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REVIEW

Pharmacotherapy of Micafungin: Clinical Review

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Abstract: Micafungin is an echinocandin that inhibits the synthesis of 1,3-β-D glucan, an essential cell wall component of *Candida* species. Micafungin, at a dosage of 100 mg daily, has been shown to be as efficacious as liposomal amphotericin B and caspofungin for the treatment of candidemia and invasive candidiasis. It is one of three echinocandins that are recommended in the Infectious Diseases Society of America guidelines for management of candidiasis as first-line therapy for candidemia. Several randomized blinded treatment trials have shown that micafungin, at a dosage of 150 mg daily, is as efficacious as fluconazole for esophageal candidiasis in patients with AIDS. For prophylaxis in the immediate post stem cell transplantation period, micafungin, 50 mg daily, has been reported to prevent invasive candidiasis and diminish the risk for the development of aspergillosis. Micafungin has a very favorable safety profile with few adverse events and minimal drug-drug interactions.

Keywords: micafungin, echinocandins, fungal infection, *Candida*

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Introduction

Invasive candidiasis has remained an important cause of morbidity and mortality in the inpatient setting for a number of years. *Candida* spp. continue to be the fourth most common cause of bloodstream infections in hospitalized patients.[1] As fluconazole use has increased, there has been a concomitant increase in the incidence of invasive *Candida* infection with species resistant to azoles.[2,3] This trend has been observed globally with non-*albicans Candida* species isolated from 40% to 60% of clinical specimens in the intensive care unit setting in Europe.[4–6] The newer azole agents, voriconazole and posaconazole, exhibit cross-resistance with fluconazole for many species of *Candida*, most notably *Candida glabrata*. Amphotericin B has activity against most *Candida* species, but its use is limited by toxicity. Thus, a need has arisen for antifungal agents that have a more favorable toxicity profile and that are active against a broad range of *Candida* spp.

The other major group of fungi that has been increasingly noted in hospitalized patients is the moulds.[7] *Aspergillus* species cause the vast majority of invasive mould infections. The rise in the number of cases of invasive aspergillosis can be directly correlated with increasing numbers of markedly immunosuppressed patients, especially those receiving stem cell or solid organ transplants.[8] Given the high degree of mortality associated with invasive aspergillosis, additional antifungal agents that are effective against these organisms are urgently needed.

Micafungin (Mycamine® Astellas Pharma US) is an echinocandin that has activity against *Candida* spp. and *Aspergillus* spp. It is one of three echinocandins now available; the other two are caspofungin (Cancidas® Merck, Inc.) and anidulafungin (Eraxis® Pfizer, Inc.). Micafungin is a high molecular weight, water-soluble, semi-synthetic lipopeptide (Fig. 1) that was created by modifying the N-acyl side chain of a fermentation product of the fungus *Coleophoma emptri* F-11899. All echinocandins are available only as intravenous formulations.

Micafungin has been licensed for use for the treatment of candidemia, *Candida* peritonitis and abscesses, and esophageal candidiasis; it is also approved for prophylaxis against invasive candidiasis for patients undergoing stem cell transplantation. In this

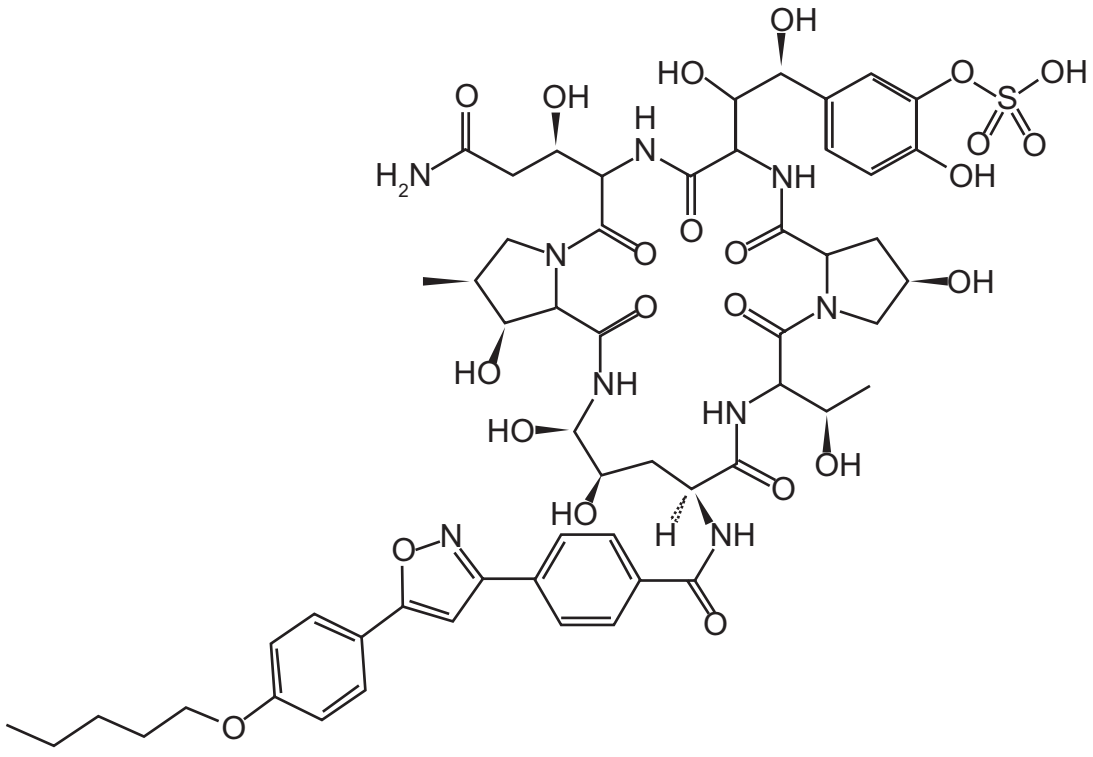

Figure 1. Micafungin chemical structure.

review, we will update what is known regarding the clinical pharmacology of micafungin, review the studies that led to its approval, and discuss the current role of micafungin in the treatment of invasive fungal infections.

In Vitro Activity

The echinocandins act in a concentration-dependent manner to inhibit 1,3-β-D-glucan synthase, an enzyme consisting of two subunits encoded by the genes *FKS1* and *FKS2*. This enzyme is responsible for the synthesis of 1,3-β-D glucan, an essential component of the cell wall of certain fungi. Thus, the spectrum of activity of the echinocandin class is limited to those fungi that have 1,3-β-D glucan as a critical component of their cell wall. Inhibition of the formation of this cell wall component leads to osmotic instability and lysis of susceptible organisms, such as *Candida* spp. for which echinocandins are considered fungicidal.

A minimum inhibitory concentration (MIC) ≤ 2 μg/mL is considered susceptible for all echinocandins.[9] Most *Candida* spp. are susceptible to micafungin; the overall average MIC_{50} is 0.015 μg/mL, which is the lowest noted with the available echinocandins.[10] Azole resistance does not confer cross-resistance to micafungin.[11] In a study evaluating 315 fluconazole-resistant *Candida* isolates from patients with invasive candidiasis, all demonstrated micafungin MICs ≤ 1 μg/mL.[12] Notably, *C. glabrata* isolates that are resistant to azoles retain susceptibility to echinocandins, including micafungin[13] Higher MIC values have been observed for *Candida parapsilosis* for all echinocandins. MIC_{90} values of 1 to 2 μg/mL are seen with almost all isolates of this species.[10] Other less common species such as *C. guilliermondii*, *C. lusitaniae* and *C. famata* also have higher MIC_{90} values that range from 0.25 to 2 μg/mL.[10]

The activity of echinocandins against filamentous fungi, such as *Aspergillus* spp. differs in that lysis of the organism does not occur, but rather inhibition of the elongation of the tips of the hyphae and growth of the cell wall. The echinocandins are therefore considered to be fungistatic for *Aspergillus* species.[14,15] This class of drug is not considered to be first line treatment for invasive aspergillosis, however it is occasionally used in combination therapy most commonly with voriconazole.[16,17] Randomized trials have not been performed to evaluate the effectiveness of this strategy.

Micafungin and other echinocandins are not active against moulds or yeast that do not contain 1,3-β-D glucan as a major part of their cell wall. For example, *Fusarium* spp., *Scedosporium* spp., *Cryptococcus* spp., and *Trichosporon* spp. are not inhibited by the echinocandins in vitro. There have been reports of patients developing breakthrough infection with *Cryptococcus neoformans* and with *Trichosporon* spp. while receiving therapy with micafungin.[18–20] Confirmation that a yeast isolated from blood cultures in a hospitalized patient is *Candida* and not *Crypto coccus* or *Trichosporon* is important when prescribing empiric therapy.

The zygomycetes have been shown to have measurable amounts of 1,3-β-D-glucan in their cell wall, but it is not a major component, and the echinocandins should not be considered as active agents against these organisms. A small single-center, retrospective study suggested that caspofungin administered in combination with an amphotericin formulation may be of clinical benefit in rhino-orbital-cerebral mucormycosis.[21] However, invasive zygomycosis has been observed to develop in a patient receiving therapy with micafungin.[22] Therefore, until further confirmatory studies are performed, micafungin does not appear to play a significant role in the treatment of these difficult to manage infections.[23]

Resistance

Resistance to echinocandins among *Candida* spp. is rare, but development of resistance as these agents are used more commonly is not unexpected.[24] In a study of over 5000 *Candida* isolates collected over 5 years, resistance to any of the echinocandins was extremely uncommon, and no isolates were found to be resistant to micafungin.[10] Although 100% of *C. parapsilosis* isolates had an MIC to micafungin of ≤2 μg/mL, 7.5% of isolates had higher MICs to anidulafungin. Overall, in multiple clinical trials, very few *Candida* clinical isolates have been found to be resistant to the echinocandins.[25,26] Resistance in clinical practice is mostly described in single case reports that have demonstrated resistance in *C. albicans, C. krusei, C. glabrata*, and *C. parapsilosis*.[27–33] In several cases, resistance was a class phenomenon, affecting

all echinocandins.[29,33] Other reports have described resistance to one echinocandin, but not others.[27,28] One example is a report of a man who had a relapse of *C. parapsilosis* prosthetic valve endocarditis while receiving caspofungin and fluconazole. The MIC for micafungin increased from 8 μg/mL to >16 μg/mL and for caspofungin from 2 μg/mL to >16 μg/mL. This same isolate retained susceptibility to anidulafungin.[27] From the same institution, a cluster of 23 *C. parapsilosis* isolates from patients in a burn unit showed resistance to micafungin (MIC_{50} = 8 μg/mL) but not caspofungin or anidulafungin (MIC_{50} = 1 μg/mL).[28]

Several mechanisms have been proposed for echinocandin resistance although only a few of these have been established in clinical isolates.[24] Mutations in the *FKS1* gene of the glucan synthase complex have been shown to increase caspofungin MIC values.[29,34] Substitutions at the *FKS1P* site have been shown to lead to echinocandin resistance in *Candida albicans* clinical isolates.[35] In an experimental construct, *FKS1* gene segments that were thought to confer decreased susceptibility to echinocandins in *Fusarium* and *Scedosporium prolificans* were transferred to *S. cervisiae*.[35] Up to an eight-fold decrease in susceptibility to micafungin was observed when certain "hot spot" segments were used. Mutations in the *FKS2* site of the glucan synthase complex have also been noted as a cause of resistance to caspofungin.[30] Increased expression of proteins that are responsible for transport of 1,3-β-D glucan to the cell surface, such as adenosine triphosphate-binding cassette transporters and golgi complex protein Sbe2p, have also been found to lead to decreased susceptibility to echinocandins.[36] Increased expression of drug efflux pumps which lead to azole resistance do not have an effect on echinocandins,[37] thus making this class ideal for management of azole-resistant *Candida* infections.

Pharmacology

Pharmacokinetics

Micafungin is not absorbed orally and must be administered by the intravenous route. In normal volunteers, the C_{max} after a 50 mg single dose was 4.95 μg/mL; the half-life was 11–17 hours, and the drug exhibited linear pharmacokinetics.[38] Protein binding is approximately 99%, and the drug is extensively bound to gamma globulin and HDL, but not to albumin.[39] Micafungin undergoes first pass degradation through the liver via hydrolysis and *N*-acetylation.[40] No significant effects on the cytochrome P450 enzymes, the P-glycopeptide transport system, or multidrug resistance protein 1 (MDR1) have been observed. Most of the drug appears to be eliminated in an unchanged form or as metabolites through the hepatobiliary system into stool.[41] Micafungin is also taken up by red blood cells.[40] Two metabolites of micafungin have antifungal activity but are detected at very low levels in plasma.[38] Less than 1% of active drug is excreted unchanged in urine.[42,43]

Pharmacokinetics in special populations

No dose adjustment is needed for patients with renal insufficiency.[44] Patients receiving continuous renal replacement therapy in the intensive care unit setting have been shown to not require dose adjustment.[45] There is no need to adjust the dosing for patients who have mild hepatic insufficiency,[44] but there are no recommendations available for patients who have severe hepatic insufficiency.

The pharmacokinetics in children appear to be linear.[46,47] However, children under the age of 9 years clear the drug more quickly than adults.[47,48] The latest recommendations are to use a dosage of 2–4 mg/kg in children under the age of 9 years and as much as 10–12 mg/kg in neonates.[49] No dosage adjustment is needed for older adults.

The echinocandins as a class are known to cross the placental barrier and can be found in the milk of lactating rats. They are classified as Pregnancy Category C and should be used only if the benefit justifies possible risk to the fetus. It is not known if these agents are found in human milk and what effects this might have on the child.

Tissue penetration

Micafungin is widely distributed after intravenous administration, but penetrates poorly into the central nervous system and ocular tissues. Rabbits administered micafungin, 2 mg/kg, showed peak plasma concentrations of 16.8 μg/mL, and drug was detectable at therapeutic levels in lung, liver, spleen, and kidney.[50] Concentrations in non-inflamed brain tissue were quite low at 0.08 to 0.18 μg/g, and the drug was undetectable in cerebrospinal fluid. Similarly low

concentrations of micafungin were found in the choroid and vitreous body. In a rat model using a dose of 1 mg/kg, there was rapid distribution to liver, kidney and lung when measured 5 minutes after infusion; tissue levels exceeded plasma concentrations throughout the dosing interval for up to 24 hours, and elimination occurred in parallel.[51] Lung penetration was studied in healthy human volunteers by measuring micafungin levels in lung fluid and alveolar macrophages. After steady state was achieved, micafungin was found to be concentrated in alveolar macrophages with levels up to 14.6 μg/mL versus 0.43 μg/mL in alveolar fluid at 24 hours.[52]

Drug-drug interactions

The echinocandins, as a class, have few drug-drug interactions. Micafungin is a mild inhibitor of CYP3A, but is not metabolized through the cytochrome P450 pathway nor is it substrate or inhibitor of P-glycoprotein.[53,54] In the licensing trials, there was no effect on cyclosporine, tacrolimus, prednisoline, fluconazole or voriconazole when micafungin was co-administered.[55] However, because of mild inhibition of CYP3A, further studies were performed to evaluate the effects of micafungin when given with calcineurin inhibitors, sirolimus, and nifedipine. In normal volunteers, it was found that micafungin had no significant effects on tacrolimus levels,[56] increased cyclosporine levels by only 16%,[56] and increased the AUC of sirolimus by 21% and of nifedipine by 18%.[55] It is therefore recommended that possible toxicity and levels of these drugs be monitored when co-administered with micafungin. Overall, the paucity of significant drug interactions is an attractive feature.

Toxicity

Overall, the echinocandins as a class are well tolerated. In general, very few drug related adverse events are observed in clinical practice. In a prospective study in Japan evaluating the effectiveness and safety of micafungin in patients with hematological malignancies and invasive fungal infections, 14% of patients were found to have a drug related adverse event.[57] The most common findings that were likely to be drug related were liver enzyme elevations (61/75 total adverse events). In other clinical studies, increased liver enzyme and bilirubin values were noted in <5% of various patient populations.[55] Histamine-mediated symptoms such as rash, facial swelling, and bronchospasm have been reported and seem to be related to rapid infusion in less than one hour. Autoimmune-mediated hemolysis with antibodies that cross react with micafungin and red blood cells has been reported in two patients with hematological malignancy that had received doses of 150 mg daily.[58] Acute pancreatitis related to micafungin was reported in one patient receiving 150 mg daily[59] and another receiving 200 mg.[60] In small studies of premature infants and neonates receiving doses from 0.75 mg/kg daily up to 15 mg/kg daily, no drug related adverse events were observed.[48,61] In adults, doses up to 8 mg/kg have been used with no drug related adverse events noted.[62] In general, since micafungin does not have a mammalian cell target and metabolism is minimal, drug toxicity has been observed uncommonly.

Clinical Use of Micafungin

Esophagitis

The earliest efficacy trials with micafungin assessed the usefulness of this agent to treat *Candida* esophagitis in patients with AIDS.[63–65] These studies took place in Africa and South America because so few patients were seen with *Candida* esophagitis in Europe and the United States after the introduction of highly active antiretroviral therapy.

An open label dose-finding trial from South Africa that used 12.5 mg, 25 mg, 50 mg, 75 mg, and 100 mg daily showed that a dose of 75 mg or greater daily for at least 10 days yielded a 100% clinical response rate. Of the 36 patients treated with 75 mg or 100 mg, 97% showed improvement in end-of-therapy endoscopic findings and 76% had endoscopic cure.[63]

Following this study, a randomized, blinded, non-inferiority treatment trial was undertaken to compare several dosages of micafungin with fluconazole for esophageal candidiasis in patients with AIDS.[64] A total of 245 patients were enrolled and received, in similar numbers, 50 mg, 100 mg, or 150 mg daily of micafungin, or 200 mg daily of intravenous fluconazole. Treatment was for 14 days, but could extend to 21 days if required. The primary efficacy endpoint was endoscopic cure (endoscopy grade = 0) at end of treatment. Overall, 199 patients received ≥10 days of drug, had endoscopy at baseline

and end of treatment, and were considered evaluable per protocol. The total group of 245 patients was evaluated in the intent-to-treat analysis. For the per-protocol analysis, the results showed a dose-dependent endoscopic cure rate for 50 mg, 100 mg, and 150 mg of micafungin of 71%, 92%, and 98%, respectively, and for fluconazole, 96%. For the intent-to-treat population, the rates for the same groups noted above were 69%, 77%, 90%, and 87%. Among all groups, approximately 50% were clinically improved by day 3 and 75% by day 7 of treatment. This study established that the cure rates for esophageal candidiasis with 100 mg or 150 mg micafungin were comparable to those for 200 mg fluconazole. Importantly, 9 patients who had been treated with micafungin and who had achieved an endoscopic cure had a relapse of clinical symptoms by the 2-week follow-up visit.

A subsequent randomized, blinded, non-inferiority trial enrolled 523 patients with esophageal candidiasis, of whom 94% had AIDS, and compared 150 mg micafungin daily to 200 mg intravenous fluconazole daily.[65] The results showed that micafungin was as effective as fluconazole; endoscopic cure rates were 88% for both groups, and clinical response rates were 94% for both groups. In this study, relapse rates 2 weeks after treatment ended were similar in the fluconazole and micafungin arms, 11% and 15%, respectively.

The reason for the higher relapse rates noted with the echinocandins in comparison to azoles in the de Wet report has not been explained,[64] but appears to be a class phenomenon. Relapse rates with the dosage of caspofungin that is approved for esophagitis (50 mg daily) are as high as 28%,[66] and for anidulafungin at 100 mg daily, as high as 36%.[42] Based on the results of the clinical trials noted above, the dosage of micafungin approved for use for *Candida* esophagitis is 150 mg daily for 14 days and is aimed at reducing the risk for relapse (Table 1). It should be noted that this is higher than the dosage recommended for treatment of candidemia and other invasive *Candida* infections.

Candidemia and invasive candidiasis

An initial open label, non-comparative international treatment trial that included salvage therapy for patients who had failed other therapy used a dosage of 50 mg daily for candidemia due to *C. albicans* and 100 mg daily for candidemia due to other *Candida* species, with the possibility to increase the dosage up to 200 mg daily if needed.[67] Approximately 40% of patients in this trial had failed other therapy, and about 50% of those were then treated with micafungin plus another agent. Excluding the latter group of patients, a total of 97 patients were analyzed as the per protocol group who were treated with micafungin alone for at least 5 days. Success, defined as clinical response and mycological cure, was found in 81 (83.5%). Success was higher (63/72, 87.5%) in the group that received micafungin as initial therapy compared with those that received micafungin as salvage therapy (19/25, 76%). Data are given only for the per-protocol group, and no information was supplied for efficacy in the intent-to-treat group of 148 patients. This is the only study that enrolled children as well as adults. Among the 20 children, 11 were neonates, 10 of whom entered the study for salvage therapy. The overall response rate among children was 75% compared with an overall response rate in all adults who received micafungin, with or without another agent, of 85%.

In a randomized, controlled, blinded international treatment trial conducted primarily in Europe, India, and Brazil, micafungin, 100 mg daily, was compared with liposomal amphotericin B, 3 mg/kg daily, for patients with candidemia or invasive candidiasis.[26] In the micafungin arm, 84% of patients were candidemic, and in the liposomal amphotericin B arm, 86%

Table 1. FDA approved Micafungin adult dosing schedule and indications.[55]

Indication	Daily dose	Length of therapy
Esophageal candidiasis	150 mg	14–21 days
Candidemia	100 mg	14 days after first negative blood culture
Disseminated candidiasis, *candida* peritonitis, abscess	100 mg	Treat until clinical and radiographic resolution
Prophylaxis after stem cell transplantation	50 mg	Treat until resolution of neutropenia

were candidemic. The non-candidemic infections included peritonitis, abscesses, disseminated infection without candidemia, endocarditis, and osteomyelitis. The primary endpoint of this study was designed to be the response at the end of therapy in those patients who had received at least 5 days of therapy with study drug. Using this per-protocol endpoint, the response rate for the 392 patients was 89.6% for micafungin and 89.5% for liposomal amphotericin B, and for those who were candidemic, 90.6% and 90.8%, respectively. However, this endpoint is not equivalent to those used in other treatment trials for candidemia, and these results should not be viewed as showing either micafungin or liposomal amphotericin B to be superior to other antifungal agents. Analysis of the modified intent-to-treat population of 494 patients revealed success rates at the end of therapy of 74% for micafungin and 70% for liposomal amphotericin B. These rates are similar to those found in other treatment trials of candidemia.

A randomized controlled blinded international treatment trial compared two doses of micafungin, 100 mg daily and 150 mg daily, with caspofungin, 50 mg daily.[25] This has been the only trial to compare the efficacy of two different echinocandins for candidemia and invasive candidiasis. In this study, which enrolled patients primarily from North America, approximately 85% of patients in all 3 arms were candidemic, and the remaining patients had peritonitis, abscesses, chorioretinitis, or disseminated infection without candidemia. Response rates for the modified intent-to-treat population who had received at least one dose of study drug were 71% for caspofungin, 73% for 100 mg micafungin, and 70% for 150 mg micafungin. For those patients who were candidemic, the success rates were 73%, 76%, and 74% respectively. Thus, micafungin was as efficacious as caspofungin, and 100 mg micafungin daily was as effective, or even slightly better, than 150 mg micafungin daily. Based on these data, the dosage of micafungin recommended for the treatment of candidemia and invasive candidiasis is 100 mg daily (Table 1).

Role of micafungin for treatment of *C. parapsilosis* infections

In the candidemia treatment trials, the question of efficacy of micafungin for *C. parapsilosis*, given its higher MIC values, has been addressed in subset analyses.[25,26,67] Overall, no statistically significant differences were noted when outcomes were analyzed for different *Candida* species. In the study reported by Pappas et al, in the modified intent-to-treat population, 50 patients in the two micafungin arms had *C. parapsilosis* infections, and the success rate for both arms combined was 74%, which did not differ from the overall success rate or the success rate for *C. albicans*. Kuse et al noted a success rate of 89% in 37 patients who had *C. parapsilosis* infections when the per-protocol population was analyzed, but did not give data for the modified intent-to-treat population. This rate of success did not differ from that reported for all species and for *C. albicans*. Finally, only 15 patients who received micafungin alone had *C. parapsilosis* fungemia in the open-label/salvage study reported by Ostrosky-Zeichner et al and 13 (87%) were successfully treated. Thus, the overall experience in this small number of patients (102 total), suggests that *C. parapsilosis* infections respond as well as infections with other *Candida* species to micafungin. In spite of these data, the IDSA guidelines for the management of invasive *Candida* infections recommend that fungemia due to *C. parapsilosis* be treated with fluconazole rather than an echinocandin.[49]

Non-candidemic invasive candidiasis

Treatment for non-candidemic forms of invasive candidiasis has not been studied in randomized treatment trials. The only data are those that are derived from subset analyses of the trials that primarily enrolled patients who had candidemia. In both large treatment trials discussed above, a total of 46 patients had peritonitis, 40 had disseminated infection without positive blood cultures, 30 had abscesses, and 11 had chorioretinitis. A handful of patients had endocarditis and osteomyelitis. In the two trials, the success rates for the non-candidemic patients overall were slightly lower than for those who were candidemic. For example, Kuse et al reported an overall success rate in the per-protocol non-candidemic patient population of 84% for the 32 cases treated with micafungin and 81.5% for the 27 cases treated with liposomal amphotericin B.[26] Pappas et al reported overall success rates of 79%, 53%, and 65% for non-candidemic patients treated with micafungin 100 mg daily, micafungin 150 mg daily, and caspofungin 50 mg

daily, respectively.[25] For peritonitis and abscesses, the success rate with micafungin 100 mg was 82%, for micafungin 150 mg, 69%, and for caspofungin, 57%. It appeared that micafungin 100 mg was better than either caspofungin or the larger dose of micafungin, but the numbers are too small to take away any meaningful conclusions.

Candida ocular and central nervous system infections

Candida eye infections occur during the course of candidemia in from 2% to 10% of patients.[68–70] The role, if any, that echinocandins should play in the treatment of *Candida* chorioretinitis, with or without vitritis, is of great interest to clinicians, but has not been systematically studied. Echinocandins are large molecules that are extensively protein bound and which would not be predicted to achieve an adequate intra-ocular concentration. Several studies have been performed in experimental animals. Rabbits administered micafungin, 2 mg/kg, showed peak plasma concentrations of 16.8 μg/mL, but the mean concentration in the choroid was only 0.162 μg/mL and in the vitreous body, 0.034 μg/mL.[50] In another rabbit model, detectable concentrations were found in the choroid only at intravenous dosages >4 mg/kg, but drug was not detectable in the vitreous body. In rabbits given 10 mg/kg of micafungin, retinal-choroid concentrations were as high as 20 μg/g, but no drug was detectable in the vitreous body.[71] The clinical relevance of this study is unclear because the dose that was given is approximately ten times the dose typically used in humans. Clinical failure with progressive endophthalmitis associated with documented low drug levels in the vitreous has been reported in a patient on caspofungin.[72] In contrast to the pharmacokinetic studies, in a neutropenic rabbit model of disseminated candidiasis, intravenous micafungin given at a dosage ≥1 mg/kg, was able to eradicate *C. albicans* from the vitreous body.[73]

Direct administration of micafungin into the vitreous has also been studied in a rabbit model of *A. fumigatus* endophthalmitis.[74] Intravitreal injections of 75 μg of amphotericin B, 150 μg of voriconazole, and 15 μg of micafungin were compared with saline control injections. Micafungin and amphotericin B preserved retinal function somewhat better than voriconazole. No significant toxicity was observed with intravitreal injection of micafungin. Similarly, topical administration of micafungin to the cornea has been shown to be non-toxic in rabbits.[75] Topical administration of a 0.1% solution of micafungin has been used successfully in 3 patients with post-operative *Candida* keratitis refractory to fluconazole and miconazole.[76] Further study is needed to determine if intravitreal and topical administration of micafungin is safe and effective.

In the clinical trial of candidemia reported by Pappas et al, 11 patients had chorioretinitis.[25] The overall rate of success was 64%, including 4/6 given 100 mg micafungin daily, 2/4 given 150 mg micafungin daily, and 1/1 given 50 mg caspofungin daily. No further information is available on the severity of retinal involvement, visual loss, or if vitreal extension was present. It is likely that patients with candidemia, many of whom are now treated with an echinocandin, have early *Candida* chorioretinitis and are cured with the standard therapy given for candidemia. However, this is conjecture and the role of echinocandins, including micafungin, for treating *Candida* eye infections is not established; these agents certainly should not be considered first-line therapy for this condition.

Meningitis caused by *Candida* is a rare complication of disseminated disease that is found most commonly in neonates. Rabbits administered micafungin, 2 mg/kg, had mean concentrations in non-inflamed brain tissue of 0.18 μg/g and undetectable concentrations in cerebrospinal fluid.[50] In a rabbit model of hematogenous *Candida* meningoencephalitis, micafungin was found to penetrate most CNS compartments only when administered at dosages >2 mg/kg, and maximal effects were seen at a dosage ≥8 mg/kg.[77] These authors postulated that neonates given micafungin at a dosage of 9 mg/kg would have equivalent serum concentrations to that of adults given 150 mg, and that this dosage or greater would be appropriate for neonates with *Candida* meningoencephalitis. Recent recommendations for micafungin dosing in neonates are to use 10–12 mg/kg daily.[49]

Fungal urinary tract infections

The echinocandins generally are not considered useful in the treatment of *Candida* urinary tract infections because these agents are not excreted into the urine as active drugs. For example, micafungin excretion in the urine as active drug is <1%.[78] Most urinary

tract infections are easily treated with fluconazole, which achieves high concentrations in the urine. However, *C. glabrata* infections respond poorly to therapy with fluconazole, and the use of echinocandins has been reported in a few patients with complicated urinary tract infections with this organism. Three patients in the caspofungin clinical trials database were reported to have responded to treatment with caspofungin for ascending *C. glabrata* urinary tract infection,[79] and 3 other patients were reported to have had a successful outcome when micafungin was used by other authors.[80,81] However, patients also have been demonstrated to have failed therapy with echinocandins.[82] In one patient with a complicated *C. glabrata* ascending urinary tract infection, failure was associated with the documented development of resistance to caspofungin (Malani, submitted for publication). For pyelonephritis and cystitis, in which tissue inflammation is prominent, echinocandins may achieve concentrations in the tissues, even though not measurable in the urine, that should be adequate to treat a *Candida* urinary tract infection. However, this remains conjecture and at this time, echinocandins, as a class, cannot be recommended for the treatment of *Candida* urinary tract infections.[83]

Prophylaxis after stem cell transplantation

Because micafungin has excellent activity against *Candida* species as well as activity against filamentous fungi and has a favorable toxicity profile, it is an attractive candidate for use in antifungal prophylaxis in the neutropenic period after stem cell transplantation. In a multi-center randomized, double blind study, 882 adult and pediatric patients received either 50 mg of micafungin or 400 mg of fluconazole during the pre-engraftment phase after bone marrow transplantation.[84] Of the patients who received micafungin, 80% had a successful outcome versus 73.5% in the fluconazole arm ($p = 0.03$). Success was defined as lack of invasive fungal infection through the prophylaxis period and for 4 weeks after the completion of therapy. In the micafungin arm there were three patients who developed candidemia with *C. lusitaniae*, *C. albicans*, and *C. parapsilosis* while on therapy, and one case each of breakthrough infection with *Aspergillus*, *Fusarium*, and a zygomycete. In the group that received fluconazole, two patients developed breakthrough candidemia with *C. krusei* and *C. parapsilosis*. The main difference in outcomes was the excessive number of infections with filamentous fungi that developed in patients who received fluconazole. There were 7 cases of proven or probable aspergillosis and 2 cases of invasive infection with *Fusarium* in this group. Therefore, in this study, micafungin was found as effective or even superior to fluconazole for prophylaxis after stem cell transplantation.

Two other studies performed in Japan had similar findings. In one prospective randomized trial, 106 adult patients received either 150 mg of micafungin or 400 mg of fluconazole.[85] Of the 52 patients that received micafungin, 94% had a successful outcome as defined as lack of invasive fungal infection versus 88% of 52 patients who received fluconazole. The overall incidence of breakthrough infection was very low in this study with no cases of breakthrough candidemia. Only one case of breakthrough aspergillosis in the fluconazole arm, and one case of infection with *Trichosporon* spp. was documented in the micafungin arm. The other infections that were reported were considered only "probable".

In a second study by a different group, 41 patients received 100 mg of micafungin as prophylaxis after stem cell transplantation, and their outcomes were compared with historical controls who received fluconazole. Because of the historical nature of the study, the results are more difficult to interpret; 87.8% of patients in the micafungin group did not develop an invasive fungal infection versus 65.5% in the fluconazole group. Although both of these studies are less robust, they support the use of micafungin for prophylaxis in the immediate post-stem cell transplantation period.

Aspergillosis

Micafungin is not FDA approved for use in the treatment of infection with *Aspergillus*; however, a few studies have been performed to evaluate efficacy and dosing. The largest of these studies had a multi-national enrollment of 331 patients, of whom 225 in the modified intent-to-treat group fulfilled enrollment criteria of having proven or probable invasive aspergillosis and having received at least one dose of study drug. Patients were treated with micafungin alone or in combination with other antifungal agents. An initial starting dose of 75 mg was used with a dose escalation scheme

for patients with refractory or progressive disease. For adult patients in the study the mean daily dose used was 111.4 ± 50.97 mg per day.[86] A complete or partial response rate was reported in 80/225 (35.5%) of patients in the modified intent-to-treat group. Only 29 patients of the 225 received micafungin as primary therapy, and 11(37.9%) responded favorably. Of the 18 patients who received micafungin alone for salvage therapy, 6(30.3%) responded. Most patients received micafungin in combination with another agent, usually an amphotericin B formulation. These small numbers make it difficult to evaluate the efficacy of micafungin as a single agent for treatment of invasive aspergillosis.

A prior smaller study performed in Japan evaluated 10 patients with invasive pulmonary aspergillosis, one with disseminated aspergillosis, 9 with chronic necrotizing aspergillosis, and 22 with pulmonary aspergilloma treated with micafungin alone. Dose escalation up to 150 mg was performed in this study. Of the 13 patients who received the maximal dose, 9 responded favorably to therapy.[87] Clearly, further study is needed to define the optimal dosing and efficacy of micafungin for the treatment of invasive aspergillosis.

Role of Micafungin in Treating Fungal Infections

Micafungin has become an important agent for the treatment of critically ill patients with candidemia, peritonitis or abscesses due to *Candida* spp., and acute disseminated candidiasis. It has activity against virtually all *Candida* spp. After initial therapy, if *C. glabrata* is isolated, ongoing treatment with an echinocandin, such as micafungin, is warranted because of frequent azole resistance of *C. glabrata*. If a fluconazole-susceptible organism is isolated, step down therapy to oral fluconazole is recommended, and if *C. parapsilosis* is isolated, most clinicians prefer to use fluconazole.

For the treatment of esophagitis, fluconazole, which can be given orally, is first-line therapy. Micafungin is a second-line agent that is used mostly for treatment of patients who fail azole therapy because of resistance or intolerance. For all echinocandins, relapse rates are higher than those noted with fluconazole, but use of the higher dosage of 150 mg of micafungin minimizes relapses.

Micafungin is used off-label, generally in combination with a third generation azole or an abmphtericin B formulation, for the treatment of aspergillosis. Micafungin should not be used alone for the primary therapy of mould infections given the absence of data to support such use. For prophylaxis in the immediate post stem cell transplantation period, low-dose micafungin, 50 mg daily, has proved to be efficacious, but it has not been studied during other high-risk periods for development of invasive aspergillosis, such as during episodes of graft versus host disease.

The favorable safety profile of micafungin with very few adverse events and minimal drug interactions make it an attractive antifungal agent. Limiting features of the drug are its ability to achieve effective concentrations in ocular structures, the central nervous system, and the urinary tract, and the need for intravenous administration.

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