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REVIEW

Pharmacotherapy of *Candida* Infections with Echinocandins

Ana Espinel-Ingroff[1], Emilia Canton[2], Estrella Martin-Mazuelos[3] and Javier Pemán[4]

[1]VCU Medical Center, Richmond, VA, USA. [2]Unidad de Microbiología Experimental, Centro de Investigación, Hospital Universitario La Fe, Valencia, Spain. [3]Hospital Universitario Valme, Sevilla, Spain. [4]Servicio de Microbiología, Hospital Universitario La Fe, Valencia, Spain. Email: avingrof@verizon.net and avingrof@vcu.edu

Abstract: The classic recommended antifungal agents for the treatment of invasive *Candida* infections were amphotericin B, a lipid formulation of amphotericin B and fluconazole in both neutropenic or nonneutropenic patients as either primary or alternative therapies. Voriconazole has been recommended when additional coverage for filamentous fungi is needed (e.g. neutropenic patients). More recently and based on well designed comparative clinical trials, the three echinocandins, caspofungin, anidulafungin and micafungin have been added as primary or alternative therapies especially for critically ill or neutropenic patients. In general, the echinocandins are most useful when patients have previously been exposed to an azole or are unstable.

Keywords: echinocandins therapy, candidal infections, micafungin, anidulafungin, caspofungin

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Introduction

The incidence and prevalence of invasive fungal infections is a major problem, especially in the large population of immunocompromized patients and/or those hospitalized with serious underlying diseases.[1,2] In addition, the mortality and morbidity of these infections is quite substantial. The most common fungal pathogens continue to be the species of *Candida* and *Aspergillus*.[3] The mortality rates associated with invasive candidiasis has been approximately 0.4 deaths per 100,000 population/year while there was a decrease with aspergillosis from 0.42 per 100,000 in 1997 to 0.25 per 100,000 in 2003 in the United States.[3] In recent years, several antifungal agents have been licensed for the treatment and prevention of these infections, two triazoles (voriconazole and posaconazole) and three echinocandins (anidulafungin [Pfizer], caspofungin [Merck] and micafungin [Astellas]).[4–6] It is hoped that the introduction of these new agents will improve these rates, because the attributed mortality rate for invasive candidiasis has been as high as 47% depending on the patient population age.[7,8] Earlier initiation of effective therapy is critical since higher mortality rates have been observed when therapy has been delayed.[9,10] However, although new laboratory diagnostic tests have been developed (e.g. detection of β-D-glucan, real-time PCR, among others),[11–13] early diagnosis of invasive candidiasis continues to be a challenge. The sensitivity of these methodologies is approximately 90%, but they need further evolution to be used in the clinical laboratory on a routine basis.

The echinocandins have a unique mechanism of action (inhibition of β-1,3-$_D$ glucan synthase) and a broad and similar spectrum of *in vitro* activity against most *Candida* spp.[14] Although the percentage of minimal inhibitory concentrations (MICs) below 2 μg/ml for *Candida parapsilosis* and *C. guilliermondii* has been lower (90.2% to 100%) than those for other *Candida* spp. (99.6% to 100%), these results do not appear to influence the response to therapy.[15–18] However, the number of infecting isolates belonging to these two species is usually lower than that for other species such as *C. albicans* and *C. glabrata*, at least in the USA. Reduced susceptibility could be a problem in infections where adequate free drug concentrations are not available (e.g. eye or central nervous system). During the last few years, mechanisms of resistance to most licensed agents, including the echinocandins, in *Candida* spp. have been elucidated.[19,20] Although resistance of common *Candida* spp. to echinocandins and azoles is rare, it has been documented and continues to be reported.[19–21] In addition, expected breakthrough of infections (e.g. trichosporonosis and disseminated zygomycosis) in patients receiving micafungin and other echinocandins has been reported[22,23] since the echinocandins have no activity against these fungal pathogens.

The purpose of this review was to summarize the reports of the therapeutic uses of echinocandins since 2005, especially of micafungin and anidulafungin in the treatment and prevention of invasive and other candidal infections for either neutropenic or nonneutropenic patients; laboratory, animal and other related studies also are summarized. Earlier reports and specific therapeutic treatment guidelines for these infections can be found elsewhere.[8,24–29]

In vitro and Animal Studies

Breakpoints and serum effect on antifungal activity

Serum-(MICs) of both caspofungin and micafungin for *C. albicans* were better predictors of *in vivo* potency than conventional MICs as measured by either hyphal growth inhibition or *Candida albicans* kidney burden measurement.[30] These results were confirmed recently by reports of the influence of serum in drug protein binding. Using *in vitro* growth assays, it has been reported that protein binding shifted the antifungal activity of echinocandins against *Aspergillus* spp. and *Candida* spp., resulting in nearly equivalent MICs or minimal effective concentrations (MECs);[31] serum decreased the sensitivity of glucan synthase to echinocandins. Because of that, it has been suggested that the susceptible breakpoint established by the Clinical and Laboratory Standards Institute of ≤2 μg/ml[32] does not apply to the three echinocandins, but only to caspofungin. Using *fks1* mutants, Garcia-Effron et al[33] have demonstrated that caspofungin serum-MICs captured all (100%) *fks1* mutants above the MIC breakpoint, but this breakpoint was less applicable for anidulafungin and micafungin. Micafungin or anidulafungin MICs of >0.5 μg/ml provided similar results (95% of the mutant isolates were captured). Their recommendation was to either lower the echincandin susceptible breakpoint or to use caspofungin *in vitro* data as a surrogate marker

to identify echinocandin resistance, since the three echinocandins have similar activity target, resistance mechanisms, spectrum and *in vitro* potency. The use of surrogates has previously been suggested for the triazoles, where fluconazole breakpoints can be used to assess patterns of susceptibility of other triazoles. Wiederhold et al[34] also provided evidence that the presence of serum can affect the *in vitro* activity of the echinocandins. Although anidulafungin had greater *in vitro* activity than caspofungin for an isolate of *C. glabrata*, this activity was attenuated in the presence of serum. Both echinocandins were similarly effective in reducing the kidney fungal burden in the immunosuppressed animal model of invasive candidiasis with this isolate. In addition to the CLSI standard methodology,[32] commercial assays are available for susceptibility testing of *Candida* spp. isolates to the three licensed echinocandins.[35]

Biofilms

C. albicans biofilms are intrinsically resistant to most antifungal agents except echinocandins and polyenes. The optimal efficacies of caspofungin and micafungin were evaluated using an *in vitro* model of *C. albicans* biofilm.[36] Caspofungin (2 mg/ml) and micafungin (5 mg/ml) could be good candidates for the reduction or control of fungal biofilms associated with silicone medical devices, as part of an antifungal lock. Both echinocandins were able to significantly and persistently reduce the yeast metabolic activity of intermediate and mature biofilms, 12 h and 5 days old, respectively, when used as catheter lock solutions.

Echinocandin combinations with other agents

The echinocandins have no activity against *Cryptococcus neoformans*. The *in vitro* interactions of micafungin with either amphotericin B, fluconazole, itraconazole or voriconazole were evaluated for different *Cryptococcus* spp.; no antagonism was observed and synergy was frequently observed with the combination of micafungin and amphotericin B.[37] Nishi et al[38] also found synergy between micafungin and either fluconazole or voriconazole against *Candida* spp.; the synergistic effect was more prominent (63%) against *C. glabrata*. In a *C. glabrata* immunosuppressed murine model, complete clearance of infection was observed when animals were treated concomitantly with either micafungin or caspofungin and liposomal amphotericin B or if the latter agent was given sequentially with caspofungin.[39] Similar results were observed against simulated *Candida* endocarditis vegetations with the combination of micafungin and flucytosine.[40] Recently, the combination of caspofungin and efungumab (a human antibody fragment) showed that efungumab enhanced the activity of caspofungin in the animal model.[41] However, more research is needed regarding the efficacy of these combinations in randomized clinical trials.

Clinical Studies

Pharmacokinetic studies

A pharmacokinetic study was conducted to determine the maximal tolerated dose of micafungin, and especially the pharmacokinetic profile when micafungin was combined with fluconazole in cancer patients undergoing either bone marrow or peripheral stem cell transplants.[42] This combination was found to be safe and the maximal tolerated dose of micafungin was not reached at 200 mg/day for four weeks. Keirns et al[43] reported that voriconazole did not affect the pharmacokinetics of micafungin and observed an absence of drug interaction in healthy adults. These are promising results, but more data from patients are needed.

Pharmacodynamics and pharmacokinetics

Pharmacodynamic results indicated that the current clinical dosing regimens of micafungin were appropriate for the treatment of infections caused by both *C. albicans* and *C. glabrata*; micafungin exposures needed for efficacy were similar.[44] Relating the results in the murine neutropenic candidiasis model to human micafungin pharmacokinetics for the 100 mg/day dosing regimen would predict an inhibitory pharmacodynamic target against both species with MICs up to 0.06 μg/ml. In addition, the free drug micafungin exposures required to produce stasis and killing endpoints were similar to those reported for anidulafungin against *C. albicans* and *C. glabrata*.[44] Other strategies regarding dosing regimen adjustment to improve micafungin efficacy also have been examined in a murine neutropenic model of invasive candidiasis[45] and in patients.[46] Furthermore, population studies have provided real inter-patient (pediatric and adult) pharmacokinetic variability.[47,48]

The pharmacokinetics of the echinocandins have been determined in adults[24–26,49] and more recently in various pediatric and neonate patient populations. Seibel et al[50] demonstrated that although the pharmacokinetics of micafungin in pediatric patients were similar to those of adults, there was an inverse relationship between age and clearance; the clearance for children 2 to 8 years old was 1.35 times that of children >9 years old among 77 febrile neutropenic pediatric patients (dose range, 0.5 and 4 mg/kg/day). In children, the daily micafungin dosage should be 2–4 mg/kg while in neonates it should be 10–12 mg/kg in order to achieve therapeutic drug concentrations.[51] Heresi et al[52] has studied the pharmacokinetics of micafungin in premature infants (>1000 g) and found that single doses of 3 mg/kg were well tolerated, but they observed a shorter half-life (8 h) as well as a more rapid clearance (~39 ml/h per kg) than those reported for older children. Benjamin et al[53] found that anidulafungin was well tolerated in neutropenic children receiving 0.75 mg/kg/day or 1.5 mg/kg/day; the latter is the required dosage. Anidulafungin concentration profiles in children were similar to those in adults receiving 50 or 100 mg/day and drug clearance was consistent across ages (2 to 11 and 12 to 17 years old). More recently, Neely et al[54] investigated the pharmacokinetics and safety of caspofungin 50 mg/m^2 daily in infants and toddlers (10 to 22 months of age); plasma concentrations were the same as those in adults. They also found that caspofungin was well tolerated and that the mean elimination phase $t_{1/2}$ (8.8 h) was reduced ~33% in comparison to that in adults (13 h), but similar to older children (8.2 h).

Candidemia and other invasive candidiasis in non-neutropenic adult patients

Echinocandins are recommended as the first-line standard treatment for patients with invasive candidiasis, including candidemia, who have moderate to severe infection, or have prior exposure to an azole and/or are at high risk to be infected with either *C. krusei* (innately resistant to fluconazole) or *C. glabrata*.[8] This recommendation is based on results obtained in several randomized clinical trials.[15,17,18,55,56] In the first of these trials,[15] caspofungin (loading dose 70 mg and then 50 mg/d) was compared with amphotericin B as first-line therapy of invasive candidiasis and candidemia (>200 patients, some neutropenic, were included). It was demonstrated that both agents had similar efficacy (73 and 61.7% successful outcomes, respectively) and there were significantly fewer drug-related adverse events in the caspofungin group. In a second phase 2 trial,[55] 123 patients with invasive candidiasis (including candidemia) were randomized to three anidulafungin intravenous regimens (50, 75, or 100 mg once daily with 84, 90, and 89% success rates, respectively) and treatment continued for two weeks following resolution or improvement of the infection; the follow up success rates were 72, 85, and 83%, respectively. A follow up study compared the efficacy of anidulafungin (loading dose 200 mg and then 100 mg/d) versus intravenous fluconazole in 245 patients (89% candidemia patients and 97% non-neutropenic patients).[18] Success rates at the end of the intravenous therapy were 73.2% with anidulafungin and 61.1% with fluconazole.

In the same year, Kuse et al[17] compared the efficacy of micafungin (100 mg/d) to that of liposomal amphotericin B for the treatment of candidemia and other invasive infections, where 264 patients were randomly assigned to the micafungin group and 267 to the other agent; data from 202 and 190 patients, respectively, were used in the final analysis. Treatment success was almost the same for the two agents (89.5 and 89.6%), but again there were fewer side effects with micafungin. Efficacy was independent of the infecting isolate, primary site of infection and the neutropenic status of the patient. Micafungin efficacy was also compared to that of caspofungin for candidemia and other forms of invasive candidiasis.[56] In this trial, two doses of micafungin (100 and 150 mg daily doses) were compared to the standard caspofungin dosage (70 mg loading dose followed by 50 mg daily) in 595 patients. Of these 595 patients, 191 and 199 were assigned to the 100 and 150 mg group, respectively, and 188 to the caspofungin group. The percentages of success were similar among the three groups (76.4, 71.4, 72.3%, respectively).

Based on those results, it was concluded that the three echinocandins were either as effective as the standard therapies or not inferior to them for the treatment of invasive candidal infections, including candidemia; also, no superiority was indicated for caspofungin over micafungin or vice versa. Although the rates of persistent candidemia have been lower with both anidulafungin and caspofungin when compared to fluconazole, Sobel and Revankar[58] stated that the superiority of echinocandins

over fluconazole is controversial and there is no real reason for avoiding the use of fluconazole, a safe and low cost agent with a similar reported efficacy to that of the echinocandins. However, an echinocandin is the preferred choice if the infecting isolate is *C. glabrata* or *C. krusei*, the same way fluconazole is preferred if the infecting isolate is *C. parapsilosis*. The echinocandins do not appear to require dosage adjustments in patients that may have compromised hepatic and renal function as it has been demonstrated for anidulafungin, which has no hepatic metabolism or renal excretion.[58]

Candidemia and other invasive candidal infections in non-neutropenic pediatric and elderly patients

Micafungin (2 mg/kg; 48 patients) was compared to liposomal amphotericin B (3 mg/kg; 50 patients) as first-line treatment of invasive candidiasis in pediatric patients (57 patients were <2 years old including 19 premature at birth).[59] Micafungin treatment success was similar to that observed with liposomal amphotericin B (72.9 and 76%, respectively); the difference adjusted for neutropenic status was 2.4%. Although both treatments were well tolerated, the rate of adverse effects that led to discontinuation of the therapy was substantially lower for micafungin than for liposomal amphotericin B (3.8 and 16.7%, respectively). Dinubile et al[60] retrospectively compared the efficacy and safety of caspofungin in elderly (≥65 years old) and non-elderly patients in two clinical trials (double-blind randomized versus amphotericin B for invasive candidiasis and versus liposomal ampotericin B as empirical therapy; caspofungin median duration was 12 days). The favorable response to caspofungin at the end of IV study therapy in invasive candidiasis was higher among the elderly than the non-elderly patients (83 and 68%, respectively). However, the favorable response was similar for the individual outcome components as well as the efficacy as an empirical agent (36 and 34%, respectively); similar results were observed on caspofungin adverse effects (clinical, 33 and 47%; laboratory, 17 and 29%). The authors concluded that caspofungin was as efficacious and well tolerated in elderly and non-elderly patients, but they cautioned against drawing firm conclusions from these results regarding the efficacy and safety of caspofungin in the elderly patients. Pappas et al[8] recommendations are to use echinocandins for neonatal candidiasis and candidal infections in adult populations for cases where resistance or intolerance precludes the use of either fluconazole, amphotericin B or its lipid formulations.

Empirical and targeted therapy in neutropenic patients

In a randomized, double-blind, multinational trial, caspofungin efficacy (556 patients) was compared to that of liposomal amphotericin B (539 patients) as empirical therapeutic agents for patients with persistent fever and neutropenia.[61] Although the overall success rates were almost the same (33.9 and 33.7%, respectively), the percentage among the patients with baseline fungal infection was higher in the caspofungin group (51.9%) than in the liposomal amphotericin B group (25.9%) as well as the percentage of patients that survived at least seven days after therapy (92.6 and 89.2%, respectively). In addition, caspofungin was better tolerated than the other agent. Contradictory results were reported when the same two agents were compared in 73 episodes of febrile neutropenia or invasive fungal infections (caspofungin, 33.3% breakthrough versus liposomal amphotericin B, 0%).[62] Meta-analysis of clinical trials comparing liposomal amphotericin B to caspofungin as empirical therapy indicated that although caspofungin is associated with fewer adverse effects, it is otherwise comparable to the former agent.[63]

Three prospective studies evaluated the efficacy of micafungin as empirical and/or first-line therapeutic agent in neutropenic, febrile patients.[64–66] Despite the small number of patients (18 and 23 patients) in two of the three studies,[64,65] the success rates (74 and 78%) defined as no fungal infections breakthrough were similar to that for caspofungin.[61] The third study[66] evaluated 197 patients. The efficacy rates were stratified as follows: 87.5% (7 of 8 patients) for candidiasis; 44.7% (17 of 38 patients) for probable invasive fungal infections; 61.9% (39 of 63 patients) for possible invasive fungal infections and 80.7% (71 of 88 patients) for patients who failed antibacterial therapy. In the febrile, neutropenic (below 500/cubic millimeter) patients, the favorable response to micafungin was 86.3% (44 of 51 patients). The drug was also well tolerated in all three studies (≤14% adverse effects). Another recent retrospective study evaluated anidulafungin as empirical therapy in 17 patients (one patient developed *C. parapsilosis*

breakthrough candidemia) and first-line treatment in 13 patients with documented fungal infections (77% efficacy).[67] In an earlier retrospective study, a 64% successful outcome was reported for primary treatment of neutropenic patients with caspofungin.[68]

The IDSA guidelines[8] recommend the use of echinocandins or a lipid formulation of amphotericin B for candidemia in neutropenic patients as primary therapies; voriconazole is also recommended in certain patients for coverage of filamentous fungi infections. However, if the infecting isolate is *C. parapsilosis*, an echinocandin should not be the initial therapy the same way if the infecting isolate is either *C. glabrata* or *C. krusei*, an echinocandin is preferred. For suspected candidiasis in both nonneutropenic or neutropenic patients, the recommendations are the same as for proven diseases.[8]

Prophylaxis therapy in neutropenic patients

The efficacy and safety of caspofungin and micafungin have also been evaluated in several studies as prophylactic therapeutic agents. Three trials were conducted to evaluate the efficacy of caspofungin as a prophylactic agent in hematological malignancies (open-label randomized trial versus itraconazole; 86 patients for itraconazole and 106 patients for caspofungin), stem cell transplant recipients (retrospective medical records review of 123 patients) and liver transplant patients (prospective, multicenter, open-label trial of 71 patients).[69–71] The efficacy of caspofungin was similar to that of itraconazole as a prophylactic agent in hematological malignancies (52% and 51% of patients did not develop fungal infections, respectively).[69] Seven patients (6.6%) developed invasive fungal infections in the caspofungin group such as candidemia, trichosporosis, aspergillosis and fusariosis. Similar results were observed when caspofungin was used as a prophylactic agent in stem cell transplant recipients (7.3% breakthrough) and in liver transplant patients (11.7% breakthrough).[70,71] Micafungin was also evaluated as a prophylactic agent in two studies. In a prospective study with 44 stem cell transplant recipients,[72] the success rate was 87.8%, defined as the absence of proven, probable or possible invasive fungal infections; the success rate was much lower in the fluconazole historical control group (65.5%) included in this study. On the other hand, micafungin (50 mg/d) was favorably compared to fluconazole (400 mg) in the prevention of fungal infection in the same group of patients.[73]

These are encouraging reports because both amphotericin B and itraconazole are limited by toxicity and/or drug-interactions and other issues.[74] As with the other indications, fluconazole (3–6 mg/d) or liposomal amphotericin B (1–2 mg/kg/d) are the first prophylactic choices in these patient populations. In stem cell transplantations both posaconazole (200 mg, three times daily) and micafungin (50 mg/d) are recommended, in addition to fluconazole, during the period that these patients are at risk of neutropenia.[8] It is important to remember that the echinocandins have no activity against a variety of mould pathogens.

Esophageal infections

The efficacy of micafungin was compared to fluconazole in a randomized, double-blind, non-inferiority trial with a total of 523 patients with esophageal infections.[75] The patients received either 150 mg/d micafungin or 200 mg/d fluconazole; the optimum micafungin dosage has been previously determined.[76] The results were similar with the two treatments, 84.8% and 88.7% of the patients, respectively (recurrence free at 4-weeks post-treatment). Similar results were obtained with caspofungin and anidulafungin when they were compared to either fluconazole[77,78] or amphotericin B.[79] Therefore, the recommended choices for esophageal infections are fluconazole, an echinocandin or amphotericin B; the species recommendations are the same as those described above for invasive disease. The echinocandins are acceptable alternatives to new triazoles and itraconazole for fluconazole refractory esophageal infections at the following intravenous dosages: anidulafungin 200 mg/day; caspofungin 50 mg/day and micafungin 150 mg/day.[8] However, the relapse rate has been documented to be higher than that noted with fluconazole.

Refractory and other less common infections

The echinocandins also have been evaluated for the treatment of refractory *Candida* infections. A total of 126 adult and pediatric patients with new (57.1%, micafungin alone) or refractory (42.9% micafungin and current therapy) candidemia were included in an open-label, noncomparative study that evaluated the

efficacy of micafungin alone (initial dose for infections due to *C. albicans* was 50 mg/d and 100 mg/d for other *Candida* spp. infections) or in combination with other agents.[16] Micafungin was effective in 83.3% of the patients (complete and partial recovery) and 75.4% had complete response. The response was similar across all the species including *C. glabrata, C. parapsilosis* and *C. tropicalis* (83.3 to 93.8%). A similarly favorable response (82 to 100%) was reported earlier for caspofungin in the treatment of 37 patients with refractory mucosal (17 esophageal and 4 oropharyngeal infections) or invasive (16 patients) *Candida* infections.[80] More recently, the efficacy of anidulafungin was evaluated for the treatment of azole refractory mucosal candidiasis in a phase 2, open-label study in 19 patients.[81] There was a 92% endoscopic and 95% clinical success rate to anidulafungin therapy; the response was maintained in 47% of the patients at follow up.

Case reports of less common invasive candidal infections treated with echinocandins began appearing in the literature since 2004. Refractory meningitis,[82] osteomyelitis,[83] and hepatosplenic[84] *Candida* infections have been successfully treated with caspofungin alone and cornea ulcers with micafungin alone as a topical application.[85]

The use of caspofungin alone for non-refractory isolated cases of endocarditis,[86–88] thrombophlebitis,[89] other less common infections[90] and arthritis[91] caused by *Candida* has been documented. Caspofungin in combination with either voriconazole[92,93] or fluconazole[94] has been also reported to treat *Candida* endocarditis and in combination with voriconazole to treat fungal endophthalmitis;[95] micafungin in combination with fluconazole was successfully used to treat a *C. albicans* knee infection.[96] Although the combination of echinocandins with triazoles or lipid formulations has been mostly favorable in patient therapy, more research is needed regarding the efficacy of these combinations in randomized clinical trials.

Conclusions

Based on well designed comparative clinical trials, the three echinocandins anidulafungin, caspofungin and micafungin have been added as primary or alternative therapies for the treatment of *Candida* spp., especially for neutropenic patients and/or in patients who have been exposed previously to an azole, are unstable or are infected with either *C. krusei* or *C. glabrata*. However, if the infecting isolate is *C. parapsilosis*, an echinocandin should not be the initial therapy.

Disclosure

The authors report no conflicts of interest.

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