade 2	Grade 3	Grade 4
Voriconazole				
Cure	20 (58.8)	72 (71.3)	34 (69.4)	11 (73.3)
Improvement	0	5 (5.0)	2 (4.1)	2 (13.3)
Failure	2 (5.9)	3 (3.0)	0	0
Not evaluable	12 (35.3)	21 (20.8)	13 (26.5)	2 (13.3)
Total	34	101	49	15
Fluconazole				
Cure	17 (68.0)	70 (82.4)	45 (71.4)	11 (64.7)
Improvement	0	2 (2.4)	4 (6.3)	3 (17.6)
Failure	1 (4.0)	6 (7.1)	1 (1.6)	1 (5.9)
Not evaluable	7 (28.0)	7 (8.2)	13 (20.6)	2 (11.8)
Total	25	85	63	17

NOTE. Data are no. (%) of patients, unless otherwise indicated.

Table 6. Number of patients with adverse events.

Adverse event	Voriconazole ^a (n = 200)	Fluconazole (n = 191)
Abnormal vision	45 (23)	15 (8)
Fever	24 (12)	16 (8)
Headache	10 (5)	13 (7)
Diarrhea	18 (9)	13 (7)
Vomiting	14 (7)	12 (6)
Elevated alkaline phosphatase	13 (7)	7 (4)
Nausea	12 (6)	12 (6)
Rash	11 (6)	10 (5)
Herpes simplex	10 (5)	6 (3)

NOTE. Data are no. (%) of patients.

^a Incidence >5%; all causality.

voriconazole in oropharyngeal and esophageal candidiasis published elsewhere [21, 22] and suggest that this new agent may be a useful alternative for the treatment these debilitating conditions. As voriconazole has been shown to be effective in patients with acute and chronic invasive aspergillosis who failed to respond to amphotericin B or itraconazole [35, 36], and fluconazole has been reported to have efficacy equivalent to that of amphotericin B in invasive candidiasis [37], clinical trials with voriconazole in patients with invasive candidiasis are underway.

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