Micafungin: A New Echinocandin

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Micafungin, a potent inhibitor of 1,3-β-D-glucan synthase, has become the second available agent in the echinocandins class that is approved for use in clinical practice. This agent shares with caspofungin an identical spectrum of in vitro activity against Candida albicans, non-albicans species of Candida, and Aspergillus species, as well as several but not all pathogenic molds. If anything, its in vitro activity appears to be superior to that of caspofungin, although the clinical relevance of this observation is unclear. The clinical role of micafungin appears to be similar to that of caspofungin, although clinical data are still lacking at this stage, with initial approval only for treatment of esophageal candidiasis and prophylaxis in subjects with neutropenia. Pharmacokinetic and pharmacodynamic studies and reports of adverse effects and safety have reported similar but not identical results to those of other agents in the echinocandin class. Factors such as acquisition costs and the potential for resistance development may be more relevant to its widespread use than in vitro and in vivo data comparisons with caspofungin.

The echinocandins are a novel class of antifungals. Caspofungin was the first echinocandin agent approved by the US Food and Drug Administration (FDA), and anidulafungin is currently in phase 3 development. Micafungin is a promising echinocandin that was recently approved by the FDA and has demonstrated activity against Candida and Aspergillus species.

MECHANISM OF ACTION

Micafungin is a water-soluble antifungal agent (molecular weight, 1292.26 Da) that is derived from Coleoptioma empedri via enzymatic cleavage of the hexapeptide FR901370, a natural product of the fungus; the addition of a fatty N-acyl side chain improves its antifungal potency [1, 2]. Micafungin acts in a concentration-dependent manner as a noncompetitive inhibitor of the formation of the enzyme 1,3-β-D glucan synthase, an enzyme necessary for synthesis of 1,3-β-D glucan, a glucose polymer crucial to the structure and integrity of the cell wall of several common fungal pathogens [3–5]. Fungal cells unable to synthesize this polysaccharide cannot maintain their shape and lack adequate rigidity to resist osmotic pressure, which results in fungal cell lysis. This mechanism is unique to the echinocandin class of antifungal agents and has the potential to be either additive or synergistic with polyenes and azoles. Glucan is essential not only to cell-wall structure and integrity but also to cell growth and division [6]. Micafungin demonstrates a prolonged concentration-dependent postantifungal effect.

Most fungal cell walls contain chitin, α- or β-linked glucans, and a variety of mannoproteins, although the quantity and relative importance of each component varies among different fungal species—thus, the selective antifungal effect on echinocandins [7]. Of significance, the cell walls of zygomycetes and cryptococcus lack 1,3-β-D glucan, which explains the poor activity of echinocandins, including micafungin, against these fungi [8].

1,3-β-D-glucan synthase, an enzyme complex, is composed of at least 2 components: the catalytic subunit FKS1p/FLs2p and a soluble regulatory subunit, Rholp GTPase. The effects of micafungin on the activity of 1,3-β-D glucan synthase can be assessed in membrane preparations of Candida albicans and Aspergillus fumigatus by measuring the incorporation of [14C]UDP-glucose into trichloroacetic acid–precipitable polymer in the presence of increasing concentrations of the drug, and impressive inhibition of the enzyme has been seen at low concentrations of micafungin [5]. Morphologic changes in C. albicans after short-term exposure to 0.1–0.5 μg/mL micafungin include abnormal swelling and an irregular shape of fungal cells, thinning of fungal cell wall, and aberrant budding, which are consistent with inhibition of cell-wall synthesis [6].
A time-dependent effect on hyphal damage has been demonstrated in *A. fumigatus*. On light microscopy, within 4 h of exposure, truncated, branched, and shortened hyphae with focal dilatations resembling blastospores are observed. These changes can be completely reversed, implying recovery, at 24 h [9]. Fungal cell recovery is thought to be due to reversible binding of drug, high turnover of cellular target enzymes, or the up-regulation of other synthetic enzymes [9]. The use of vital stains have, nevertheless, shown some in vitro cell death of *A. fumigatus* exposed to micafungin.

In in vitro experiments, micafungin blocked adherence of *C. albicans* to epithelial cells and demonstrated activity against *C. albicans* biofilms, which indicates a potential role in the prevention and treatment of catheter-related *Candida* infections [10, 11]. Micafungin also enhances in vitro neutrophil fungicidal activity against *Candida* pseudohyphae [12].

**IN VITRO ACTIVITY**

Standardized susceptibility testing methods for echinocandins have not been established, and results of in vitro susceptibility tests do not necessarily correlate with in vivo or clinical outcomes. Potent but slow fungicidal activity has been shown by micafungin against clinical isolates of *C. albicans*, *Candida dubliniensis*, *Candida tropicalis*, *Candida glabrata*, and *Candida krusei*, with somewhat higher MIC₉₀ for *Candida parapsilosis*, *Candida lusitaniae*, and *Candida guilliermondii* (table 1) [13–15]. Fluconazole-resistant clinical isolates of *Candida* demonstrated no cross-resistance to micafungin [15, 16]. Overall, micafungin is more active than is amphotericin B, fluconazole, or itraconazole, with MICs against most *Candida* species generally <0.25 μg/mL. In vitro studies have demonstrated a 5–10-fold increase in the inhibitory activity of micafungin, compared with that of caspofungin, against *C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. dubliniensis* [14].

Micafungin has no in vitro activity against basidiomycetous yeasts, *Cryptococcus neoformans*, or *Trichosporon* species, but it has potent in vitro inhibitory activity against *Aspergillus* species at lower concentrations than amphotericin B and itraconazole [8, 15–17]. However, in contrast to these agents, micafungin was not fungicidal against *Aspergillus* species. Micafungin has demonstrated activity against few species of *Penicillium* species, *Paecilomyces lilacinus*, and *Paecilomyces variotii* [16]. Variable, usually moderate, in vitro activity has been demonstrated against dematiaceous fungi, including *Cladosporium trichoides*, *Scedosporium* species, *Exophiala* species, and *Fonsecaea pedrosoi* [8]. In contrast, micafungin has no activity against *Zygomycetes* and *Fusarium* species and *Pseudallescheria boydii* [8, 15, 16]. Although it exhibits potent activity against the mycelial forms of *Histoplasma capsulatum*, *Blastocystis dermatitidis*, and *Coccidioides immitis*, only weak activity is seen against yeast forms. Similar observations have been made for *P. brasiliensis*, *P. marneffei*, and *Sporothrix schenckii*. Because the cyst form of *Pneumocystis jiroveci* contains 1,3-β-d glucan synthase, micafungin demonstrates potent activity against this pathogen but has no direct effect on trophozoite proliferation [18].

Antifungal combination therapy can be assessed in vitro by using checkerboard (microdilution), time-kill metazolium exclusion, and radiometric checkerboard assays [19]. To date, combinations of micafungin and amphotericin B against *Aspergillus* species were largely indifferent but never antagonistic. In contrast, the combination of micafungin and nikkomycin Z against *A. fumigatus* was synergistic but indifferent to other *Aspergillus* and *Fusarium* species [9]. Groll et al. [19] described an in vitro additive effect with combinations of micafungin and voriconazole.

**RESISTANCE**

Acquired resistance to echinocandins in susceptible fungal yeast species has been extremely rare to date. The majority of mutations conferring resistance have been associated with the *FKS* genes [4]. In the laboratory, repeated passages of *C. albicans* to subinhibitory concentrations of micafungin resulted in negligible changes in MIC values, which emphasizes the low likelihood of the development of resistance in clinical disease situations. Only rare reports of resistance in clinical practice have been reported, and it appears to be more likely to develop in *C. parapsilosis* [20]. The frequency of micafungin resistance in clinical isolates of *Aspergillus* species is unknown.

**METABOLISM AND CLINICAL PHARMACOKINETICS**

Pharmacokinetics have been investigated in healthy adult human volunteers, as well as in ill, hospitalized subjects. Micafungin was not significantly absorbed when it was administered orally. With a dose-proportional increase in maximum concentration (Cₘₐₓ) and the area under the curve for 0–24 h (AUC₀–2₄) observed, investigators determined linear plasma pharmacokinetics for intravenous micafungin (table 2). The half-life ranged from 14 to 15 h (total protein binding was at least 99%). The mean peak plasma concentration (± SD) (day 7) was 2.46 ± 0.27 μg/mL [21].

Micafungin is metabolized in the liver and excreted in an inactive form into bile and urine, with <1% of the drug found in urine in an unchanged form [22]. Micafungin is not metabolized by the CYP 450 system. In patients with moderate hepatic dysfunction, the mean Cₘₐₓ and clearance of infused micafungin were not statistically different from that of matched controls; however, statistically significant differences were found in the AUC₀–₇₂ [19]. Severe renal failure does not affect the kinetics of micafungin; hence, dose adjustments are unnecessary. Similarly, in elderly persons, no charges in Cₘₐₓ, AUC,
shown a lack of antagonism when micafungin is combined with itraconazole [32]. Clearly, data from animal models of aspergillosis have demonstrated synergy or an additive effect with a combination of micafungin and ravuconazole in a neutropenic rabbit model of invasive pulmonary aspergillosis [34]. On the other hand, a significant reduction in mortality, residual fungal burden, and anatomical cure was noted in persistently neutropenic rabbit model of invasive pulmonary aspergillosis compared with control animals, but no reduction in fungal burden in the lungs was noted in transiently neutropenic guinea pig model, although no antagonism was seen, synergy was not demonstrated with micafungin plus voriconazole [35].

Synergy or an additive effect was noted with a combination of micafungin and amphotericin B in mouse models of pulmonary aspergillosis [30, 31, 36, 37]. Micafungin was also effective against itraconazole-resistant strains of *A. fumigatus* and *A. terreus* in a mouse model of disseminated infection [32]. Clearly, data from animal models of aspergillosis have shown a lack of antagonism when micafungin is combined with an azole or polyene. Which combination of drugs is most effective is unclear; however, the data suggest that monotherapy with micafungin may not be optimal for invasive aspergillosis. Prospective clinical trials evaluating combination therapy for invasive aspergillosis are urgently needed.

**DATA FROM ANIMAL MODELS**

Micafungin has been studied in several animal models of invasive candidiasis or aspergillosis [19, 25–34]. In a mouse model of disseminated azole-resistant *C. albicans* infection, survival and residual fungal burden in kidneys were similar with micafungin (1 mg/kg) and amphotericin B [26].

As a single agent, micafungin improved survival, compared with control animals, but no reduction in fungal burden in the lungs was noted in persistently neutropenic rabbit model of invasive pulmonary aspergillosis [34]. On the other hand, a combination of micafungin and ravuconazole in a neutropenic rabbit model of aspergillosis (caused by *A. fumigatus*) led to significant reductions in mortality, residual fungal burden, and serum galactomannan antigenemia, compared with each individual drug [28]. However, in a transiently neutropenic guinea pig model, although no antagonism was seen, synergy was not demonstrated with micafungin plus voriconazole [35].

Synergy or an additive effect was noted with a combination of micafungin and amphotericin B in mouse models of pulmonary aspergillosis [30, 31, 36, 37]. Micafungin was also effective against itraconazole-resistant strains of *A. fumigatus* and *A. terreus* in a mouse model of disseminated infection [32].

**Table 1. Comparative in vitro activity of micafungin (MFG) and other antifungal agents against common Candida species.**

<table>
<thead>
<tr>
<th><em>Candida</em> species</th>
<th>No. of isolates</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; in μg/mL by antifungal agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>733</td>
<td>AmB 0.25 5FC 1 FLU 0.5 ITR 0.13 POS 0.06 VOR 0.5 AFG 0.03 CFG 0.03 MFG 0.03</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>458</td>
<td>AmB 0.5 5FC 0.13 FLU 32 ITR 4 POS 2 VOR 1 AFG 1 CFG 1 MFG 1</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>317</td>
<td>AmB 0.5 5FC 0.13 FLU 2 ITR 0.25 POS 0.13 VOR 0.06 AFG 2 CFG 2 MFG 2</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>307</td>
<td>AmB 0.5 5FC 0.5 FLU 16 ITR 1 POS 1 VOR 0.13 MFG 0.06</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>50</td>
<td>AmB 0.5 5FC 32 FLU &gt;64 ITR 1 POS 0.5 VOR 1 AFG 1 CFG 2 MFG 2</td>
</tr>
<tr>
<td><em>C. lusitaniae</em></td>
<td>20</td>
<td>AmB 0.5 5FC 0.13 FLU 2 ITR 0.25 POS 0.13 VOR 0.25 AFG 2 CFG 2 MFG 2</td>
</tr>
<tr>
<td><em>C. dubliniensis</em></td>
<td>19</td>
<td>AmB 0.13 5FC 0.13 FLU 0.5 ITR 0.05 POS 0.06 VOR 0.03 AFG 0.06 CFG 0.03 MFG 0.03</td>
</tr>
<tr>
<td><em>C. guilliermondii</em></td>
<td>9</td>
<td>AmB 0.06 5FC 0.13 FLU 4 ITR 0.5 POS 0.06 VOR 1 AFG 1 CFG 1 MFG 0.5</td>
</tr>
</tbody>
</table>

NOTE: Data are from [14]. 5FC, 5-flucytosine; AFG, anidulafungin; AmB, amphotericin B; CFG, caspofungin; FLU, fluconazole; ITR, itraconazole; MFG, micafungin; POS, posaconazole; VOR, voriconazole.

* Median MIC.
for the 2 higher doses of micafungin (83.5%) were comparable to that of 200 mg of fluconazole per day (86.7%). All Candida species were highly susceptible to micafungin, and 2 isolates (both C. albicans) were fluconazole resistant. This study established micafungin as a valuable intravenous drug in the treatment of esophageal candidiasis in HIV-positive patients. A larger trial was conducted involving 523 predominantly HIV-positive adults with documented esophageal candidiasis. This multinational, double-blind, noninferiority study compared a single high dose of micafungin (150 mg/day) with fluconazole multinationally, double-blind, noninferiority study compared a positive adults with documented esophageal candidiasis. This larger trial was conducted involving 523 predominantly HIV-positive patients. A standard micafungin as a valuable intravenous drug in the treatment of esophageal candidiasis in HIV-positive patients. A study that compares intravenous micafungin with intravenous caspofungin for candidemia and invasive candidiasis is in progress. An interesting report noted a successful outcome with topical application of micafungin in the treatment of refractory yeast-related corneal ulcers in 3 patients [46].

Mold infections. The treatment of invasive aspergillosis with micafungin has not been examined in a randomized, controlled manner. Most data available are from open trials of micafungin for the treatment of refractory aspergillosis. In a large, open-label, phase-2 multinational study that assessed the efficacy of micafungin as primary or salvage therapy for invasive aspergillosis, 283 adults and children (22%) were enrolled [47]. A response was seen in 45% in the monotherapy group and 35% in the combination group. Results were similar for adults and children. Another study involving stem cell transplant (SCT) recipients evaluated the safety and efficacy of micafungin in combination with other antifungal drugs for the treatment of refractory aspergillosis [48]. In this open-label, noncomparative multinational study, there were 85 patients (69 adults and 16 children; 75 allogeneic and 10 autologous SCT recipients), 50 of whom had proven infection. They received 7 days of micafungin in combination with amphotericin B (71 patients), an azole (1 patient), or both (13 patients). The mean daily dose was 112 mg, and the mean duration of therapy was 63 days. Twenty-two patients (26%) had neutropenia at the onset of therapy. Complete or partial treatment success, as assessed by an expert panel and the investigators, was seen in 28% and 39% patients, respectively. Again, success rates were similar in children (6 of 16 patients) and adults (27 of 69 patients). Sixty-seven percent of patients died; 54% of deaths were deemed to be secondary to fungal infection. An open-label micafungin study from Japan reported success rates of 60% (6 of 10 patients) for invasive pulmonary aspergillosis—67% (6 of 9) for chronic necrotizing pulmonary aspergillosis, and 55% (12 of 22) for pulmonary aspergillus [45]. Overall, 57% of Aspergillus-infected patients had a satisfactory response.

In an open-label, noncomparative study of micafungin for the treatment of candidemia in 119 patients (101 adults and 18 children), overall success was noted in 83.2% of patients [43]. Sixty (88.2%) of 68 patients with a newly diagnosed candidemia and 39 (76.5%) of 51 patients with refractory infection were successfully treated with micafungin at 50–100 mg/day in adults and 1–2 mg/kg day in children. The average daily dose was 71 mg, and the mean duration of therapy was 20 days. Success rates were similar for patients with (73%) and without (86%) neutropenia. On the basis of candidal species, the response rates were 85% (39 of 46 patients) for C. albicans, 93% (28 of 30 patients) for C. glabrata, and 86% (18 of 21 patients) for C. parapsilosis; in vitro susceptibilities of the organisms were not reported. The results of several smaller trials also supported the efficacy of micafungin in the management of candidemia [44, 45]. A study that compares intravenous micafungin with intravenous caspofungin for candidemia and invasive candidiasis is in progress. An interesting report noted a successful outcome with topical application of micafungin in the treatment of refractory yeast-related corneal ulcers in 3 patients [46].

<table>
<thead>
<tr>
<th>Pharmacokinetic value</th>
<th>Caspofungin</th>
<th>Micafungin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; at 70–75 mg/day, μg/mL (range)</strong></td>
<td>12.1 (11.1–13.2)</td>
<td>10.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Steady-state AUC&lt;sub&gt;0-24&lt;/sub&gt;, μg h/mL (range)</strong></td>
<td>100.5 (87.9–114.8)</td>
<td>111.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>β for T&lt;sub&gt;1/2&lt;/sub&gt;, h</strong></td>
<td>10.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>11–17</td>
</tr>
<tr>
<td><strong>Clearance, mL/min</strong></td>
<td>10–12.5</td>
<td>~10.5</td>
</tr>
<tr>
<td><strong>Volume of distribution, L/kg</strong></td>
<td>...</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;1/2&lt;/sub&gt; of hepatic impairment, h ± SD</strong></td>
<td>&quot;Prolonged&quot;</td>
<td>14.4 ± 0.8</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;1/2&lt;/sub&gt; of severe renal impairment, h ± SD</strong></td>
<td>NA</td>
<td>14.2 ± 1.9</td>
</tr>
<tr>
<td><strong>Protein binding, %</strong></td>
<td>96</td>
<td>99.8</td>
</tr>
<tr>
<td><strong>Urine concentration, % of plasma</strong></td>
<td>1.4</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>CSF concentration</strong></td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

**NOTE.** Data are means and are from [3]. AUC<sub>0-24</sub>, area under the curve for 0–24 h; C<sub>max</sub>, maximum concentration; CSF, cerebrospinal fluid; T<sub>1/2</sub>, half-life.

<sup>a</sup> Range, 1–51.
<sup>b</sup> SD, 14.1.
<sup>c</sup> SD, 1.1.
Table 3. Salient comparative features of micafungin and caspofungin.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Caspofungin</th>
<th>Micafungin</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal candidiasis relapse rate</td>
<td>More than that for fluconazole</td>
<td>Equal to that for fluconazole</td>
<td>[39, 42]</td>
</tr>
<tr>
<td>Candidemia/candidiasis</td>
<td>Effective; data from randomized, controlled trials available</td>
<td>Effective; no data from randomized trials available (open trial data available)</td>
<td>[43, 61]</td>
</tr>
<tr>
<td>Empirical therapy for febrile neutropenia</td>
<td>Effective; randomized, controlled data available</td>
<td>No data</td>
<td>[62]</td>
</tr>
<tr>
<td>Prophylaxis during neutropenia in HSCT</td>
<td>No data</td>
<td>Effective; data from randomized, controlled trials available</td>
<td>[52]</td>
</tr>
<tr>
<td>Invasive aspergillosis (refractory)</td>
<td>Effective; open trials</td>
<td>Effective; data from open trials available</td>
<td>[47, 48, 63]</td>
</tr>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loading dose</td>
<td>Necessary (70 mg followed by 50 mg/day)</td>
<td>Not necessary (50–150 mg/day)</td>
<td></td>
</tr>
<tr>
<td>Adjustment in renal disease</td>
<td>Not necessary</td>
<td>Not necessary</td>
<td></td>
</tr>
<tr>
<td>Adjustment in liver disease</td>
<td>Necessary</td>
<td>Not necessary in mild to moderate disease&lt;sup&gt;a&lt;/sup&gt;</td>
<td>[54]</td>
</tr>
<tr>
<td>Data on children</td>
<td>Limited</td>
<td>More extensive</td>
<td>[43, 47, 49, 52, 64]</td>
</tr>
<tr>
<td>Adverse effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>+</td>
<td>?</td>
<td>[3]</td>
</tr>
<tr>
<td>Local phlebitis</td>
<td>+</td>
<td>?</td>
<td>[3]</td>
</tr>
<tr>
<td>Liver function abnormalities</td>
<td>+</td>
<td>?</td>
<td>[3]</td>
</tr>
<tr>
<td>Drug interactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Yes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No&lt;sup&gt;c&lt;/sup&gt;</td>
<td>[52, 58–60]</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Yes</td>
<td>No</td>
<td>[56, 58]</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>CYP 450 inducers (e.g., rifampin)</td>
<td>Decreased caspofungin levels</td>
<td>No</td>
<td>[58]</td>
</tr>
<tr>
<td>Cost of esophageal candidiasis, $&lt;sup&gt;d&lt;/sup&gt;</td>
<td>8485.26</td>
<td>5890.50</td>
<td>[58]</td>
</tr>
</tbody>
</table>

NOTE. HSCT, hematopoietic stem-cell transplantation; ?, less frequent, +, relatively more frequent.

<sup>a</sup> One recent trial suggested that dose adjustment is needed.

<sup>b</sup> Two recent small studies suggested a lack of interaction.

<sup>c</sup> One recent study recommended monitoring cyclosporin levels.

<sup>d</sup> Therapy for 21 days in patient weighing 70 kg, at the highest dose.

Prophylaxis. A phase 3, large, randomized, double-blind, multi-institutional comparative study was conducted in the United States and Canada that evaluated the efficacy of micafungin (50 mg or 1 mg/kg for patients weighing <50 kg) versus fluconazole (400 mg or 8 mg/kg for patients weighing <50 kg) as prophylaxis during the pre-engraftment period of neutropenia in 882 adults and children undergoing SCT [52]. Prophylaxis was considered to be successful if the patients remained free of invasive fungal infection during the 4 weeks after therapy and required no switches to polyene therapy for persistent neutropenic fever. Overall, the efficacy of micafungin was superior to that of fluconazole (80% vs. 73.5%; \(P = .03\)), despite the low dose of micafungin used. Benefit with micafungin was seen with all subgroups, including children and elderly patients, allogeneic and autologous SCT recipients, and patients with persistent neutropenia. Fewer courses of empirical antifungal therapy were required in the micafungin arm (15.4% vs. 21.4%; \(P = .024\)). Breakthrough candidal infections were similar in the 2 arms (0.9% vs. 0.4%; \(P = .44\)), and micafungin prevented more cases of aspergillosis (1 case in the micafungin arm vs. 7 cases in the fluconazole arm [0.2% vs. 1.5%; \(P = .071\)); however, the rate of documented aspergillosis was low. Not surprisingly, colonization with \(C. glabrata\) during therapy was more common in the fluconazole arm (32.4% vs. 2.9%). An important criticism of the study was that most patients, who were determined to have experienced treatment failure, received empirical therapy for a suspected but not confirmed fungal infection. Micafungin was as well tolerated as fluconazole. Adverse effects were responsible for fewer discontinuations in the micafungin-treated patients (4.2%), compared with fluconazole-treated patients (7.2%; \(P = .058\) vs. micafungin). Whether micafungin should be preferred to fluconazole as prophylaxis during the pre-engraftment period in SCT recipients and whether the improved long-term survival seen with flu-
conazole will also be seen with micafungin are important questions that need to be addressed [53].

ADVERSE EFFECTS

As a class, echinocandins have remarkably few adverse effects, because their target is unique to fungal cells and is absent in mammalian cells. Micafungin is well tolerated, without evidence of dose- or duration-related toxicities. Adverse events caused by micafungin that led to drug discontinuation occurred infrequently in all published studies [52]. Hyperbilirubinemia (3.3%), nausea (2.4%), diarrhea (2.1%), leukopenia, and eosinophilia have been reported [38, 39]; local phlebitis and thrombophlebitis at the injection site have also been reported in patients receiving micafungin via a peripheral vein. Such events were similar in type and frequency in children and adults. Possible histamine-mediated symptoms—such as rash, pruritus, facial swelling, and vasodilation—and isolated cases of anaphylaxis and hemolysis have been described. The drug has no significant effect on renal function.

DRUG INTERACTIONS

Drug interactions are expected to be uncommon with micafungin, because, unlike the azoles, the drug is not metabolized via the cytochrome P450 pathway, and it is not a substrate for intestinal or tissue p-glycoprotein. In studies of healthy volunteers or patients with hematologic disorders who received micafungin with tacrolimus, no significant changes were noted with any of the pharmacokinetic parameters [54, 55]. In a study of SCT recipients, 169 received both micafungin and cyclosporin for ~19 days; neither increases in hepatic enzymes nor an interaction between cyclosporin and micafungin was observed [52]. A pharmacokinetic study of healthy volunteers noted micafungin to be a mild inhibitor of cyclosporine metabolism; thus, monitoring cyclosporine levels is prudent when the 2 drugs are coadministered [56]. In the presence of steady-state micafungin, serum concentrations of sirolimus and nifedipine increased by 21% and 18%, respectively [57]. Patients who receive sirolimus or nifedipine in combination with micafungin should be monitored for sirolimus or nifedipine toxicity, and doses of those drugs should be reduced, if necessary. No drug interactions have been described between micafungin and many other drugs, including mycophenolate mofetil, rifampicin, ritonavir, warfarin, diazepam, fluconazole, and methotrexate. On the other hand, caspofungin is associated with more drug interactions; it decreases serum levels of tacrolimus by 20%, and when it is coadministered with cyclosporine, plasma concentrations of caspofungin are increased by 35%, along with transient abnormalities in liver function [58]. However, the latter data have been disputed by 2 recent small studies [59, 60]. In the absence of directly comparative data of caspofungin and micafungin, the exact differences in the frequency and severity of drug interactions are not known. Table 3 demonstrates the salient comparative features of micafungin and caspofungin.

DOSAGE

Micafungin is administered intravenously as a 1-h infusion once daily. The recommended adult dose is 50 mg/day for antifungal prophylaxis during the pre-engraftment period in SCT recipients and 150 mg/day for the treatment of esophageal candidiasis. Dose adjustments are not required for elderly persons or for patients with renal dysfunction. Likewise, mild to moderate hepatic impairment does not warrant changes in dose; the pharmacokinetics of the drug have not been adequately studied in persons with severe liver damage.

CONCLUSIONS

Micafungin, the second available echinocandin for clinical use in the United States, is active against Candida (albicans and non-albicans) and Aspergillus species but not Zygomycetes or Cryptococcus species or many emerging molds, such as Fusarium and Scedosporium species. Available data support its efficacy in the treatment of esophageal and systemic candidiasis. Against Aspergillus species, the drug is "fungistatic"; however, open-label data have suggested that micafungin might be useful in the treatment of refractory aspergillosis. The lack of antagonism when micafungin is combined with other antifungal drugs is encouraging; however, clinical trials are critical to determine whether combination therapy (e.g., micafungin plus voriconazole) is superior to monotherapy (e.g., voriconazole) for invasive aspergillosis. Conventional dosing, an excellent safety profile, and remarkably few drug interactions make micafungin a welcome addition to the expanding antifungal armamentarium.

Micafungin and caspofungin are remarkably similar, with a greater discrepancy in acquisition costs than in vitro and in vivo activity. Micafungin and caspofungin have an identical microbial spectrum of activity, with only minor differences in pharmacokinetics, pharmacodynamics, adverse effects, and drug interactions. Whether the enhanced in vitro activity exhibited by micafungin against Candida species will translate into a clinical advantage is unknown. Similarly, the relative rates of resistance development after the extensive clinical use of these 2 agents requires additional study. The significantly lower acquisition costs of micafungin will undoubtedly determine which echinocandin receives local hospital formulary selection when the FDA eventually approves micafungin for the more common candidemia and invasive candidiasis—thus the importance of the rapid completion of ongoing clinical studies comparing micafungin and caspofungin. Moreover, the costs of micafungin will similarly influence the wholesale costs of anidulafungin when it is introduced in the future. Overall, the costs of all echinocandins are considerable, compared with
those of conventional amphotericin B and generic fluconazole. This consideration will weigh heavily in the selection of antifungal agents in candidiasis.

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References


