Drug Design, Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

# Review of the pharmacology and clinical studies of micafungin

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
9 December 2009
Number of times this article has been viewed

Alison M Bormann[1]
Vicki A Morrison[2]

[1]Division of Infectious Diseases, University of Minnesota, Minneapolis, MN, USA; [2]Division of Hematology/Oncology and Infectious Disease, Minneapolis Veterans Affairs Medical Center, Minneapolis, MN, USA

**Abstract:** Micafungin, like other members of the echinocandin class, has a unique mechanism of action that inhibits the synthesis of 1,3-β-D glucans in the fungal cell wall. It has been approved for treatment of esophageal candidiasis, invasive candidiasis including candidemia, and for prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation. Although efficacy and safety have also been demonstrated in pediatric populations, micafungin is approved for this indication in Europe and Japan, but not in the United States. It has demonstrated activity against *Candida* spp. including those that are azole-resistant as well as *Aspergillus* and a few other clinically important molds. It is administered intravenously as a once daily infusion and does not require dose adjustments for renal or moderate hepatic dysfunction. Its safety record, favorable tolerability profile, and few drug interactions make it an important agent for the treatment of invasive fungal infections.
**Keywords:** micafungin, antifungal therapy, echinocandins, fungal infections, *Candida*, *Aspergillus*

## Introduction

The echinocandins are the newest class of antifungal agents to be approved for the treatment of invasive fungal infections. Caspofungin was the first to gain approval followed by micafungin and then anidulafungin. These compounds have a unique mechanism of action targeted to the fungal cell wall; therefore their toxicity profile is quite favorable. They demonstrate potent activity *in vitro* and *in vivo* against all *Candida* species, as well as activity against *Aspergillus* species and select less common fungal pathogens, such as *Paecilomyces* and *Penicillium*. Of the echinocandin class, caspofungin has been approved for the broadest array of indications including invasive candidal infections, candidemia, empiric therapy in febrile neutropenia, and as salvage therapy for invasive aspergillosis. Micafungin has been specifically approved for candidemia, invasive candidal infections, and as antifungal prophylaxis prior to hematopoietic stem cell transplant. These drugs may be used as single agent therapy for these infectious processes and may be considered as a component of combination antifungal therapy for more serious yeast or mold infections. In this review, we will focus on micafungin, discussing the chemistry, mechanism of action, efficacy, pharmacology, and safety, with a particular focus on the clinical trial data with this compound.

Correspondence: Vicki A Morrison
Division of Hematology/Oncology and Infectious Disease, 111E, Veterans Affairs Medical Center, One Veterans Dr., Minneapolis, MN, 55417, USA
Tel +1 (612) 467-4123
Fax +1 (612) 725-2149
Email morri002@.umn.edu

## Chemical structure, mechanism of action, and resistance

Micafungin, formerly known as FK463, is a semisynthetic derivative of FR901370, a natural compound isolated from culture broth of *Coleophoma empedri*.[1] It is a water

soluble cyclic hexapeptide with a fatty acyl side chain, similar in structure to the other echinocandins.[2] Micafungin is a noncompetitive inhibitor of the formation of 1,3-β-D glycan synthase, an enzyme unique to fungi that is necessary for the production of 1,3-β-D glucan, which is an integral component of the fungal cell wall necessary to maintain cell shape and osmotic stability.[3] Micafungin exhibits fungicidal activity against *Candida* species (spp.), but is fungistatic against *Aspergillus* spp. This differential activity is potentially explained by wider distribution 1,3-β-D glucan in the cell wall of *Candida* spp. than that of *Aspergillus* spp. Micafungin, as well as the other echinocandins, exerts no activity against the zygomycetes and *Cryptococcus*, which lack 1,3-β-D glucan in their cell walls.[4]

The antifungal effect of micafungin on *Candida* spp. was studied by observing changes in cell morphology and structure using both light and electron microscopy.[5] After a short duration of exposure to micafungin, *C. albicans* cells showed abnormal swelling, irregular shape, and increased size by light microscopy, and deformation of contour, abnormal septum formation, and cell wall thinning especially at sites of active budding by electron microscopy. A lesser effect was noted on the cell membrane and cytomplasmic organelles. These results suggest that micafungin primarily affects normal cell wall formation in growing *Candida* cells. Similar studies with *Aspergillus fumigatus* revealed disruption of hyphal walls with eventual hyphal collapse and damage to membranous structures including the cell membrane, nuclear membrane, and endoplasmic reticula.[6]

Micafungin is also active against *Candida* biofilms and has demonstrated reduced adherence of both azole-susceptible and azole-resistant *C. albicans* strains to epithelial cells.[7] Another study showed comparable activity of micafungin to both biofilm and planktonic forms of *C. albicans* and *C. parapsilosis*.[8] These studies suggest that micafungin may have a role in treating *Candida* catheter-related infections, in which biofilm formation is pertinent to clinical infection. Micafungin also been enhances the oxidative burst effect of neutrophils in *in vitro* studies with *Candida* pseudohyphae.[9]

Acquired resistance or reduced susceptibility to micafungin and the other echinocandins has been reported only rarely, with the majority of cases associated with mutations in the FKS1 genes.[10,11] These mutations in *Candida* spp. lead to altered drug binding and thus cross-resistance to all echinocandins. No resistance data in *Aspergillus* species are available.

## Pharmacokinetics

Micafungin has a large molecular weight and is not well-absorbed orally. Pharmacokinetics of intravenous administration have been studied in healthy volunteers as well as ill patients with presumed/proven fungal infections. Micafungin exhibits a linear, dose-dependent relationship, with increasing doses resulting in proportionate increases in mean maximum serum concentrations ($C_{max}$) and area under the concentration (AUC)-time curve from 0 to 24 hours ($AUC_{0–24}$).[12] Similar linear kinetics have also been observed in pediatric patients.[13]

In healthy adult volunteers, a single 100 mg dose of micafungin has a mean half-life of 14.6 hours and is >99% protein-bound.[14] Micafungin is hepatically metabolized to inactive metabolites and is excreted primarily through the biliary system into the feces, with <1% excreted unchanged in the urine. Micafungin is not metabolized via the CYP450 system. When studied in patients with moderate hepatic dysfunction (Child–Pugh score 7–9), a significantly lower $AUC_{0–24}$, with no difference in the $C_{max}$, was found, as compared with healthy adults.[14] No differences in pharmacokinetics were found in patients with moderate renal dysfunction (creatinine clearance <30 mL/min).

## *In vitro* activity

Potent *in vitro* activity of the echinocandins has been demonstrated for most *Candida* spp. including those with high-level azole resistance.[1,15–17] In one study of 2000 *Candida* bloodstream isolates, most species (*C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. dubliniensis*) exhibited minimum inhibitory concentrations (MICs) of 0.03 to 0.06 μg/mL.[15] The MICs for *C. krusei* and *C. lustitaniae* were slightly higher (0.6–2.0 μg/mL), with *C. parapsilosis* having the highest MIC (1–2 μg/mL). Findings have been similar for *C. guilliermondii* (MIC 0.125 μg/mL).[1] In this latter study, azole-resistant strains demonstrated no cross-resistance to micafungin, and overall, the isolates had lower MICs to micafungin than to amphotericin B, fluconazole, and itraconazole. The Clinical and Laboratory Standards Institute (CLSI) has recently established susceptibility breakpoints for echinocandins against *Candida* spp. A MIC ≤ 2 μg/mL for all three echinocandin agents is classified as susceptible, and a value >2 μg/mL is considered non-susceptible.[18] Time-kill assays have also shown fungicidal activity for most *Candida* strains.[1,19] A post-antifungal effect has also been shown, and may be enhanced with higher drug concentrations.[19]

Micafungin also has potent *in vitro* activity against *Aspergillus* spp., including *A. fumigatus*, *A. flavus*, *A. niger*, *A. versicolor*, *A terreus*, and *A. nidulans*.[1,20] MIC ranges of 0.0078–0.0156 ug/mL have been reported against these *Aspergillus* spp., however standard susceptibility breakpoints

for the echinocandins against molds have not been established.[1] The minimum effective concentration (MEC), which is the minimum concentration noted to produce short and aberrant hyphal branching under the microscope, has been proposed as an alternative measure, and has been reported as ≤0.125 μg/mL for several *Aspergillus* spp., including *A. fumigatus*, *A. flavus*, *A. niger*.[20] *In vitro* activity has also been demonstrated against *Paecilomyces* and *Penicillium*,[21] as well as the mycelial forms of *Histoplasma capsulatum*, *Blastocystis dermatitidis*, and *Coccidiodes immitis*.[22] The clinical significance of the latter finding is unclear, as the yeast forms of the dimorphic fungi are the pathogenic forms implicated in causing human disease. Micafungin has no activity against *Cryptococcus*, *Trichosporon*, *Fusarium*, *Pseudoallescheria*, *Alternaria*, zygomycetes, or *Scedosporium*.[1,4,21]

## Clinical trials

Micafungin is approved for treatment of esophageal candidiasis, invasive candidiasis and candidemia, and for the prophylaxis of *Candida* infections in individuals undergoing hematopoietic stem cell transplant (HSCT). This drug has not been studied in candidal endocarditis, osteomyelitis, or meningitis. It also has been shown to have efficacy in the treatment of invasive aspergillosis, but it has not been approved for this indication. Although micafungin has been studied in both adults and children, in the United States it is currently approved for use only in adults. However, in Europe and Japan, it has a pediatric indication for treatment of invasive candidiasis, prophylaxis in HSCT, treatment of *Aspergillus* infections, and empiric therapy for febrile neutropenia.

### Esophageal candidiasis

The efficacy of micafungin for the treatment of esophageal candidiasis was established in an open-label, dose-range trial and two prospective, randomized, double-blind clinical trials. The first study to demonstrate efficacy of micafungin for the treatment of esophageal candidiasis was an open-label study to determine dosing and safety in 120 HIV patients with endoscopically proven esophageal candidiasis.[23] Patients were randomly assigned to receive 12.5 mg, 25 mg, 50 mg, 75 mg, or 100 mg of micafungin daily for planned treatment duration of 14 days. The primary endpoint was clinical response, defined by cure or improvement in clinical signs and symptoms, and the secondary endpoint was improvement in esophageal mucosal lesions. The efficacy analysis included 84 patients that had documented positive cultures for *Candida* and received at least 1 dose of study drug. A dose-dependent relationship was found, with clinical improvement seen with all doses, and those patients receiving 100 mg achieving a 95% cure rate. Patients receiving 75 or 100 mg had a 2- to 3-fold greater reduction in endoscopic mucosal lesions at the end of treatment as compared to the lower dose groups. Response was rapid, with most patients experiencing considerable improvement within the first 3 to 5 days. No serious renal, hepatic, or drug-related reactions were reported.

The efficacy of micafungin as compared to fluconazole for the treatment of esophageal candidiasis was established in 2 randomized, double-blind trials. In the first, 245 adult HIV patients with esophageal candidiasis confirmed by endoscopy and culture were randomized to receive either micafungin (50, 100, or 150 mg per day) or standard-dose fluconazole (200 mg per day) for 14 to 21 days.[24] The primary endpoint was endoscopic cure rate at the end of treatment. In the intent-to-treat analysis of 245 patients, the cure rate for micafungin was found to be dose-dependent, with the 50, 100, and 150 mg groups achieving cure rates of 69%, 77%, and 90%, respectively ($P = 0.024$). The cure rate for fluconazole was 87%. Overall, the endoscopic cure rates were similar between the combined micafungin 100 and 150 mg group (84%) and the fluconazole group (87%) (95% CI for the cure rate −14 to 7.7). Microbiologic cure was achieved in 35.1%, 78.3%, and 57.1% for the micafungin 50 mg, 100 mg, and 150 mg groups, respectively. Microbiologic cure was 67.3% in the fluconazole group. During the 2-week post-treatment period, 9 patients who had received micafungin were considered to have relapsed and either developed worsening symptoms or were treated with non-prophylactic doses of antifungal agents, although only 1 person experienced reversion to baseline clinical symptoms. No patients in the fluconazole arm experienced relapse. Adverse event rates were comparable among the two arms. In the second randomized, double-blind study, 523 predominantly HIV-positive adults with symptomatic and endoscopically confirmed esophageal candidiasis were randomized to micafungin 150 mg per day or fluconazole 200 mg per day, for a minimum of 14 days.[25] The primary endpoint was endoscopic cure. In the intent-to-treat analysis of 518 patients who received at least 1 dose of study drug, there was no difference in efficacy, with endoscopic cure rates of 88% in both groups (95% CI –5.9 to 5.3). Relapse rates through 4 weeks after treatment were also similar (15.2% in the micafungin arm, 11.3% in the fluconazole arm [$P = 0.257$]). There was also no difference in incidence of adverse events between the two groups. These studies

indicated that micafungin was safe and as effective as fluconazole for the treatment of esophageal candidiasis.

## Candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses

Micafungin has also been approved for the treatment of candidemia and other forms of invasive candidiasis. Micafungin was first studied for the treatment of candidemia in an open-label, noncomparative, international trial of 148 pediatric and adult patients.[26] Patients with newly diagnosed candidemia and less than 48 hours of prior antifungal therapy received micafungin, 50 mg/day for *C. albicans* infections and 100 mg/day for non-*albicans* infections. Pediatric patients weighing <40 kg received doses of 1 mg/kg/day for *C. albicans* and 1 to 2 mg/kg/day for non-*albicans* infections. Patients with refractory disease could also be enrolled if they had failed prior antifungal therapy (no response after at least 5 days of therapy), and received micafungin alone or in combination with their prior antifungal agent. The dose of micafungin could be increased in 50-mg increments (1 mg/kg in pediatric patients) after 5 days of therapy. Treatment duration was a minimum of 5 days and maximum of 6 weeks. The primary endpoint was complete or partial response at the end of therapy, based on the investigator's overall assessment of clinical and mycological response. The per-protocol set included 126 patients who received at least 5 doses of study drug, including 72 newly diagnosed patients and 54 refractory patients (25 receiving micafungin, 29 treated with combination therapy). The overall treatment success rate was 84% (105/126) including 88% (63/72) in the newly diagnosed patients, 76% (19/25) in refractory patients receiving monotherapy, and 79% (23/29) in refractory patients treated with combination therapy. Infections with non-*albicans* species occurred in 64% of patients. High success rates were seen in the most common *Candida* spp. including *C. albicans* (85%), *C. glabrata* (94%), *C. parapsilosis* (86%), *C. tropicalis* (83%), and *C. krusei* (64%). Overall, serious adverse events were rare and the drug was generally well tolerated. In this study, micafungin showed promising efficacy as therapy for newly diagnosed or refractory candidemia caused by both *C. albicans* and non-*albicans* species.

In another randomized, double-blind, multi-center, noninferiority trial, micafungin was compared to liposomal amphotericin B in the treatment of candidemia and invasive candidiasis.[27] A series of 531 adults with invasive candidal infections with positive cultures from either blood or another sterile site were randomized to receive micafungin (100 mg/day) or liposomal amphotericin B (3 mg/kg/day) for a minimum of 14 days. The primary endpoint was the overall treatment success rate based on both clinical and mycological responses. The per-protocol analysis group consisted of 392 patients who had a confirmed candidal infection and received five doses of the study drug. Treatment success was achieved in 90% (181/202) of the micafungin group and 90% (170/190) of the liposomal amphotericin B group (95% CI –5.9 to 6.2). Infections were caused by *C. albicans* and non-*albicans* species in both arms, and treatment success was comparable against all *Candida* species in both arms. There were fewer overall and serious adverse events reported in the micafungin group, with significant reductions in the rates of hypokalemia, elevated serum creatinine, and infusion-related reactions with micafungin as compared to amphotericin B ($P < 0.5$).

A second substudy was performed with pediatric patients (<16 years of age) with documented invasive candidiasis in which patients were randomized to treatment with either micafungin (2 mg/kg/day) or liposomal amphotericin B (3 mg/kg/day).[28] The primary endpoint was overall treatment success rate based on both clinical and mycological responses. By the similarly defined per-protocol analysis, treatment success was achieved in 85% (35/41) and 88% (37/42) of cases in the micafungin and liposomal amphotericin B groups, respectively (95% CI –16.4 to 12.7). Both therapies were well tolerated, with similar overall and serious adverse event rates. However, there were fewer adverse events leading to discontinuation of treatment in the micafungin group (3.8%) than the amphothericin group (16.7%) ($P = 0.05$). These studies demonstrated the safety and efficacy of micafungin for the treatment of invasive candidiasis in both adult and pediatric populations.

In a subsequent randomized, double-blind, noninferiority study, micafungin was compared to caspofungin for the treatment of candidemia or invasive candidiasis.[29] A total of 595 adults with documented candidemia or positive candidal culture from a sterile site were randomized to one of three therapies: micafungin 100 mg/day, micafungin 150 mg/day, or caspofungin, 70 mg on day one followed by 50 mg/day, all for a minimum 14 days of therapy. The primary endpoint was treatment success, defined as clinical and mycological success at the end of therapy. Efficacy data based on 578 patients with documented candidal infection who received at least 1 dose of study drug comprised the modified intention-to-treat analysis. Treatment success was achieved in 76% (146/191) of patients treated with 100 mg of

micafungin, 71% (142/199) of those receiving 150 mg of micafungin, and 72% (136/188) treated with caspofungin. Again, both *C. albicans* and non-*albicans* infections were studied, and the overall response rates were similar across all *Candida* spp. Adverse events were similar among all groups. The authors concluded that micafungin at a dose of either 100 or 150 mg/day was non-inferior to and as safe as caspofungin in the treatment of invasive candidal infections.

## Antifungal prophylaxis for hematopoietic stem cell transplant recipients (HSCT)

Micafungin has also been approved for antifungal prophylaxis for patients undergoing HSCT.[30] In a randomized, double-blind, comparative, phase III trial, 889 patients were randomized to micafungin 50 mg/day (or 1 mg/kg for body weight <50 kg) or fluconazole 400 mg/day (or 8 mg/kg for body weight <50 kg) for prophylaxis of invasive fungal infections. Prophylactic therapy was initiated by day 2 of the conditioning phase, and was continued until one of the following criteria was reached: day 5 after engraftment (defined as rise in absolute neutrophil count to >500 cells/mm$^3$), day 42 post-HSCT, development of a proven, probable, or suspected invasive fungal infection, or discontinuation due to adverse toxicity. The primary endpoint was treatment success, defined as the absence of proven, probable, or suspected systemic fungal infection at the end of prophylactic therapy, as well as the absence of proven or probable systemic fungal infection at the end of the four week post-treatment period. Median treatment duration was 18 days. The modified intention-to-treat analysis was based upon 882 of the 889 enrolled patients who received at least 1 dose of study drug. The overall treatment success rate was significantly higher with micafungin than with fluconazole (80% [340/425] vs 74% [336/457], respectively [$P = 0.03$]). Adverse events were similar among the two groups, although patients receiving micafungin tended to discontinue therapy because of adverse events less often (4%, as compared to 7% with fluconazole, $P = 0.058$). Although not statistically significant, there was an increased frequency of breakthrough proven or probable *Aspergillus* infections in the fluconazole arm compared with micafungin (7 vs 1 case, respectively, $P = 0.071$). One limitation of the study was that micafungin was continued only through 5 days after engraftment or for a maximum of 42 days, and patients were followed through day 28 post-treatment; therefore patients who develop late-onset, invasive mold infections would not be included. This was the first study to compare micafungin to fluconazole for antifungal prophylaxis for HSCT patients, and demonstrated the superior efficacy of micafungin, with comparable safety to fluconazole.

A recent Japanese study evaluated a higher dose of micafungin for the prevention of invasive fungal infections in HSCT recipients.[31] Micafungin, 100 mg/day, was administered to 44 HSCT patients for antifungal prophylaxis. These patients were then compared to 29 historical controls given prophylactic fluconazole 400 mg/day. The primary endpoint was treatment success, defined as the absence of proven, probable, or possible invasive fungal infection through day 21 post-HSCT. The median duration of treatment for micafungin and fluconazole were 36 and 34 days, respectively. The efficacy analysis included 41 patients receiving micafungin. Treatment success was achieved in 88% (36/41) of the patients receiving micafungin compared to 66% (19/29) of patients receiving fluconazole ($P = 0.038$). Although not a prospective, comparative, randomized trial, the 100 mg dose of micafungin for antifungal fungal prophylaxis in this population was shown to be safe and efficacious.

Another recent prospective, randomized, open-labeled study conducted in Japan compared micafungin 150 mg/day to fluconazole 400 mg/day for antifungal prophylaxis in 104 adult HSCT patients.[32] The primary outcome was treatment success, defined as the absence of proven, probable, or suspected invasive fungal infection at the end of therapy and the absence of proven or probable systemic fungal infection at the end of the 4-week post-treatment period. In the modified intention-to-treat analysis of the 100 patients who received at least one dose of study drug, the efficacy of micafungin was comparable to fluconazole with treatment success rates of 94% (47/50) vs 88% (44/50), respectively ($P = 0.295$). The number of patients requiring empiric antifungal therapy was 4% in the micafungin group compared to 12% in the fluconazole group. Although the study was small and not powered to measure differences in success rates, it suggested that 150 mg/day of micafungin was safe and had similar efficacy to fluconazole for HSCT antifungal prophylaxis.

# Alternative uses of micafungin

## Febrile neutropenia

Micafungin has also been studied in the treatment of febrile neutropenia that is unresponsive to empiric, broad-spectrum antibacterial therapy. Amphotericin derivatives have typically been the standard of care in this clinical scenario, although they may be associated with multiple adverse effects including electrolyte abnormalities, renal failure, and infusion-related reactions. Micafungin was studied in a prospective, non-randomized, open-label study at a

single center in Japan.[33] In this study, 31 adults with acute leukemia and febrile neutropenia were empirically started on broad-spectrum antibiotics. Indications for initiation of micafungin therapy were a positive fungal culture or serum assay for β-D glucan, persistent fevers after five days of antibiotic therapy, or recurrent fevers. Micafungin doses ranged from 50 to 150 mg/day, although three patients had doses of 200 or 300 mg/day. The primary endpoint was treatment success, defined as fever defervescence during the neutropenic period and cure of any baseline invasive fungal infections, if present. Treatment failure was defined as breakthrough fungal infection, discontinuation of micafungin because of adverse event or lack of efficacy, required addition of other antifungal drugs, or death from any cause. Therapy was continued until the absolute neutrophil count rose was >500 cells/mm$^3$ and the patient was afebrile for 48 hours. If the patient remained neutropenic, therapy could be discontinued if the patient was afebrile for at least five days and was clinically stable. Median duration of micafungin treatment was 9.5 days. The efficacy analysis included 18 patients who fulfilled the protocol criteria and received micafungin therapy. Treatment success was achieved in 78% (14/18) of the patients. Overall, most reported adverse events were minor and included elevated liver function tests, hypokalemia, and skin rash. Only one patient required drug discontinuation due to refractory hypokalemia.

In another prospective, open-labeled, single-center trial with the same inclusion criteria and primary endpoint, the efficacy and safety of micafungin for febrile neutropenia in hematologic malignancy patients was assessed.[34] The efficacy analysis included 23 of the 32 enrolled patients who fulfilled the inclusion criteria and received micafungin for a mean duration of 17.8 days. The overall treatment success rate was 74% (17/23). Micafungin doses ranged from 50 to 300 mg/day, and those treated with at least 100 mg/day tended to have a better outcome. Adverse events, specifically elevated liver function tests, were reported in 5 (22%) of patients, with none resulting in discontinuation of micafungin therapy. Although small, these studies suggested that micafungin may be safe as well as efficacious for empiric treatment of febrile neutropenia.

## Invasive aspergillosis

Micafungin has been studied in patients with chronic immunosupression or prolonged neutropenia who developed invasive fungal infection, including aspergillosis. In a prospective, open-label, multicenter Japanese trial, the efficacy of micafungin was evaluated in adults with deep-seated fungal infections, including pulmonary aspergillosis, chronic necrotizing pulmonary aspergillosis, pulmonary aspergilloma, candidemia, and esophageal candidiasis.[35] A total of 70 patients were enrolled and received micafungin 12.5 to 150 mg/day for up to 56 days. The primary endpoint was success in overall clinical response, based upon clinical, mycologic, and serologic response, and improvement in diagnostic imaging abnormalities. For the efficacy analysis, which included 54 patients who received at least 7 doses of micafungin, overall successful response rates were 60% (6/10) for pulmonary aspergillosis, 67% (6/9) for chronic necrotizing pulmonary aspergillosis, and 55% (12/22) for pulmonary aspergilloma. Therapy of candidemia and esophageal candidiasis was also successful, in 100% (6/6) and 71% (5/7) of patients, respectively.

Micafungin has also been studied alone and in combination with other antifungal agents for the treatment of invasive aspergillosis (IA) in a prospective, open-label, multinational, non-comparative trial.[36] Both adults and pediatric patients who met diagnostic criteria for proven or probable IA (only pulmonary aspergillosis could be considered probable) were enrolled. Of the 331 patients, 225 who met diagnostic criteria and received at least 1 dose of micafungin were analyzed as part of the modified full analysis set. The majority of patients had undergone HSCT, received chemotherapy for hematologic or solid tumor malignancies, or undergone solid organ transplantation. The primary treatment group consisted of patients who were newly diagnosed and had received <48 hours of antifungal therapy, while the salvage group consisted of patients who been treated for >72 hours and experienced disease progression or lack of improvement. Patients in both groups received micafungin, either as a single agent or in combination with other antifungal therapy. Patients received an initial micafungin dose of 75 mg/day (1.5 mg/kg for patients weighing <40 kg), which could be increased by 75 mg (1.5 mg/kg) increments after 7 days of therapy. The mean duration of treatment was 53.6 days. A favorable response at the end of therapy, defined as complete or partial response, was seen in 36% (80/225) of all patients. Of those receiving single agent micafungin, a favorable response was seen in 50% (6/12) of patients receiving primary treatment and 41% (9/22) in the salvage therapy group. The corresponding results for the micafungin combination therapy were 29% (5/17) in the primary treatment group and 35% (60/174) in those receiving salvage therapy. In this study, the use of micafungin was safe and showed promising efficacy.

The use of micafungin alone and in combination with other antifungal therapy was then examined in the subset

of 98 HSCT recipients with IA from this trial.[37] Patients were categorized as either newly diagnosed (<48 hours of antifungal therapy) or refractory disease after 72 hours of systemic antifungal therapy. The majority of patients received combination antifungal therapy. A partial or complete response was seen in 26% (25/98) of patients. Response rates were 38% (3/8) in the monotherapy group (1 newly diagnosed and 2 patients with previous antifungal toxicity with a favorable response), and 24% (22/90) in the combination group (1 newly diagnosed and 21 in the refractory group with a favorable response). The overall response rate was lower in this HSCT subset, likely related to high rates of graft vs host disease (GVHD), prolonged neutropenia, and more cases of refractory infection. Nonetheless, the use of micafungin was safe and provided some efficacy alone or in combination for the treatment of IA.

## Safety and adverse events

Overall, the use of micafungin has proven to be safe and well-tolerated, similar to the other echinocandins. Significant adverse events infrequently reported have included hypersensitivity and anaphylactic reactions, intravascular hemolysis and hemolytic anemia, and hepatic dysfunction with hyperbilirubinemia and/or acute hepatitis (package insert). The more common less severe side effects include diarrhea, nausea, and vomiting, as well as fever and electrolyte abnormalities. Lastly, a black-box warning for this agent has been issued in Europe, based upon an increased number of liver tumors observed in rat models. No such black-box warning has been included in the US label.

The pharmacokinetics, maximum tolerated dose, and safety of micafungin have been studied in several trials. In one series of 74 adult HSCT patients, antifungal prophylaxis consisted of fluconazole with either micafungin or placebo.[12] Micafungin, in doses ranging from 12.5 to 200 mg/day, was administered to 62 patients. The maximum tolerated dose was not reached, and adverse events were few in number. The most common side effects included headache (7%), arthralgias (7%), hypophosphatemia (4%), insomnia (4%), and rash (4%). Mean kidney and liver function tests were similar at the end of treatment in all groups, but 4 patients treated with micafungin had liver function tests 2.5 times the upper limit of normal (2 had elevated alanine aminotransferse levels and 2 had elevated total bilirubin). No interactions were detected between micafungin and fluconazole. A similar dose escalation study was conducted in 77 pediatric patients with febrile neutropenia.[13] In this study, micafungin was started at the onset of fever along with broad spectrum antibiotics, in doses ranging from 0.5 to 4 mg/kg. Nine (12%) patients experienced an adverse event thought to be related to the study drug which included headache (n = 2), diarrhea (n = 2), and vomiting (n = 2). Kidney and liver function tests again remained unchanged from baseline.

## Conclusion

Micafungin was the second drug in the echinocandin class approved in the United States and is active against *Candida* and *Aspergillus* spp. It has specifically been approved for use in treating esophageal candidiasis, invasive candidal infections and candidemia, and as anti-fungal prophylaxis prior to hematopoietic stem cell transplant in adult patients. Clinical trials have also demonstrated its efficacy in combination with other antifungal agents for the treatment of invasive *Aspergillus* infections. Although efficacy and safety has been demonstrated in pediatric populations, this agent is currently approved for the pediatric population only in Europe and Japan. Overall, micafungin has proven to be safe, well tolerated, and to have few drug interactions. Future direction should include additional studies for use alone and as a component of combination antifungal therapy for invasive and refractory mold infections.

## Disclosures

The authors declare no conflicts of interest.

## References


1. Tawara S, Ikeda F, Maki K, et al. *In vitro* activities of a new lipopeptide antifungal agent, FK463, against a variety of clinically important fungi. *Antimicrob Agents Chemother*. 2000;44(1):57–62.
2. Mikamo H, Sato Y, Tamaya T. *In vitro* antifungal activity of FK463, a new water-soluble echinocandin-like lipopeptide. *J Antimicrob Chemother*. 2000;46(3):485–487.
3. Kurtz MB, Douglas CM. Lipopeptide inhibitors of fungal glucan synthase. *J Med Vet Mycol*. 1997;35:79–86.
4. Nakai T, Uno J, Otomo K, et al. *In vitro* activity of FK463, a novel lipopeptide antifungal agent, against a variety of clinically important molds. *Chemotherapy*. 2002;48(2):78–81.
5. Nishiyama Y, Uchida K, Yamaguchi H. Morphological changes of *Candida albicans* induced by micafungin (FK463), a water-soluble echinocandin-like lipopeptide. *J Electron Microsc (Tokyo)*. 2002;51(4): 247–255.
6. Nishiyama Y, Hasumi Y, Ueda K, et al. Effects of micafungin on the morphology of *Aspergillus* fumigates. *J Electron Microsc (Tokyo)*. 2005;54(1):67–7.
7. Borg-von Zepelin M, Zaschke K, Gross U, et al. Effect of micafungin (FK463) on *Candida albicans* adherence to epithelial cells. *Chemotherapy*. 2002;48(3):148–153.
8. Kuhn DM, George T, Chandra J, et al. Antifungal susceptibility of *Candida* biofilms: unique efficacy of amphotericin B lipid formulations and echinocandins. *Antimicrob Agents Chemother*. 2002;46(6): 1773–1780.
9. Gil-Lamaignere C, Salvenmoser S, Hess R, et al. Micafungin enhances neutrophil fungicidal functions against *Candida* pseudohyphae. *Antimicrob Agents Chemother*. 2004;48(7):2730–2732.

10. Park S, Kelly R, Kahn JN, et al. Specific substitutions in the echinocandin target Fks1p account for reduced susceptibility of rare laboratory and clinical *Candida* spp. Isolates. *Antimicrob Agents Chemother*. 2005;49(8):3264–3273.
11. Laverdiere M, Lalonde RG, Baril J, et al. Progressive loss of echinocandin activity following prolonged use for treatment of *Candida albicans* oesophagitis. *J Antimicrob Chemother*. 2006;57(4):705–708.
12. Hiemenz J, Cagnoni P, Simpson D, et al. Pharmacokinetic and maximum tolerated dose study of micafungin in combination with fluconazole versus fluconazole alone for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. *Antimicrob Agents Chemother*. 2005;49(4):1331–1336.
13. Seibel NL, Schwartz C, Arrieta A, et al. Safety, tolerability, and pharmacokinetics of micafungin (FK463) in febrile neutropenic pediatric patients. *Antimicrob Agents Chemother*. 2005;49(8):3317–3324.
14. Hebert MF, Smith HE, Marbury TC, et al. Pharmacokinetics of micafungin in healthy volunteers, volunteers with moderate liver disease, and volunteers with renal dysfunction. *J Clin Pharmacol*. 2005;45(10):1145–1152.
15. Ostrosky-Zeichner L, Rex JH, Pappas PG, et al. Antifungal susceptibility survey of 2,000 bloodstream *Candida* isolates in the United States. *Antimicrob Agents Chemother*. 2003;47(10):3149–3154.
16. Pfaller MA, Boyken L, Hollis RJ, et al. *In vitro* susceptibility of invasive isolates of *Candida* spp. to aniduloafungin, caspofungin, and micafungin: six years of global surveillance. *J Clin Microbiol*. 2008;46(1):150–156.
17. Cuenca-Estrella M, Gomez-Lopez A, Mellado E, et al. Activity profile *In vitro* of micafungin against spanish clinical isolates of common and emerging species of yeasts and molds. *Antimicrob Agents Chemother*. 2009;53(5):2192–2195.
18. Pfaller MA, Diekma DJ, Ostrosky-Zichner L, et al. Correlation of MIC with outcome for *Candida* species tested against caspofungin, anidulafungin, and micafungin: analysis and proposal for interpretive MIC breakpoints. *J Clin Microbiol*. 2008;46(8):2620–2629.
19. Ernst EJ, Roling EE, Petzold CR, et al. *In vitro* activity of micafungin (FK-463) against *Candida* spp.: microdilution, time-kill, and postantifungal-effect studies. *Antimicrob Agents Chemother*. 2002; 46(12):3846–3853.
20. Arikan S, Yurdakul P, Hascelik G. Comparison of two methods and three end points in determination of *In vitro* activity of micafungin against *Aspergillus* spp. *Antimicrob Agents Chemother*. 2003;47(8): 2640–2643.
21. Uchida K, Nishiyama Y, Yokota H, et al. *In vitro* antifungal activity of a novel lipopeptide antifungal agent, FK463, against various fungal pathogens. *J Antibiot*. 2000;53(10):1175–1181.
22. Nakai T, Uno J, Ikeda F, et al. *In vitro* antifungal activity of micafungin (FK463) against dimorphic fungi: comparison of yeast-like and mycelial forms. *Antimicrob Agents Chemother*. 2003;47(4): 1376–1381.
23. Pettengell K, Mynhardt J, Kluyts T, et al. Successful treatment of oesophageal candidiasis by micafungin: a novel systemic antifungal agent. *Aliment Pharmacol Ther*. 2004;20(4):475–481.
24. de Wet N, Llanos-Cuentas A, Suleiman J, et al. A randomized, double-blind, parallel-group, dose-response study of micafungin compared with fluconazole for the treatment of esophageal candidiasis in HIV-positive patients. *Clin Infect Dis*. 2004;39(6):842–849.
25. de Wet NT, Bester AJ, Viljoen JJ, et al. A randomized, double blind, comparative trial of micafungin (FK463) vs fluconazole for the treatment of oesophageal candidiasis. *Aliment Pharmacol Ther*. 2005;21(7):899–907.
26. Ostrosky-Zeichner L, Kontoyiannis D, Raffalli J, et al. International, open-label, noncomparative, clinical trial of micafungin alone and in combination for treatment of newly diagnosed and refractory candidemia. *Eur J Clin Microbiol Infect Dis*. 2005;24(10):654–661.
27. Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. *Lancet*. 2007;369(9572): 1519–1527.
28. Queiroz-Telles F, Berezin E, Leverger G, et al. Micafungin versus liposomal amphotericin B for pediatric patients with invasive candidiasis: substudy of a randomized double-blind trial. *Pediatr Infect Dis J*. 2008;27(9):820–826.
29. Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin Infect Dis*. 2007;45(7):883–893.
30. van Burik JA, Ratanatharathorn V, Stepan DE, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis*. 2004;39(10):1407–1416.
31. Hashino S, Morita L, Takahata M, et al. Administration of micafungin as prophylactic antifungal therapy in patients undergoing allogeneic stem cell transplantation. *Int J Hematol*. 2008;87(1):91–97.
32. Hiramatsu Y, Maeda Y, Fujii N, et al. Use of micafungin versus fluconazole for antifungal prophylaxis in neutropenic patients receiving hematopoietic stem cell transplantation. *Int J Hematol*. 2008;88(5): 588–595.
33. Yanada M, Kiyoi H, Murata M, et al. Micafungin, a novel antifungal agent, as empirical therapy in acute leukemia patients with febrile neutropenia. *Intern Med*. 2006;45(5):259–264.
34. Toubai T, Tanaka J, Ota S, et al. Efficacy and safety of micafungin in febrile neutropenic patients treated for hematological malignancies. *Int Med*. 2007;46(1):3–9.
35. Kohno S, Masaoka T, Yamaguchi H, et al. A multicenter, open-label clinical study of micafungin (FK463) in the treatment of deep-seated mycosis in Japan. *Scand J Infect Dis*. 2004;36(5):372–379.
36. Denning DW, Marr KA, Lau WM, et al. Micafungin (FK463), alone or in combination with other systemic antifungal agents, for the treatment of acute invasive aspergillosis. *J Infect*. 2006;53(5):337–349.
37. Kontoyiannis DP, Ratanatharathorn V, Young JA, et al. Micafungin alone or in combination with other systemic antifungal therapies in hematopoietic stem cell transplant recipients with invasive aspergillosis. *Transpl Infect Dis*. 2009;11(1):89–93.