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Micafungin (FK463), alone or in combination with other systemic antifungal agents, for the treatment of acute invasive aspergillosis☆

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Summary *Background:* Micafungin (FK463) is a new lipopeptide compound (echinocandin) with activity against *Aspergillus* and *Candida* species. This study evaluated the safety and efficacy of micafungin in patients with proven or probable invasive aspergillosis (IA).
Methods: A multinational, non-comparative study was conducted to examine proven or probable (pulmonary only) *Aspergillus* species infection in a wide variety of patient populations. The study employed an open-label design utilizing

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micafungin alone or in combination with another systemic antifungal agent. Criteria for IA and therapeutic responses were judged by an independent panel.
Results: Of the 331 patients enrolled, only 225 met diagnostic criteria for IA as determined by the independent panel and received at least one dose of micafungin. Patients included 98/225 who had undergone hematopoietic stem cell transplantation (HSCT) (88/98 allogeneic), 48 with graft versus host disease (GVHD), and 83/225 who had received chemotherapy for hematologic malignancy. A favorable response rate at the end of therapy was seen in 35.6% (80/225) of patients. Of those only treated with micafungin, favorable responses were seen in 6/12 (50%) of the primary and 9/22 (40.9%) of the salvage therapy group, with corresponding numbers in the combination treatment groups of 5/17 (29.4%) and 60/174 (34.5%) of the primary and salvage treatment groups, respectively. Of the 326 micafungin-treated patients, 183 (56.1%) died during therapy or in the 6-week follow-up phase; 107 (58.5%) deaths were attributable to IA.
Conclusions: Micafungin as primary or salvage therapy proved efficacious and safe in high-risk patients with IA, although patient numbers are small in the micafungin-only groups.

Introduction

Invasive aspergillosis (IA) is a life-threatening infection that often occurs in adults or children with significant immunosuppression, particularly related to neutropenia or corticosteroid treatment. The frequency of IA varies substantially from one risk group to another and by locality, but is perhaps most influenced by the diagnostic approach taken in any given unit. Recent examples of incidence in high-risk groups include acute myeloid leukemia (8%),[1] acute lymphocytic leukemia (6.3%),[1] autologous hematopoietic stem cell transplantation (HSCT) (1.5%),[2] allogeneic stem cell transplantation after non-myeloablative conditioning (11%),[3,4] allogeneic HSCT after myeloablative conditioning (15%; 11%),[5,6] lung transplantation (6.2%; 12.8%),[7,8] heart–lung and small bowel transplantation (11%),[1] liver transplantation (3%),[9] and acquired immunodeficiency syndrome (AIDS) (2.1%).[10] Increasingly, recognized risk groups include medical intensive care unit patients,[11,12] those with chronic pulmonary disease treated with corticosteroids,[13,14] those receiving anti-tumor necrosis factor monoclonal antibody therapy (such as infliximab),[15] and severe acute respiratory syndrome (SARS).[16] Mortality due to IA is high.[17–19] A review of 1223 cases reported crude mortality rates of 86%, 66%, and 99% for pulmonary, sinus, and cerebral aspergillosis, respectively,[17] with only occasional reports of improvement seen since, despite the introduction of new agents in the last 10 years.

Micafungin (FK463) is a new lipopeptide compound (echinocandin) synthesized through the chemical modification of a product from *Coleophoma empetri*.[20,21] Its antifungal activity resides at the cell wall as it inhibits the synthesis of (1,3)-beta-D-glucan. Pre-clinical studies indicate that micafungin has fungicidal activity against almost all *Candida* species, including azole-resistant *Candida albicans*, and kills the growing tips of *Aspergillus* species, like other echinocandins. The median minimum inhibitory concentration (MIC) values for *Aspergillus* species (including *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus*) were substantially lower than those of other non-echinocandins tested (ie, 0.0078 μg/mL compared with 0.5–2 μg/mL for amphotericin B), indicating the potential for greater clinical activity than itraconazole and amphotericin B in the same clinical isolates.[21] In murine models of IA (both *A. fumigatus* and *A. terreus*) micafungin was highly effective in preventing mortality (and superior to liposomal amphotericin B against an *A. terreus* infection), although cultures tend to remain positive in tissues.[22–25] A dose response from 1 mg/kg to 5 mg/kg was observed.[24] Micafungin has also been shown to confer synergistic activity to amphotericin B in vitro[26] and in murine aspergillosis models.[27–29]

Initial studies in male volunteers, adult HSCT recipients, and human immunodeficiency virus (HIV) patients indicated that micafungin was well tolerated over a wide range of doses.[30] The objective of the current study was to evaluate the safety and efficacy of micafungin, when administered alone or in combination with other systemic antifungal agents, in patients with proven or probable invasive infections due to *Aspergillus* species.

Methods

Study design

This study, utilizing two identical protocols with two exceptions (see below) (FG463-21-01 in Europe and protocol 98-0-046 in the rest of the world), was an open-label, non-comparative, multinational study in adult and pediatric patients enrolled from 1998 to 2002. Ethical approval was obtained from all 62 participating sites. The study was designed to demonstrate the safety and efficacy of micafungin in the treatment of acute IA that had failed to respond to prior therapy (labeled ''refractory''; inadequate response to, or failure of, $\geq$72 h of systemic antifungal therapy), or in patients who were unable to take alternative therapy because of adverse events associated with that therapy (labeled ''toxicity failure''). In addition, patients with newly diagnosed IA who had received $\leq$48 h of systemic antifungal therapy were eligible for enrollment. These patients were labeled ''primary''.

Inclusion/exclusion criteria

Adult and pediatric patients of any age, except premature neonates, with a proven or probable invasive infection due to *Aspergillus* species were enrolled. Only patients with pulmonary aspergillosis could be enrolled as probable cases. (In the European protocol, patients $<$18 years of age and patients classified as primary were excluded.) Proven IA was defined as either tissue from an infected site showing hyphae consistent with *Aspergillus* spp. with or without confirmatory culture from the same site, or as a positive culture from a sterile site (ie, percutaneous aspiration). Probable IA (only pertaining to pulmonary infection) was defined as clinical features of IA with either radiological features consistent with the diagnosis or a positive respiratory culture (sputum or bronchoalveolar lavage).

Patients were excluded from the study if they were pregnant or nursing; had markedly abnormal liver test parameters defined as transaminase $>10\times$ upper limit of normal (ULN), total bilirubin $>5\times$ ULN, or alkaline phosphatase $>5\times$ ULN; or had a life expectancy judged to be less than 5 days.

Dose and duration of treatment

Micafungin (Astellas Pharma US, Inc. [formerly Fujisawa Healthcare, Inc.], Deerfield, IL, USA) was administered intravenously in either an inpatient or an outpatient setting. Based on results of earlier studies,[31–33] patients received micafungin once daily as a 1-h infusion at an initial dose of 75 mg per day (1.5 mg/kg per day for patients weighing $\leq$40 kg). If there were continued positive culture findings, or if the patient experienced progression of disease or no improvement based on clinical signs and symptoms, and if micafungin was well tolerated, the dose of micafungin could be increased in 75 mg increments (1.5 mg/kg per day increments for patients weighing $\leq$40 kg) after at least 7 days of any dose of micafungin at the investigator's discretion. For patients enrolled in the non-European protocol, dose increases above 225 mg (4.5 mg/kg per day for patients weighing $\leq$40 kg) required the approval of the medical monitor. Dose escalation was not allowed above 200 mg per day for patients enrolled in the European protocol. Micafungin was administered intravenously for at least 7 days and up to a maximum of 90 days unless an extension was approved by the sponsor's medical monitor. Intermittent dosing of the same daily dose (a minimum of 3 days a week) was permitted after a response to micafungin was recorded, in the event daily therapy was no longer possible. The duration of follow-up post-treatment was 6 weeks.

Refractory patients could receive micafungin alone or in addition to their current systemic antifungal therapy, without alteration of dose or preparation, at the discretion of the investigator. If the patient was in the toxicity failure group, micafungin dosing was to commence after discontinuation of the previous systemic antifungal agent.

Drug safety assessment

Patients underwent blood collection for determination of clinical laboratory profile at baseline and at scheduled times during therapy, and at Week 6 following treatment. All adverse events through 72 h after the last administration of study drug, whether ascertained through patient interview, physical examination, laboratory findings, or other means, were recorded. Ongoing adverse events were followed for as long as necessary to adequately evaluate the patient's safety or until the event stabilized. Adverse events, coded using a modified Coding System for Thesaurus of Adverse Reactions Terms (COSTART) dictionary, were tabulated by patient group, age group, relationship to study drug, and intensity, and for those patients who discontinued study drug.

Independent data review

An independent review was conducted by three reviewers (DWD, TFP, KAM), with the objective of providing consistent assessments of the baseline diagnosis of IA and disease status on study entry for efficacy failure patients, the efficacy outcome following micafungin treatment, and the causality of death with regard to aspergillosis. Patients were classified as primary, efficacy failure (refractory), or toxicity failure. ''Primary'' patients received 48 h or less of prior antifungal therapy for the infection. Efficacy failure patients had infection that progressed or failed to improve while on therapeutic doses of systemic antifungal therapy for at least 72 h. Toxicity failure patients had significant renal or hepatic toxicity at the time micafungin was started. Furthermore, refractory patients were further categorized into two groups: patients who received micafungin in addition to their current antifungal therapy (combination therapy), and patients who received only micafungin (micafungin alone).

Outcome criteria

The primary endpoint was treatment success at end of therapy. Responses were categorized as complete response (CR), partial response (PR), stabilization (S) of disease, or failure (F), based on radiological, mycological, and clinical response, or failure. The criteria for response were identical to those used in evaluation of the response to caspofungin,[34] and two of the reviewers were common to both independent panels. A favorable response was defined as a complete or partial response. The reemergence of *Aspergillus* infection or a new fungal infection and the use of additional antifungal therapy during the 6-week post-treatment period were also assessed. The causality of death was assessed with regard to the *Aspergillus* infection.

Statistical methodology

Two analyses were pre-specified: all patients who received at least one dose of micafungin (full analysis set [FAS]) were included in the safety analysis, and a per protocol set (PPS) was defined as those patients who had proven or probable IA at baseline and had received at least seven doses of study drug. All patients who received at least one dose of study drug and who met the protocol-specified criteria as determined by the independent review panel were analyzed as a modified full analysis set (mFAS).

Treatment success rate was based on the global assessment of efficacy at the end of therapy following the independent review. A two-sided 95% confidence interval (CI) was constructed based on the large sample normal approximation of the binomial distribution. The primary endpoint was analyzed by key demographic variables and fungal infection risk factors. Selected laboratory data, including hematology and serum chemistry data, were tabulated by patient group (primary, efficacy failure micafungin and other, efficacy failure micafungin alone, and toxicity failure). Summary statistics for each assessment time and changes from baseline were generated.

Results

A total of 331 patients were enrolled in the study: 224 were from the United States, 38 from Germany, 17 from Brazil, 17 from Canada, 12 from the United Kingdom, seven from South Africa, five from France, four from Italy, three from Peru, two from Spain, and two from Sweden. Of these, 326 patients received at least one dose of study drug and were evaluated as the FAS. The PPS comprised 204 patients who had proven or probable IA infection at baseline and received at least seven doses of study drug. Of the 326 patients who received at least one dose of study drug, 101 were excluded because the diagnosis did not meet the protocol-specified criteria as determined by the independent review panel. The resultant 225 patients comprised the mFAS — patients who had proven or probable IA infection at baseline and received at least one dose of study drug.

The demographics of the patients enrolled (mFAS) are described in Table 1. Of note, 58 subjects were children (25.8%) and, of these, 27 (12.0%) were under the age of 10 years. The youngest patient enrolled was 3 months of age; the oldest was 82 years. Only 66 patients (29.3%) had profound neutropenia at enrollment, although 32.9% (74/225) had this as their primary risk factor for IA. Thirty-six of the 66 patients with profound neutropenia at baseline (54.5%) had recovery of neutropenia during treatment with micafungin, but the timing of recovery was not recorded systematically.

Within the mFAS group there were 29 patients with IA in whom micafungin was used as primary therapy. Among the mFAS, 192/225 (85.3%) patients were enrolled as refractory patients and four (1.8%) as toxicity failures. Of the 192 refractory patients, 153 (79.7%) had documented progression, 35 (18.2%) had stable disease at baseline, and four were indeterminate, as

Table 1 Patient demographics, baseline characteristics, underlying disease, and risk factors of modified full analysis set

	Primary		Refractory/toxicity failure[a]		Total ($N = 225$)	p-Values
	Micafungin in combination ($n = 17$)	Micafungin alone ($n = 12$)	Micafungin in combination ($n = 174$)	Micafungin alone $n = 22$)		
Demographics						
Gender						
Male	13 (76.5%)	9 (75.0%)	108 (62.1%)	13 (59.1%)	143 (63.6%)	
Race						
Caucasian	15 (88.2%)	9 (75.0%)	156 (89.7%)	19 (86.4%)	199 (88.4%)	
Age (years)						
Mean ± SD	33.6 ± 18.9	50.8 ± 16.6	34.3 ± 20.9	46.5 ± 18.5	36.1 ± 20.9	
Range	6–63	14–79	0.2–84.0	15.0–73.0	0.2–84.0	
$N < 16$ years	3 (17.6%)	1 (8.3%)	53 (30.5%)	1 (4.5%)	58 (25.8%)	
$N < 10$ years	3 (17.6%)	0	24 (13.8%)	0 (0.0%)	27 (12.0%)	
Neutropenia at baseline						
<500 cells/mm^3	5 (29.4%)	2 (16.7%)	56 (32.2%)	3 (13.6%)	66 (29.3%)	0.1665
Underlying conditions						
HSCT	6 (35.3%)	3 (25.0%)	83 (47.7%)	6 (27.3%)	98 (43.6%)	0.0704
Allogeneic	6 (35.3%)	3 (25.0%)	74 (42.5%)	5 (22.7%)	88 (39.1%)	
GVHD at baseline	2 (11.8%)	1 (8.3%)	41 (55.4%)	4 (80.0%)	48 (49.0%)	0.2454
Autologous	0	0	9 (5.2%)	1 (4.5%)	10 (4.4%)	
Chemotherapy						
Leukemia	6 (35.3%)	3 (25.0%)	62 (35.6%)	12 (54.5%)	83 (36.9%)	0.1917
Solid tumor	0	0	6 (3.4%)	0 (0.0%)	6 (2.7%)	
Solid organ transplant	2 (11.8%)	3 (25.0%)	6 (3.4%)	2 (9.1%)	13 (5.8%)	
Kidney	1 (5.9%)	0	0	0	1 (0.4%)	
Liver	0	1 (8.3%)	0	0	1 (0.4%)	
Lung	0	0	2 (1.1%)	2 (9.1%)	4 (1.8%)	
Heart	1 (5.9%)	2 (16.7%)	4 (2.3%)	0	7 (3.1%)	
COPD	0	0	3 (1.7%)	0	3 (1.3%)	
HIV/AIDS	1 (5.9%)	0	4 (2.3%)	1 (4.5%)	6 (2.7%)	
Others	2 (11.8%)	3 (25.0%)	6 (3.4%)	2 (9.1%)	13 (5.8%)	

HSCT = hematopoietic stem cell transplantation, COPD = chronic obstructive pulmonary disease, HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome, GVHD = graft versus host disease.

[a] Four patients who had failed previous therapy due to toxicities (increased creatinine) are included in the micafungin-alone group.

determined by the independent reviewers. Within the refractory group, a large proportion of patients (148/192 [77.1%]) had received a lipid preparation of amphotericin B for a mean duration of 23 days and mean daily dose of 6.09 mg/kg (Table 2). Many of these patients had received amphotericin B deoxycholate as well (86/192 [44.8%]). Itraconazole had been given to 66 patients (34.4%) for a mean of 47 days. Small numbers had received prior voriconazole (five), posaconazole (five), and caspofungin (seven).

Drug administration

For all adult patients (FAS), the mean daily dose of micafungin was 111.4 ± 50.97 mg per day (1.7 ± 0.82 mg/kg per day) with a median of 96.8 mg per day (1.5 mg/kg per day). Primary-treated patients tended to have higher mean daily doses (121.9 ± 64.9 mg) and a longer duration of therapy (mean 61.3 days). The mean duration of therapy was 53.6 ± 50.95 (range 7–284) days (median 35.0) in adults. At least one dose escalation step was made in 217 of 326 (67%) patients in the FAS group. For patients <16 years of age, the mean daily dose (2.1 ± 1.25 mg/kg) and the mean maximum dose (2.8 ± 1.70 mg/kg) on a mg/kg per day basis were both slightly higher than for adults (1.7 ± 0.82 mg/kg and 2.2 ± 1.17 mg/kg, respectively). The highest dose administered in a pediatric (<16 years of age) patient was 325 mg per day (8.6 mg/kg per day). Twelve pediatric patients received a dose of 4.0 mg/kg per day or higher, and five pediatric patients received a dose of 200 mg per day or higher. The overall mean duration of therapy was 92.7 ± 122.02 (range 7–681) days. Refractory patients had the longest duration of therapy (96.3 days).

Of the 225 patients in the mFAS, 191 received combination therapy. In all cases micafungin was added to the patient's existing (ie, failing) regimen.

Response to therapy

In the independent review, 121 of 326 patients (37.1%) in the FAS demonstrated a complete or partial response. However, detailed analysis of efficacy results are reported based on the mFAS as defined by the independent review panel (unless otherwise noted). A total of 35.6% of the patients achieved a favorable response, with an additional 11.1% of the patients experiencing stabilization of disease (Table 3). (A favorable response [CR + PR] was seen in 139/266 (52.3%), based on the investigator global assessment at end of therapy.) The highest rate of success was 75% (3/4), in the toxicity failure group. Importantly, 11/29 (37.9%) in the primary therapy group responded, five of 17 (29.4%) receiving combination therapy and six of 12 (50%) receiving micafungin monotherapy (Table 3). Just over one half of the patients (120/225 [53.3%]) experienced progression of their fungal infections on study. Favorable responses for patients only treated with micafungin (18 were refractory patients, 12 were primary patients, and four were toxicity failure patients) were seen in 44.1% (15/34). Favorable responses were observed in 30/96 (31.3%) patients in the mFAS who did not have at least one dose increase above the initial dose of 75 mg per day

Table 2 Refractory patients ($n = 192$)

Prior antifungal therapy	No. of patients	Duration of therapy (days)		Last dose administered (mg)	
		Mean	Range	Mean	Range
Amphotericin B (lipid) (mg/kg)	148	23	1–237	341.5 (6.09)	25–1425 (1.8–19.2)
Fluconazole	87	32	1–356	211.1	22–400
Amphotericin B (deoxycholate) (mg/kg)	86	16	1–130	54.2 (0.94)	9–110 (0.1–2.3)
Itraconazole	66	47	1–1786	299.7	30–800
Caspofungin	7	24	1–71	39.3	15–50
Voriconazole	5	57	12–144	326.4	72–700
Posaconazole	5	13	4–25	680	200–800
Flucytosine	3	7	4–9	3633.3	2000–6400
Terbinafine	2	35	29–41	625	250–1000

Note: Patients may have received more than one antifungal prior to enrollment.

Table 3 Efficacy at end of therapy

	Primary (%)		Refractory/toxicity failure[a] (%)		Total (%) ($N = 225$)
	Micafungin in combination ($n = 17$)	Micafungin alone ($n = 12$)	Micafungin in combination ($n = 174$)	Micafungin alone ($n = 22$)	
Complete response	2 (11.8)	0	13 (7.5)	3 (13.6)	18 (8.0)
Partial response	3 (17.6)	6 (50.0)	47 (27.0)	6 (27.3)	62 (27.6)
Favorable response	*5 (29.4)*	*6 (50.0)*	*60 (34.5)*	*9 (40.9)*	*80 (35.6)*
Stabilization	3 (17.6)	2 (16.7)	17 (9.8)	3 (13.6)	25 (11.1)
Progression	9 (52.9)	4 (33.3)	97 (55.7)	10 (45.5)	120 (53.3)
Not successful	*12 (70.6)*	*6 (50)*	*114 (65.5)*	*13(59.1)*	*145 (64.4)*

[a] Four patients who had failed previous therapy due to toxicities are included in the micafungin-alone group.

(1.5 mg/kg/day in patients <40 kg). Treatment success based on underlying disease, primary site of infection, and implicated species of *Aspergillus* is described in Table 4.

Sixty-six patients were neutropenic at baseline. Recovery of neutropenia was recorded in 36/66 (54.5%) patients, and the favorable response rate in this group was 50% (18/36) compared with 5/30 (16.7%) patients without neutrophil recovery. In all allogeneic HSCT patients a favorable response rate of 25.0% was achieved. Good response rates were also seen in chemotherapy-treated patients with leukemia or solid tumor (49.4%). Poor responses were seen in HIV/AIDS patients (16.7%). The response rate in children was 44.8% (26/58) overall and 44.4% (12/27) in children <10 years of age.

The independent reviewers attempted to assess what impact surgery might have made on the response. This assessment was based on the nature of the surgery, location of disease, and post-surgical findings. In the mFAS, 80 patients had invasive surgery, and reviewers considered it to have possibly had an impact in 27/80 patients (33.8%) who had a positive (non-lethal) outcome.

Adverse events

Adverse events that were considered by the investigator to be possibly or probably related to the study drug were reported for 104/326 patients (31.9%). Overall, the more common study of drug-related adverse events were bilirubinemia (4.3%), nausea (4.3%), vomiting (2.8%), increased serum glutamic pyruvic transaminase (SGPT) (2.8%), increased alkaline phosphatase (2.8%), diarrhea (2.1%), and hypertension (2.1%). A total of 78/326 (23.9%) patients who had an adverse event considered by the investigator to be related to study drug had at least one adverse event of moderate to severe intensity, and 10/326 (3.1%) patients had at least one adverse event that was considered to be life threatening. Treatment was stopped due to an adverse event in 85/326 patients (26.1%), including 17/70 children (24.3%). Adverse events considered related to study drug which lead to study drug discontinuation are described in Table 5.

Mortality

Of the 326 patients enrolled, 183 (56.1%) died during therapy or in the 6-week follow-up phase. Of these deaths, 107 (58.5%) were considered attributable to IA, 30 (16.4%) to another cause but with IA at death, and 18 (9.8%) to another cause without aspergillosis; 28 (15.3%) were of indeterminate cause. The more common primary direct causes of death were sepsis (24/326 [7.4%]), pulmonary mycosis (17/326 [5.2%]), shock (16/326 [4.9%]), non-fungal infection (15/326 [4.6%]), respiratory failure (14/326 [4.3%]), and relapsed malignancy (4/326 [1.2%]). Thirty-four patients died while on therapy, 18 (52.9%) due to IA; 149 patients died after micafungin treatment was stopped, 90 (60.4%) due to IA. However, most of these post-treatment deaths were in the week following micafungin discontinuation, and were related to decisions to withdraw support or institution of another (unsuccessful) antifungal treatment.

Ten patients died due to non-*Aspergillus* fungal infections, or a non-*Aspergillus* fungal infection contributed to the patient's death: five patients with mucormycosis, two with *Alternaria* sp., one with *Chaetomium* sp., one with *Scedosporium* sp., and one with invasive scopulariopsis. Two patients

Table 4 Treatment success

Status	Favorable response
Overall	80/225 (35.6%)
Efficacy failure group	
Prior progression ($N = 153$)	53/153 (34.6%)
Prior stabilized ($N = 35$)	11/35 (31.4%)
Indeterminate status ($N = 4$)	2/4 (50.0%)
Underlying disease/condition	
Stem cell transplant (HSCT)	25/98 (25.5%)
Allogeneic	22/88 (25.0%)
Autologous	3/10 (30.0%)
Chemotherapy[a]	44/89 (49.4%)
HIV positive or AIDS	1/6 (16.7%)
Solid organ transplant	6/13 (46.2%)
Others	3/17 (17.6%)
Primary site of infection	
Pulmonary	61/172 (35.5%)
Sinus only	5/11 (45.5%)
Disseminated	6/18 (33.3%)
CNS/brain	0/1 (0.0%)
Lung and sinus	2/11 (18.2%)
Skin	2/3 (66.7%)
Others	4/10 (40.0%)
Species of *Aspergillus*	
A. fumigatus	30/102 (29.4%)
A. flavus	15/31 (48.4%)
A. niger	1/8 (12.5%)
A. nidulans	2/4 (50%)
A. terreus	0/10 (0%)
A. versicolor	1/1 (100%)
A. flavipes	0/1 (0.0%)
A. fischerianus	0/1 (0.0%)
Aspergillus spp. not otherwise specified	34/80 (42.5%)

HSCT = hematopoietic stem cell transplantation; HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome; CNS = central nervous system.

[a] For hematological malignancy and solid tumor.

had multiple fungal organisms that contributed to their deaths: one patient with *Aspergillus* and *Rhizopus*, and one with *Aspergillus* and *Candida*.

Follow-up

A total of 145 patients in the mFAS were assessed during the 6-week follow-up visit. Of those patients, 47 (32.4%) had a complete or partial response.

Discussion

The study design was a prospective, open-label, non-comparative, multinational study. The study was initiated prior to the licensing of both voriconazole and caspofungin. Rarity of the disease usually hinders rapid patient accrual in this therapeutic area but, in fact, 331 patients were enrolled in less than 4 years in 62 centers. As a result, efficacy and safety information on a wide variety of *Aspergillus* species infections and patient populations was obtained. Although a previous trial with caspofungin, which enrolled 90 patients, has already been published,[34] this paper describes the largest therapeutic study to date of IA treated with an echinocandin. In the independent review, 80 of 225 patients (35.6%) in the mFAS demonstrated a complete or partial response to micafungin, comparable to the modified intent-to-treat result seen with caspofungin (44.6%).[34]

There is no consensus on the enrollment criteria for clinical failure (salvage) in acute IA. For instance, how many days of primary therapy are necessary before primary therapy can be considered a failure? Also, the variety of at-risk populations and extent of disease at presentation, including extrapulmonary dissemination in some, make a uniform definition suspect. Some patients have very extensive pulmonary infection at diagnosis, which is usually fatal, and so any worsening of disease is synonymous with death. Indeed in all prospective studies of acute IA, including this study, early deaths are a constant feature. Other patients have limited single or multifocal disease that typically responds well to treatment, even if enlarging in volume before shrinking.[35] In fact, most rapidly progressive pulmonary lesions do enlarge in the first few days of antifungal therapy,[35] making a realistic early determination of response difficult. Likewise, fever and other clinical signs often take several days before starting to resolve. In the present study, patients had to have had at least 3 days of antifungal therapy before enrollment. Most patients, however, were heavily pretreated. For example, the 148 patients in receipt of a lipid amphotericin B had actually received a mean of 23 days therapy at a mean dose of 6.09 mg/kg immediately prior to enrollment. Because of the heterogeneity of previous therapy, the extent and progressive nature of disease, and different underlying poor prognostic factors, a planned independent review placed patients into different categories to facilitate comparison with other studies.

One such category was primary treatment, and 11/29 (37.9%) in this group responded. Another category was efficacy failure or refractory patients. Unfortunately, for the purposes of analysis, only 18 patients in this group received

Table 5 Incidence of treatment-emergent adverse events related to study drug leading to study drug discontinuation[a]

	Primary[a] (%) ($n = 23$)	Refractory (%)		Toxicity failure[a] (%) ($n = 23$)	Total (%) ($N = 326$)
		Micafungin in combination[a] ($n = 257$)	Micafungin alone[a] ($n = 23$)		
Peripheral vascular disorder	0	1 (0.4%)	0	0	1 (0.3%)
Anorexia	0	1 (0.4%)	0	0	1 (0.3%)
Leukopenia	0	2 (0.8%)	0	1 (4.3%)	3 (0.9%)
Pancytopenia	0	1 (0.4%)	0	0	1 (0.3%)
Thrombocytopenia	0	1 (0.4%)	0	0	1 (0.3%)
Bilirubinemia	0	2 (0.8%)	0	0	2 (0.6%)
Creatinine increased	1 (4.3%)	0	0	0	1 (0.3%)
Arthralgia	0	1 (0.4%)	0	0	1 (0.3%)

[a] Subcategories are according to the investigator's assessment (not independent panel), and includes all patients (FAS).

monotherapy with micafungin, and 6/18 (33.3%) responded. These response rates compare with complete and partial response rates of primary therapy at 12 weeks with itraconazole of 31%,[36] amphotericin B deoxycholate of 23% and 32%,[37,38] amphotericin B colloidal dispersion of 18%,[37] and voriconazole of 58% and 53%[38,39] in heterogeneous patient groups. Variation in types of patients enrolled and response criteria applied can considerably alter rates of therapeutic success, but notwithstanding this inevitable variation, micafungin therapy compares favorably with the response rates shown with other agents, although larger studies are needed.

Among refractory/toxicity patients, 22 received only micafungin and 9/22 (40.9%) responded. This compares with response rates of 38% with voriconazole[39] and 39% with caspofungin,[34] as assessed by modified intention-to-treat analyses.

Combination therapy for IA has been much discussed, but there are few published data describing the use of combination therapy in human subjects.[40–44] Few data describing the use of micafungin as part of combination therapy are available, despite support from in vitro and in vivo studies.[25,45–48] The primary argument for considering combination treatment is to enhance overall response rates. Secondary arguments include increasing the antifungal spectrum in empiric therapy to encompass more pathogens including resistant fungi; realizing better pharmacodynamic parameters of one agent over another for certain body sites; preventing the development of resistance; and (possibly) being able to use reduced doses of one or both drugs without loss of activity while minimizing toxicity. During the time in which this study was performed, physicians were only likely to use combination therapy for very ill patients with a high mortality probability. That is probably what happened in this trial, as it was a physician's choice to add or substitute micafungin for refractory cases. Of the 202 amphotericin B-treated patients (36 amphotericin B deoxycholate + 166 lipid-associated amphotericin) treated with the combination of micafungin and an amphotericin preparation, 75 (37.2%) responded.

In the past, HSCT patients with IA have been reported to have very poor prognosis.[49] Even in the late 1990s, a 3-month clinical success rate of only 13% was suggested in a large survey for this patient population.[18] Favorable responses with micafungin, usually in combination with another agent, were seen in 22/88 (25%) allogeneic HSCT patients. In recent prospective studies with single drugs, caspofungin treatment yielded a salvage response rate of 14.3% (3/21)[34] compared with voriconazole and amphotericin B, as primary therapy, which had response rates of 32.4% (12/37) and 13.3% (4/30), respectively.[38] Data were not always available to evaluate detailed host risks that are known to impact prognosis of therapy, such as severity of graft versus host disease (GVHD), cumulative exposure to steroids, relapsed malignancy, or graft failure.

The initial dose of 75 mg per day of micafungin used in this study would now be considered a relatively low-treatment dose.[50] Nevertheless, among the 96 patients in the mFAS who did not have a dose increase above the initial dose of 75 mg per day (1.5 mg/kg in patients $<$40 kg), 30 (31.3%) responded. This initial dose of micafungin was partially effective regardless of patient group (primary versus efficacy failure/toxicity failure) or site/species of infection. Increasing the dose of micafungin was apparently effective in achieving

therapeutic responses in a number of patients. For those patients who had a dose increase, favorable responses were seen in 38.8% (50/129), including both primary and efficacy failure patients at mean daily doses exceeding 200 mg per day without significant toxicity.

Micafungin has proven efficacy in the treatment of esophageal candidiasis[31,50–52] and candidemia,[33,53,54] and in the prophylaxis of candidemia in patients undergoing HSCT.[55] This study demonstrated that micafungin, primarily in combination with amphotericin B, is efficacious in the treatment of acute IA in adult and pediatric patients who had failed to respond to prior therapy, or in patients who were unable to tolerate alternative therapy. Micafungin, alone and in combination with amphotericin B, was generally well tolerated. These results suggest that micafungin, either alone or in combination, is a viable option in the treatment of invasive aspergillosis. Randomized trials will be necessary to determine if combination therapy adds therapeutic benefit to one drug alone.

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