Micafungin in a nutshell: state of affairs on the pharmacological and clinical aspects of the novel echinocandin

Micafungin is one of three echinocandin antifungals approved by the US FDA and the European Medicines Agency (EMA). Like all echinocandin antifungals, micafungin inhibits the synthesis of 1,3-β-D-glucan, a main component of the cell wall of many medically important fungi; thus, exerting fungicidal activity against most *Candida* spp., as well as fungistatic activity against many *Aspergillus* spp. Micafungin displays linear pharmacokinetics over the therapeutic range with a long half-life, allowing once-daily intravenous administration. Steady state serum concentrations are achieved after 3 days. Since therapeutic concentrations of micafungin are achieved after the administration of a standard dose there is no need for a loading dose. Interactions of micafungin with the cytochrome P450 (CYP3A4) system are marginal; and, consequently, no severe drug–drug interactions have been reported so far. Furthermore, micafungin exhibited favorable profiles for tolerability and safety; no dose-limiting toxicity has been established yet. However, despite its favorable characteristics, these are no unique features among the echinocandins. Nevertheless, micafungin is the only echinocandin that has been approved for the prophylaxis of *Candida* spp. infections in patients undergoing hematopoietic stem cell transplantation.

KEYWORDS: antifungal agents ■ aspergillosis ■ candidiasis ■ dose–response relationship ■ drug administration schedule ■ drug interactions ■ lipoproteins ■ mycoses ■ peptides

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The incidence of invasive fungal diseases (IFDs) has increased, mainly owing to the growing number of immunocompromised patients in recent years. The most common pathogens of IFDs in the immunocompromised host are *Candida* spp. and *Aspergillus* spp. Infections caused by *Candida* spp. account for 8–10% of all nosocomial bloodstream infections in US hospitals [1]. Despite new antifungal therapies, the attributable mortality rate of up to 49% remains unacceptably high [2]. The emergence of infections caused by *Candida* spp. other than *Candida albicans* has been repeatedly reported [1,3].

Aspergillus spp. are ubiquitous soil-dwelling fungi that may cause life-threatening IFD in immunocompromised patients. The most common (80–90%) form of invasive aspergillosis (IA) is invasive pulmonary aspergillosis.

Echinocandin class

Echinocandin antifungals are a recent addition to the antifungal armamentarium. They target the fungal cell wall by inhibiting the production of 1,3-β-D-glucan. Currently, three antifungals of the echinocandin class are commercially available. The first echinocandin to gain approval from the US FDA was caspofungin. Approval was granted for the following indications: empirical treatment of presumed fungal infections in patients with febrile neutropenia (FN), treatment of esophageal candidiasis, candidemia and other *Candida* spp. infections, as well as the treatment of IA in patients who are refractory or intolerant to other therapies [101]. Micafungin has been approved by the European Medicines Agency (EMA) in April 2008 and the FDA in March 2005 for the treatment of patients with esophageal candidiasis, invasive candidiasis and the prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (HSCT) [101,102]. Anidulafungin is the latest antifungal agent of this class and has been approved by the FDA for the treatment of esophageal candidiasis, candidemia and other *Candida* spp. infections [103]. The EMA approved anidulafungin for the treatment of invasive candidiasis in adult non-neutropenic patients [104].

Micafungin

Micafungin is derived from the water-soluble echinocandin-like fermentation product (lipopeptide FR901379) of *Coleophoma empetri* F-11889, by replacement of the lipophilic side chain, which results in a reduced hemolytic potential [101].

The chemical designation of micafungin sodium is pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)

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phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine], monosodium salt, with an empirical formula of $C_{56}H_{70}N_9NaO_{23}S$ and a molecular weight of 1292.26 g/mol (FIGURE 1).

Mode of action

Micafungin acts as a noncompetitive inhibitor of 1,3-β-D-glucan synthesis; hence, inhibiting the production of a main component of the cell wall in many medically important fungi. Consequently, the fungal cell walls become less stable and unable to resist osmotic pressure, which ultimately leads to cell lysis. It has been demonstrated that even low concentrations of micafungin result in a marked effect on the cell wall, in other words, morphological changes and occasional cell lysis, of *Candida albicans* [4,5]. The *in vitro* activity of micafungin was determined against 5346 invasive (bloodstream or sterile site) isolates of *Candida* spp. collected from over 90 medical centers worldwide. Micafungin demonstrated high activity against *Candida* spp. with minimal inhibitory concentrations (MIC) of 0.015 µg/ml for 50% (MIC_{50}) and 1 µg/ml for 90% (MIC_{90}) of all tested isolates (TABLE 1). Micafungin at doses of 2 µg/ml or less successfully inhibited all isolates. The least micafungin-susceptible strains, with MIC_{90} ranging from 1 to 2 µg/ml, were *Candida parapsilosis*, *Candida guilliermondii* and *Candida famata*. In an *in vitro* time-to-kill study, micafungin did not exhibit fungicidal activity against *C. parapsilosis* [6]. *In vivo,* however, the treatment response rate of micafungin against *C. parapsilosis* was comparable to those against other *Candida* spp. [7]. No significant changes in the activity against strains of *Candida* were noticed during the 6-year study period from January 2001 to December 2006 [8]. Resistance to micafungin may be caused by mutations within highly conserved regions of the *FSK1*, and, to a lesser extent, *FSK2* genes, which encode for certain subunits of the 1,3-β-D-glucan synthase [9]. However, recent results from a large and geographically diverse *Candida* spp. collection (n = 133) demonstrated that mutations of the *FSK1* gene remain uncommon among isolates with various MIC levels [10].

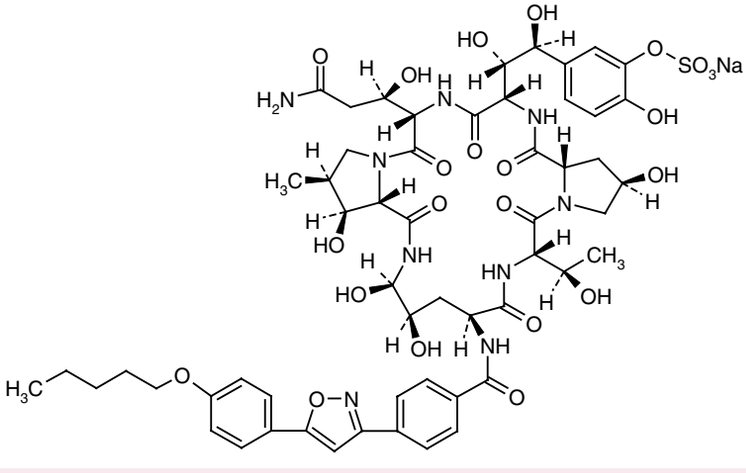

Figure 1. Micafungin sodium.
Reproduced with permission from [102].

Micafungin also demonstrated good *in vitro* antifungal activity against clinical isolates of *Aspergillus flavus* (n = 18), *Aspergillus fumigatus* (n = 35), *Aspergillus nidulans* (n = 3), *Aspergillus niger* (n = 20), *Aspergillus terreus* (n = 12) and *Aspergillus versicolor* (n = 3). However, minimum effective concentrations were not reported [11–13]. In an experimental model of guinea pigs suffering from invasive pulmonary aspergillosis, micafungin was markedly less effective than voriconazole or amphotericin B [14]. In another model, micafungin failed to eliminate invasive pulmonary aspergillosis caused by a clinical isolate of *A. fumigatus* in 27 neutropenic rabbits [15]. However, in the treatment of an experimental murine CNS aspergillosis, micafungin was more efficacious than voriconazole, caspofungin and conventional liposomal amphotericin B [16].

The *in vitro* activity of micafungin on dimorphic fungi considerably depends on their growth form. Micafungin demonstrated good activity against mycelial forms of *Histoplasma capsulatum*, *Blastomyces dermatitidis* and *Coccidioides immitis* (MIC range 0.0078–0.0625 µg/ml), as well as some activity against mycelial forms of *Sporothrix schenckii* (MIC ≤1 µg/ml) and *Penicillium marneffei* (MIC ≤2 µg/ml). However, against the yeast-like forms of these fungi and both forms of *Paracoccidioides brasiliensis*, the activity of micafungin was weak (MIC range from 4 to >64 µg/ml) [17]. The reported MIC of micafungin against zygomycetes was greater than 8 µg/ml [11,13]. Micafungin does not posses *in vitro* activity against important basidiomycetes, such as *Cryptococcus* spp., *Rhodotorula* spp. and *Trichosporon* spp. [12,13].

Pharmacodynamics, pharmacokinetics & metabolism

Micafungin is like all echinocandins, only available for intravenous administration. It exhibits a linear relationship between dose and area under the plasma concentration–time curve (AUC)

over the therapeutic dosing range of 50–150 mg daily [18]. According to the package insert, no clinically relevant effects on the pharmacokinetics of micafungin attributable to age, gender and ethnicity have been observed [105].

The AUC and the maximum concentration (C_{max}) in patients undergoing bone marrow or peripheral blood stem cell transplantation were evaluated in a dose-escalation study. On day 1, AUC and C_{max} were approximately proportional to the administered dose, ranging from 12.5 to 200 mg. The mean terminal half-life time of approximately 13 h remained consistent following repeated and increasing doses of micafungin. The maximum tolerated dose, however, was not reached in this study [18].

Although C_{max} and AUC were approximately 22% lower in patients with moderate hepatic dysfunction (Child–Pugh score of 7–9; n = 8), this finding may have been caused by differences in the body weight of the subjects and controls; thus, dose adjustments are not required [19].

Furthermore, no difference in the pharmacokinetics of micafungin caused by severe renal impairment (creatinine clearance <30 ml/min; n = 9) was observed [19], and since micafungin is highly protein bound (>99%), primarily to albumin, no additional dosing is necessary after hemodialysis [105].

In an open-label dose-escalation study in pediatric patients with FN (n = 77) the pharmacokinetic profile showed a linear relationship with the administered doses ranging from 0.5 to 4.0 mg/kg. The exhibited overall pharmacokinetic profile was similar to that observed in adults. However, the clearance in patients aged 2–8 years was increased approximately 1.35-fold compared with that of patients aged 9 years and older [20].

In a similar sequential-dose trial involving premature neonates (n = 23) the pharmacokinetic profile also appeared to be linear; although the terminal half-life was shorter (8 vs 13 h) and an even more rapid clearance of micafungin was observed compared with that in children and adults [21]. Recently, the population pharmacokinetics of micafungin in neonates and young infants from three clinical trials have been published. The analysis used data from 47 infants with a proven or presumptive diagnosis of disseminated candidiasis, who received micafungin at 0.75–15.00 mg/kg. The pharmacokinetics of micafungin were linear. The weight-normalized estimates of clearance and volume distribution approximated those previously described for adults [22].

Table 1. *In vitro* susceptibilities of 5346 clinical isolates of *Candida* spp. to micafungin.

Organism	Number of isolates	MIC_{90} [µg/ml]
Candida albicans	2869	0.030
Candida parapsilosis	759	2.000
Candida glabrata	747	0.015
Candida tropicalis	625	0.060
Candida krusei	136	0.120
Candida guilliermondii	61	1.000
Candida lusitaniae	58	0.250
Candida kefyr	37	0.060
Candida famata	24	1.000
Candida spp.	30	0.500
Total	5346	1.000

MIC_{90}: Minimal inhibitory concentration at which at least 90% of isolates are inhibited. Adapted from [8].

The bronchopulmonary disposition of micafungin was observed in a recently published study of 15 healthy volunteers [23]. Following three 150 mg doses of micafungin daily, a bronchoalveolar lavage was performed at either 4, 12 or 24 h after the last dose. It was demonstrated that micafungin predominantly concentrates within alveolar macrophages with complete (106%) penetration relative to the total drug plasma exposure, achieving steady-state concentrations above the minimum effective concentration for germinated *A. fumigatus* [23]. In a comparable study, the intrapulmonary pharmacokinetics and pharmacodynamics of micafungin in adult lung transplant patients were investigated. In contrast to the study with healthy volunteers, only one dose (instead of three doses) of micafungin was administered prior to the pharmacokinetic sampling; hence, the AUC in plasma was lower, but the AUCs within the epithelial lining fluid and alveolar cells were similar [24].

Micafungin is metabolized by acrylsulfatase (to the catechol form, M1) with secondary metabolism by catechol-*O*-methyltranferase (to the methoxy form, M2). Another metabolite (M5) is formed by hydroxylation of the side chain catalyzed by cytochrome P450 (CYP3A4) isozymes; although hydroxylation by CYP3A4 is not a major pathway for micafungin metabolism. None of these metabolites exhibit antifungal activity [105].

The elimination of micafungin has been studied by tracing ^{14}C micafungin in radioactivity assays from urine and feces of healthy volunteers after the administration of a single radiolabeled dose (25 mg). The fecal radioactivity accounted for 71% of the administered dose, while the urine contained only trace amounts of unchanged micafungin [105].

Pharmacokinetic *in vitro* data suggest that micafungin is unlikely to cause drug–drug interactions by inhibition of CYP3A4 and the multidrug resistance protein-1 [25]. However, micafungin does alter the pharmacokinetics of sirolimus, nifedipine and itraconazole, increasing the AUC of these substances by 21, 18 and 22%, respectively [105]. Therefore, these levels should be monitored. The clearance of cyclosporine is decreased by 10% during concomitant administration of micafungin [26].

Coadministration of micafungin does not significantly affect the plasma levels of tacrolimus [27,28], voriconazole [29], fluconazole [105], amphotericin B deoxycholate [30], mycophenolate mofetil [105] and prednisolone [105].

Concomitant therapy with rifampin [31,105], ritonavir [31,105], mycophenolate mofetil [105], cyclosporine A [26,105], tacrolimus [28,105], prednisolone [105], sirolimus [105], nifedipine [105], fluconazole [105], voriconazole [29], itraconazole [32] and amphotericin B [30] does not significantly affect the plasma levels of micafungin [31].

Clinical efficacy

The efficacy of micafungin for the treatment of patients with esophageal candidiasis, invasive candidiasis and the prophylaxis of *Candida* spp. infections in patients undergoing HSCT was demonstrated in clinical Phase III trials.

Esophageal candidiasis

The efficacy and safety of micafungin for the treatment of esophageal candidiasis has been evaluated in two double-blind studies. The first study compared the efficacy of micafungin (50, 100 and 150 mg/day) to fluconazole (200 mg/day) in patients with confirmed esophageal candidiasis (n = 245). It was demonstrated that micafungin at doses of 100 and 150 mg/day was more effective than at 50 mg/day. The efficacy of micafungin at dosages of 100 and 150 mg/day was comparable to that of fluconazole [33].

The noninferiority of micafungin 150 mg/day versus intravenous fluconazole 200 mg/day for the treatment of esophageal candidiasis was demonstrated in a large, randomized, double-blind trial with 518 patients. The overall therapeutic response rates were 87.3 and 87.2% for micafungin and fluconazole, respectively. No clinically meaningful differences in the incidence of possibly treatment-related adverse events between both treatment groups were observed. While patients in similar settings, treated with other echinocandins, such as caspofungin and anidulafungin, showed higher relapse rates than patients treated with fluconazole [34,35], no significant difference was observed between relapse rates of micafungin and fluconazole [36].

Prophylaxis of invasive fungal infections

Another large, randomized, double-blind trial (n = 882) focused on the efficacy of micafungin preventing IFD in patients undergoing autologous (46%) or allogeneic (54%) HSCT. Patients either received micafungin 50 mg (1 mg/kg for patients weighing <50 kg) or fluconazole 400 mg (8 mg/kg for patients weighing <50 kg). The primary end point was treatment success, defined as the absence of proven, probable or suspected systemic fungal infection until the end of prophylaxis, as well as the absence of a proven or probable systemic fungal infection to the end of the 4 week post-treatment period. The overall success rate in preventing IFD was significantly higher in the micafungin arm compared with the fluconazole arm (80 vs 73.5%, respectively; p = 0.03). Patients in the micafungin arm needed significantly less empirical antifungal treatment compared with patients in the fluconazole arm (15.1 vs 21.4%; p = 0.02). There was a trend towards less breakthrough aspergilloses among patients treated with micafungin (one probable versus four proven and three probable cases for fluconazole; p = 0.07). However, since fluconazole is not the standard treatment for patients undergoing autologous HSCT, one should take note of the differences between the success rates with regard to the transplant type. While the treatment success rates for patients undergoing autologous HSCT were 89.2% for micafungin and 80.1% for fluconazole, the differences in the success rates for patients undergoing allogeneic HSCT were much smaller (71.4% for micafungin vs 68.4% for fluconazole) [37].

Candidemia & other invasive *Candida* infections

A total of 148 (n = 126 per protocol) pediatric, neonatal and adult patients with newly diagnosed or refractory candidemia were enrolled in a noncomparative open-label study with micafungin alone and in combination with other antifungals. The daily doses of micafungin were 50 mg/day (1 mg/kg for patients <40 kg) for infections caused by *C. albicans* and 100 mg/day (2 mg/kg for patients <40 kg) for infections caused by other *Candida* species. Dose escalation was allowed. Success (complete or partial response) was observed in 83.3% of the patients per protocol population and serious adverse events related to micafungin were uncommon [7].

The efficacy of micafungin for the treatment of candidemia and other invasive *Candida* spp. infections has been studied in two randomized trials with either liposomal amphotericin B [38] or caspofungin [39] as the comparators.

Micafungin 100 mg was compared with liposomal amphotericin B (3 mg/kg) in a double-blind, randomized, multinational noninferiority study as the first-line treatment of candidemia and invasive candidiasis. While micafungin caused less adverse events than liposomal amphotericin B, the overall success rates were similar (74.1 and 69.6%, respectively). Hence, both compounds were equally effective for first-line treatment of candidemia and invasive candidiasis [38].

In a *post-hoc* analysis of the same study, the efficacy of micafungin versus liposomal amphotericin B was analyzed for intensive care unit (ICU) and non-ICU patients. In non-ICU patients, the treatment success rate was significantly higher among patients receiving micafungin than in those receiving liposomal amphotericin B (85 vs 72.1%, respectively; p = 0.0113). For ICU patients the treatment success rates of micafungin and liposomal amphotericin B were similar (62.5 vs 66.4%, respectively), and lower than the corresponding treatment success rates of the non-ICU patients [40].

The efficacy of micafungin 100 and 150 mg for the treatment of candidemia and other forms of invasive candidiasis compared with caspofungin 50 mg was studied in another randomized, blinded trial with 595 patients. Of the 578 patients in the modified intent-to-treat population, 492 (85.1%) were diagnosed with candidemia, while the remainder had non-candidemia invasive candidiasis. At the end of the blinded therapy, the success rates of both echinocandins were equivalent (72.3, 76.4 and 71.4% for caspofungin 50 mg/day, micafungin 100 mg/day and micafungin 150 mg/day, respectively). No significant differences in mortality, relapse and emergent infections, or adverse events were observed between the study arms. Therefore, micafungin at both dosages (100 and 150 mg/day) was noninferior to a standard dosage of caspofungin [39].

Febrile neutropenia

Data on the efficacy and safety of micafungin in patients with hematological malignancies with fever resistant to broad-spectrum antibiotic therapy are limited, and are only based on noncomparative or retrospective studies. In a single-arm study with a small number of patients (32; of whom 23 fulfilled the protocol-defined criteria) the treatment success rate was 17 out of 23 (73.9%). None of the six patients who were considered treatment failures developed a documented fungal breakthrough infection, and discontinued the drug owing to lack of efficacy or died during the study period. One or more adverse events, of which none was above grade two toxicity, occurred in five (27.7%) patients [41]. The efficacy and safety of micafungin for the treatment of invasive fungal infections in patients with hematological malignancies (n = 277) was assessed in a noncomparative multicenter study with 197 evaluable patients, receiving 50–300 mg/day of micafungin. A total of 51 patients were diagnosed with FN (neutrophils below 500/µl) refractory to broad-spectrum antibacterial treatment (>48 h). A favorable response to micafungin was observed in 44 out of 51 (86.3%) of the patients diagnosed with FN. The response rates for patients diagnosed with probable, possible and suggested (fever refractory to antibacterial treatment) invasive fungal infections were 17 out of 38 (44.7%), 39 out of 63 (61.9%) and 71 out of 88 (80.7%), respectively [42].

A recently published sequential cohort analysis compared the efficacy of micafungin and caspofungin for the treatment of FN (n = 323). In this retrospective analysis, micafungin did not appear to differ significantly from caspofungin in terms of safety profile or efficacy [43].

Invasive aspergillosis

Data on the efficacy of micafungin for the treatment of aspergillosis only stem from single-armed studies.

The efficacy of micafungin, alone or in combination with other antifungals, as primary or salvage therapy for IA has been studied in a noncomparative open-label trial. However, the data of this trial are difficult to interpret since only few patients (n = 34), who fulfilled the diagnostic criteria for IA also received micafungin monotherapy. A favorable response to micafungin monotherapy was observed in six out of 12 (50%) and nine out of 22 (40.9%) patients in the primary therapy and the salvage therapy group, respectively. In combination with other antifungals, response rates were five out of 17 (29.4%) and 60 out of 174 (34.5%) for the primary and the salvage therapy groups, respectively [44].

In another noncomparative open-label trial, the efficacy and safety of micafungin for the treatment of deep-seated mycosis in Japanese patients was evaluated. Of 70 patients, 56 were evaluable

for efficacy, and received 12.5–150 mg/day of micafungin for up to 56 days. The overall clinical response rate in patients diagnosed with aspergillosis was 57% (24 out of 42 patients) [45], which roughly matches the rate of successful outcome (52.8%) observed in a double-blind study for voriconazole versus amphotericin B [46].

However, since comparative trials on micafungin for this indication have not been reported, micafungin has not been approved for the treatment of aspergillosis by either the FDA or the EMA [101,102].

A comparative Phase II trial on micafungin as salvage monotherapy for IA was recently stopped due to difficulties in recruitment and changes in the standard of care for IA [105]. At www.clinicaltrials.gov there is only one recruiting trial registered with micafungin for the treatment of aspergillosis, which has the objective to compare caspofungin with micafungin in adult Japanese patients with deep-seated *Candida* spp. or *Aspergillus* spp. infections [106].

Safety & tolerability

Micafungin, similar to other echinocandins, is a well-tolerated antifungal drug. The safety, tolerability and pharmacokinetic profile of micafungin was evaluated in a dose-escalation study in pediatric patients with FN (n = 77). The patients were stratified by age: 2–12 years (n = 57) and 13–17 years (n = 20). Therapy was initiated at 0.5 mg/kg/day and escalated to higher doses up to 4.0 mg/kg. The most common overall adverse events in the study population were diarrhea (19.5%), epistaxis (18.2%), abdominal pain (16.9%) and headache (16.9%). A moderate increase in liver-related laboratory parameters, possibly related to the study drug, was observed in two patients aged 13–17 years, who received micafungin 0.5 mg/kg/day. There was neither evidence of other toxicities, especially nephrotoxicity, nor any evidence of a dose-limiting toxicity [20].

The safety of micafungin was compared with that of fluconazole in patients with esophageal candidiasis and patients undergoing HSCT [33,36,37]. Neither of these studies revealed any clinical meaningful difference between micafungin and fluconazole in severe or serious adverse events. The most common treatment-related adverse events during the prophylaxis study for patients undergoing HSCT were gastrointestinal- (5.9% for micafungin vs 9.2% for fluconazole), hepatic- (5.2 vs 6.8%) and cardiovascular- (1.9 vs 3.1%) related adverse events. Fewer (p = 0.058) patients in the micafungin group (18; 4.2%) discontinued the study treatment owing to adverse events than in the fluconazole control group (33; 7.3%).

The safety of micafungin has also been evaluated in Phase III trials for the treatment of candidemia and other invasive *Candida* infections [38,39]. Compared with caspofungin, no significant difference of treatment-related adverse events was observed for micafungin at both dosages (100 and 150 mg/day) [39]. However, compared with liposomal amphotericin B, the safety profile of micafungin was better in terms of renal function, infusion-related events and electrolyte disturbances [38].

In a preclinical experiment, rats receiving micafungin for either 3 or 6 months at 32 mg/kg/day developed foci of altered hepatocytes and hepatocellular tumors. Although the increase in carcinomas did not reach statistical significance, the persistence of altered hepatocellular foci subsequent to micafungin administration, and the presence of adenomas and carcinomas in the recovery periods suggest a causal relationship between micafungin sodium, altered hepatocellular foci and hepatic neoplasms [102]. Hence, the EMA, but not the FDA, included a warning in the label that micafungin should only be used if other antifungals are not appropriate. The decision to use micafungin should take into account the potential risk for the development of liver tumors [107].

Conclusion

Micafungin is a potent inhibitor of the 1,3-β-D-glucan synthase. Owing to its favorable profile for safety, tolerability and drug–drug interactions, micafungin has become an attractive option for the therapy of invasive candidiasis and azole-resistant esophageal candidiasis. Besides fluconazole, micafungin is the only drug that has been approved for *Candida* spp. prophylaxis in HSCT patients not undergoing high-dose immunosuppressive therapy for graft versus host disease. However, micafungin has not yet proven to be superior to current treatment options of choice, and since reliable clinical research on micafungin and its possible applications is coming along slowly, it has not yet been approved for the treatment of IA or fever of unknown origin.

Future perspective

Owing to its low interaction profile, micafungin is an interesting drug, especially for transplant patients in need of cyclosporine A, sirolimus or tacrolimus therapy. According to a recently published retrospective cohort study comparing caspofungin and micafungin in patients with

persistent FN, both echinocandins did not appear to differ significantly in terms of safety profile or efficacy. Therefore, in this setting, a Phase III clinical trial is warranted. Despite its promising results in open-label studies, no comparative trials for the efficacy and safety of micafungin in IA have been conducted; hence, micafungin received a CIII recommendation for the primary and salvage therapy of IA by the Infectious Diseases Working Party of the German Society of Hematology and Oncology [47].

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Executive summary

Mechanism of action

- Micafungin inhibits fungal 1,3-β-D-glucan synthesis, causing severe damage to the fungal cell wall.
- Micafungin is fungicidal against almost all *Candida* spp. and fungistatic against many *Aspergillus* spp.

Pharmacokinetic properties

- Micafungin is only available as an intravenous solution owing to its poor bioavailability.
- Its long half-life allows once-daily administration.
- No dose adjustments are needed for intermediate hepatic or severe renal failure.
- No loading dose is required.
- Steady-state concentration is achieved after three doses.

Clinical efficacy

- Micafungin is noninferior for the treatment of esophageal candidiasis and invasive candidiasis.
- It has superior overall efficacy in preventing invasive fungal infections in hematopoietic stem cell transplantation patients.

Safety & tolerability

- No dose-limiting toxicity has yet been established.
- Few incidences of drug-induced toxicity.

Drug interaction

- Micafungin shows (only) marginal interactions with the cytochrome P450 (CYP3A4) system.
- Cyclosporine A clearance is slightly decreased by micafungin.
- Sirolimus and nifedipine area under the plasma concentration–time curve is slightly increased by micafungin.
- Micafungin does not interact with tacrolimus, rifampine and voriconazole.

Dosage & administration

- Available in 50 mg vials for preparation of intravenous solution.
- Dose: 50–150 mg administered once daily.

Bibliography

Papers of special note have been highlighted as:
- of interest

1 Pfaller MA, Diekema DJ: Epidemiology of invasive candidiasis: a persistent public health problem. *Clin. Microbiol. Rev.* 20(1), 133–163 (2007).

2 Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB: Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin. Infect. Dis.* 39(3), 309–317 (2004).

3 Pappas PG, Rex JH, Lee J *et al.*: A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. *Clin. Infect. Dis.* 37(5), 634–643 (2003).

4 Angiolella L, Maras B, Stringaro AR *et al.*: Glucan-associated protein modulations and ultrastructural changes of the cell wall in *Candida albicans* treated with micafungin, a water-soluble, lipopeptide antimycotic. *J. Chemother.* 17(4), 409–416 (2005).

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.* 51(4), 247–255 (2002).

6 Canton E, Espinel-Ingroff A, Peman J, Del Castillo L: *In vitro* fungicidal activities of echinocandins against *Candida metapsilosis*, *C. orthopsilosis,* and *C. parapsilosis* evaluated by time-kill studies. *Antimicrob. Agents Chemother.* 54(5), 2194–2197 (2010).

7 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.* 24(10), 654–661 (2005).

8 Pfaller MA, Boyken L, Hollis RJ *et al.*: *In vitro* susceptibility of invasive isolates of *Candida* spp. To anidulafungin, caspofungin, and micafungin: six years of global surveillance. *J. Clin. Microbiol.* 46(1), 150–156 (2008).

▪ **Comprehensive study on the *in vitro* susceptibilities of clinical isolates to echinocandin antifungals.**

9 Niimi K, Monk BC, Hirai A *et al.*: Clinically significant micafungin resistance in *Candida albicans* involves modification of a glucan synthase catalytic subunit GSC1 (FKS1) allele followed by loss of heterozygosity. *J. Antimicrob. Chemother.* 65(5), 842–852 (2010).

▪ **An interesting article on micafungin resistance in *Candida albicans*.**

10 Castanheira M, Woosley LN, Diekema DJ, Messer SA, Jones RN, Pfaller MA: Low prevalence of *fks1* hotspot 1 mutations in a worldwide collection of *Candida* spp. *Antimicrob. Agents Chemother.* 54(6), 2655–2659 (2010).

11 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* 48(2), 78–81 (2002).

12 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.* 44(1), 57–62 (2000).

13 Uchida K, Nishiyama Y, Yokota N, Yamaguchi H: *In vitro* antifungal activity of a novel lipopeptide antifungal agent, FK463, against various fungal pathogens. *J. Antibiot.* 53(10), 1175–1181 (2000).

14 Chandrasekar PH, Cutright JL, Manavathu EK: Efficacy of voriconazole plus amphotericin B or micafungin in a guinea-pig model of invasive pulmonary aspergillosis. *Clin. Microbiol. Infect.* 10(10), 925–928 (2004).

15 Petraitis V, Petraitiene R, Groll AH *et al.*: Comparative antifungal activities and plasma pharmacokinetics of micafungin (FK463) against disseminated candidiasis and invasive pulmonary aspergillosis in persistently neutropenic rabbits. *Antimicrob. Agents Chemother.* 46(6), 1857–1869 (2002).

16 Clemons KV, Espiritu M, Parmar R, Stevens DA: Comparative efficacies of conventional amphotericin B, liposomal amphotericin B (ambisome), caspofungin, micafungin, and voriconazole alone and in combination against experimental murine central nervous system aspergillosis. *Antimicrob. Agents Chemother.* 49(12), 4867–4875 (2005).

17 Nakai T, Uno J, Ikeda F, Tawara S, Nishimura K, Miyaji M: *In vitro* antifungal activity of micafungin (FK463) against dimorphic fungi: comparison of yeast-like and mycelial forms. *Antimicrob. Agents Chemother.* 47(4), 1376–1381 (2003).

18 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.* 49(4), 1331–1336 (2005).

19 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.* 45(10), 1145–1152 (2005).

20 Seibel NL, Schwartz C, Arrieta A *et al.*: Safety, tolerability, and pharmacokinetics of micafungin (FK463) in febrile neutropenic pediatric patients. *Antimicrob. Agents Chemother.* 49(8), 3317–3324 (2005).

▪ **Comprehensive work on the safety of micafungin in febrile neutropenia.**

21 Heresi GP, Gerstmann DR, Reed MD *et al.*: The pharmacokinetics and safety of micafungin, a novel echinocandin, in premature infants. *Pediatr. Infect. Dis. J.* 25(12), 1110–1115 (2006).

22 Hope WW, Smith PB, Arrieta A *et al.*: Population pharmacokinetics of micafungin in neonates and young infants. *Antimicrob. Agents Chemother.* 54(6), 2633–2637 (2010).

23 Nicasio AM, Tessier PR, Nicolau DP *et al.*: Bronchopulmonary disposition of micafungin in healthy adult volunteers. *Antimicrob. Agents Chemother.* 53(3), 1218–1220 (2009).

▪ **Bronchopulmonary disposition of antifungals and possible effects on their efficacy is an interesting field of research.**

24 Walsh TJ, Goutelle S, Jelliffe RW *et al.*: Intrapulmonary pharmacokinetics and pharmacodynamics of micafungin in adult lung transplant patients. *Antimicrob. Agents Chemother.* 54(8), 3451–3459 (2010).

▪ **Bronchopulmonary disposition of antifungals and possible effects on their efficacy is an interesting field of research.**

25 Sakaeda T, Iwaki K, Kakumoto M *et al.*: Effect of micafungin on cytochrome p450 3a4 and multidrug resistance protein 1 activities, and its comparison with azole antifungal drugs. *J. Pharm. Pharmacol.* 57(6), 759–764 (2005).

26 Hebert MF, Townsend RW, Austin S *et al.*: Concomitant cyclosporine and micafungin pharmacokinetics in healthy volunteers. *J. Clin. Pharmacol.* 45(8), 954–960 (2005).

27 Shimoeda S, Ohta S, Kobayashi H *et al.*: Analysis of the blood level of micafungin involving patients with hematological diseases: new findings regarding combination therapy with tacrolimus. *Biol. Pharm. Bull.* 28(3), 477–480 (2005).

28 Hebert MF, Blough DK, Townsend RW *et al.*: Concomitant tacrolimus and micafungin pharmacokinetics in healthy volunteers. *J. Clin. Pharmacol.* 45(9), 1018–1024 (2005).

29 Keirns J, Sawamoto T, Holum M, Buell D, Wisemandle W, Alak A: Steady-state pharmacokinetics of micafungin and voriconazole after separate and concomitant dosing in healthy adults. *Antimicrob. Agents Chemother.* 51(2), 787–790 (2007).

30 Undre NA, Stevenson P, Wilbraham D: Amphotericin B does not affect the pharmacokinetics of micafungin (FK463). Presented at: *17th European Congress of Clinical Microbiology and Infectious Diseases.* Munich, Germany, 31 March–3 April 2007.

31 Undre NA, Stevenson P, Amakye DD: Rifampicin and ritonavir do not affect the pharmacokinetics of micafungin (FK463), an echinocandin antifungal. *Clin. Microbiol. Infect.* 10(3), 279 (2004).

32 Undre NA, Stevenson P, Brooks A: Itraconazole does not affect the pharmacokinetics of micafungin (FK463). Presented at: *17th European Congress of Clinical Microbiology and Infectious Diseases.* Munich, Germany, 31 March–3 April 2007.

33 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.* 39(6), 842–849 (2004).

34 Krause DS, Simjee AE, Van Rensburg C *et al.*: A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. *Clin. Infect. Dis.* 39(6), 770–775 (2004).

35 Villanueva A, Gotuzzo E, Arathoon EG *et al.*: A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. *Am. J. Med.* 113(4), 294–299 (2002).

36 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.* 21(7), 899–907 (2005).

37 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.* 39(10), 1407–1416 (2004).

38 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* 369(9572), 1519–1527 (2007).

39 Pappas PG, Rotstein CM, Betts RF *et al.*: Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin. Infect. Dis.* 45(7), 883–893 (2007).

40 Dupont BF, Lortholary O, Ostrosky-Zeichner L, Stucker F, Yeldandi V: Treatment of candidemia and invasive candidiasis in the intensive care unit: *post hoc* analysis of a randomized, controlled trial comparing micafungin and liposomal amphotericin B. *Crit. Care* 13(5), R159 (2009).

41 Toubai T, Tanaka J, Ota S *et al.*: Efficacy and safety of micafungin in febrile neutropenic patients treated for hematological malignancies. *Intern. Med.* 46(1), 3–9 (2007).

42 Tamura K, Urabe A, Yoshida M *et al.*: Efficacy and safety of micafungin, an echinocandin antifungal agent, on invasive fungal infections in patients with hematological disorders. *Leuk. Lymphoma* 50(1), 92–100 (2009).

43 Kubiak DW, Bryar JM, Mcdonnell AM *et al.*: Evaluation of caspofungin or micafungin as empiric antifungal therapy in adult patients with persistent febrile neutropenia: a retrospective, observational, sequential cohort analysis. *Clin. Ther.* 32(4), 637–648 (2010).

44 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.* 53(5), 337–349 (2006).

45 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.* 36(5), 372–379 (2004).

46 Herbrecht R, Denning DW, Patterson TF *et al.*: Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N. Engl. J. Med.* 347(6), 408–415 (2002).

47 Bohme A, Ruhnke M, Buchheidt D *et al.*: Treatment of invasive fungal infections in cancer patients – recommendations of the infectious diseases working party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann. Hematol.* 88(2), 97–110 (2009).

Websites

101 Merck. Cancidas® (label) www.accessdata.fda.gov/drugsatfda_docs/label/2009/021227s023lbl.pdf

102 Astellas Pharma US Inc. Mycamine® (label) www.accessdata.fda.gov/drugsatfda_docs/label/2008/021506s008lbl.pdf

103 Pfizer. Eraxis® (label) www.accessdata.fda.gov/drugsatfda_docs/label/2006/021632s000,021948s000lbl.pdf

104 Pfizer. Ecalta® (label) www.ema.europa.eu/humandocs/humans/EPAR/ecalta/ecalta.htm

105 Astellas Pharma OK, USA: Mycamine® product information www.mycamine.com

106 Micafungin salvage monotherapy in invasive aspergillosis http://clinicaltrials.gov/ct2/show/NCT00376337

107 Astellas Pharma Europe. Mycamine® (label) www.emea.europa.eu/humandocs/Humans/EPAR/mycamine/mycamine.htm