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Micafungin

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Contents

Abstract

▲ Micafungin, an echinocandin antifungal agent with a novel mechanism of action, inhibits β-(1,3)-D-glucan synthase interfering with fungal cell wall synthesis. It shows excellent antifungal activity against a broad range of *Candida* spp., including azole-resistant strains, and *Aspergillus* spp. in *in vitro* and animal studies.

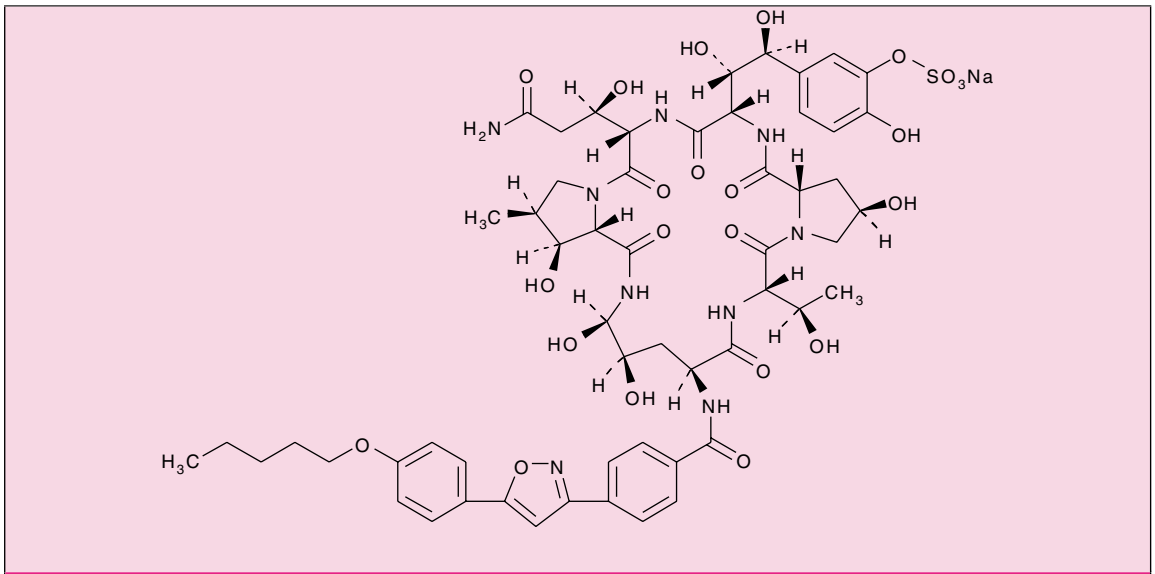
▲ In HIV-positive patients, intravenous micafungin 50–150 mg/day dose-dependently eradicated endoscopically confirmed oesophageal candidiasis, with micafungin 100 and 150 mg/day being more effective than micafungin 50 mg/day and as effective as fluconazole 200 mg/day in a double-blind trial.

▲ In nonblind trials, micafungin (monotherapy or combination therapy) was effective against invasive aspergillosis, candidiasis and candidaemia in paediatric and adult patients with newly diagnosed or refractory infections.

▲ Micafungin 50 mg/day provided significantly better antifungal prophylaxis than fluconazole 400 mg/day in 882 haematopoietic stem cell transplant recipients in a randomised, double-blind trial. Respective overall success rates were 80% and 73.5%.

▲ Micafungin is generally well tolerated. Adverse events were not dose- or infusion-related with micafungin 12.5–900 mg/day; no histamine-like reactions occurred. Micafungin was as well tolerated as fluconazole, with numerically fewer micafungin recipients discontinuing treatment (4.2% vs 7.2%).

Features and properties of micafungin (FK463)	
Potential indications	
Prophylaxis against fungal infections in patients undergoing haematopoietic stem cell transplants; treatment of invasive fungal infections in patients refractory to or intolerant of other antifungal agents	
Mechanism of action	
Interferes with fungal cell wall synthesis by inhibiting β-(1,3)-D-glucan synthase	
Dosage and administration (initial dosage in clinical trials, with dosage escalation permitted)	
Invasive aspergillosis: 75 mg/day (1.5 mg/kg/day if weight <40kg)	
Candida albicans: 50 mg/day (1 mg/kg/day if weight <40kg)	
Non-albicans *Candida* spp.: 100 mg/day (2 mg/kg/day if weight <40kg)	
Route of administration	Intravenous infusion
Frequency of administration	Once daily
Mean pharmacokinetic parameters in adult patients receiving 1-hour intravenous infusions of 50 mg/day	
Plasma concentration	4.95–4.97 mg/L
Volume of distribution at steady state	0.228–0.239 L/kg
Terminal elimination half-life	14.9–15.2h
Total plasma clearance	0.011–0.012 L/h/kg
Adverse events	
Most common treatment-emergent	Diarrhoea, bilirubinaemia, nausea



Micafungin

Advances in medicine in recent decades have resulted in an increased incidence of invasive fungal infections. Patients at risk of such infections include those with compromised immune systems due to aggressive cancer chemotherapy or immunosuppressive drug treatment and those with implanted devices such as central venous catheters.[1] AIDS has also fostered an increase in the incidence of fungal infections, as patients with this condition are highly susceptible to certain fungi.[1]

In particular, central venous catheter-related blood stream infections, 8% of which are associated with *Candida* spp., increase mortality in hospitalised patients and are estimated to cost the US health care system $US25 000 per episode.[2] The total cost of caring for patients with such infections has been estimated to be ≥$US300 million.[2]

In the US, 10% of *C. albicans* bloodstream isolates were resistant to fluconazole according to a US surveillance programme; moreover, 48% of candidal bloodstream infections were caused by non-albicans species (*C. glabrata*, *C. krusei*), which are more likely to be resistant to fluconazole or itraconazole than *C. albicans*.[2] Thus, there is a clear need for alternative antifungal agents that are effective against a broad range of *Candida* species including azole-resistant strains.[2]

Traditional systemic antifungal agents have targeted ergosterol in fungal cell membranes. Azole antifungal agents (e.g. fluconazole, itraconazole) inhibit synthesis of ergosterol; amphotericin B, a polyene agent, disrupts membranes by binding to this substance. Echinocandin antifungal agents are a new and unique class, in that they inhibit synthesis of a distinct, major cell wall component, β-(1,3)-D-glucan.[3]

Micafungin, the focus of this review, is an echinocandin antifungal agent synthesised from a naturally occurring compound isolated from the culture broth of the fungus *Coleophoma empetri*.[4] The drug inhibits β-(1,3)-D-glucan synthase resulting in morphological changes to the cell wall.[5]

1. Pharmacodynamic Profile

In Vitro Activity

Several studies have evaluated the antifungal properties of micafungin *in vitro*. Studies described below used standard procedures to test minimum

inhibitory concentrations (MICs) as laid out in the National Committee for Clinical Laboratory Standards (NCCLS M27-A).[6] It is important to note that susceptibility breakpoints for echinocandin agents, including micafungin, have not been established.

- When tested *in vitro* against clinical isolates, micafungin was active against a range of *Candida* species including *C. albicans* (range of MIC for 90% of strains [MIC_{90}] 0.0156–0.5 mg/L),[7-12] *C. dubliniensis* (0.5 mg/L),[7] *C. glabrata* (0.0156–0.25 mg/L),[8-11] *C. guillermondii* (2 mg/L),[11] *C. krusei* (0.0125–0.125 mg/L),[8,9,11,12] *C. tropicalis* (0.0313–0.5 mg/L)[8-12] and *C. parapsilosis* (1–<8 mg/L).[8-12]

- Minimum fungicidal concentrations of micafungin for *Candida* spp. did not differ more than 2-fold from the respective MIC_{90} values in one study that reported these.[9]

- Micafungin was also active against azole-resistant clinical isolates of *C. albicans*, for which MIC_{90} values were generally ≤2-fold higher than those for azole-sensitive clinical isolates.[8,10,11,13] MIC data for 164 isolates of *Candida* spp., including azole-resistant strains, obtained from blood cultures in cancer patients treated in two Canadian hospitals between 1996 and 2000 are presented in figure 1.[10]

- Micafungin was active against clinical isolates of *Aspergillus fumigatus*, *A. flavus*, *A. niger* and *A. terreus* (MIC_{90} values all ≤0.0156 mg/L).[8,11,13]

- With respect to pathogenic dimorphic fungi, micafungin was active against the mycelial forms of *Blastomyces dermatidis*, *Histoplasma capsulatum* and *Coccidioides immitis* (MIC_{90} 0.0078–0.0625 mg/L) but, paradoxically, was inactive against the yeast-like growth forms of these spp.[14] Micafungin was inactive against *Cryptococcus neoformans* (MIC_{90} >64 mg/L).[8,11,13]

- There was no evidence of antagonism when micafungin was combined with amphotericin B in an *in vitro* broth macrodilution checkerboard experiment involving ten clinical *Aspergillus* isolates.[15] In another *in vitro* study, micafungin showed additive or synergistic effects or no antagonism against *Aspergillus* and *Fusarium* spp. when used in combination with amphotericin B.[16] The synergistic activity of micafungin plus amphotericin B was supported by another *in vitro* study of *A. fumigatus* isolates using a radiometric assay.[17]

- In combination with nikkomycin Z, a chitin synthase inhibitor, synergistic inhibition of growth of *A. fumigatus* (as measured by broth microdilution and significant [$p < 0.001$] synergistic hyphal damage) was demonstrated using an MTT (1-dimethylthiazole-5-thiol) assay over a broad range of concentrations.[18]

- Micafungin showed additive activity against three clinical isolates of *A. fumigatus* when combined with voriconazole in an *in vitro* broth macrodilution checkerboard experiment.[19] The additive activity against *A. fumigatus* was confirmed in another *in vitro* study using a radiometric assay.[17] These two agents also showed time-dependent synergistic hyphal damage after 12 and 24 hours of incubation.[19]

- Micafungin had a measurable post-antifungal effect (PAFE) against isolates of *C. albicans*, *C. glabrata*, *C. krusei* and *C. tropicalis*.[20] The drug was fungicidal against *Candida* spp. at concentrations ranging from 4 to 16 times the MIC. At concentrations equal to the MIC, the PAFE for *Candida*

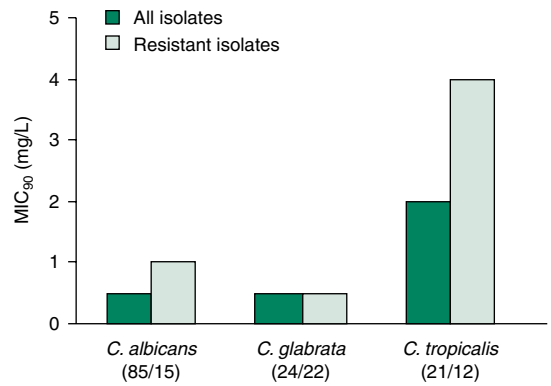


Fig. 1. *In vitro* activity of micafungin against clinical isolates of *Candida* spp. *In vitro* activity of micafungin as determined in broth microdilution assays versus isolates of *Candida* spp. obtained between 1996 and 2000 in blood cultures from cancer patients in two Canadian hospitals.[10] The number of isolates are indicated in brackets as follows: all isolates/isolates resistant to fluconazole and/or itraconazole. Data are not presented for 16 isolates of *C. parapsilosis*, for which the MIC_{90} was >8 mg/L, and eight isolates of *C. krusei* for which the MIC_{90} ranged from 0.06 to 2 mg/L. **MIC_{90}** = minimum inhibitory concentration for 90% of strains.

spp. ranged from −0.27 to 20.1 hours, with a concentration-dependent increase in the PAFE observed at four times the MIC.

- Against *A. fumigatus*, the PAFE of micafungin was the same as that of caspofungin (both PAFE ≤0.5 hours), whereas that of amphotericin B (7.5 hours) was prolonged.[21] The PAFEs of ravuconazole (PAFE 0.38 hours), itraconazole (0.5 hours) and posaconazole (0.75 hours) were also relatively short.
- The addition of 4% human serum albumin increased the MICs for *Candida* spp. and *A. fumigatus* more than 32-fold when tested *in vitro*.[11]
- In contrast to triazole antifungal agents and amphotericin B, micafungin, caspofungin and lipid formulations of amphotericin B were effective against both planktonic and biofilm-associated *C. albicans* and *C. parapsilosis*.[22]
- Micafungin (0.0155–10 mg/L) dose-dependently inhibited adherence of *C. albicans* to epithelial cells by up to 90% compared with control.[23] In contrast, the maximal inhibition of adherence achieved with fluconazole (4–62.5 mg/L) was 30%.[23]

In Animal Studies

Micafungin has been investigated in various animal models of fungal infections. The drug has been studied in mice with disseminated *C. albicans*,[24,25] disseminated *C. tropicalis*,[26] disseminated *A. fumigatus* or *A. terreus*,[27] disseminated[25,28] or pulmonary aspergillosis,[29,30] and in persistently neutropenic rabbits with disseminated candidiasis or invasive pulmonary aspergillosis.[31] Micafungin has also been evaluated as prophylaxis against *Pneumocystis jiroveci* (previously known as *P. carinii*) in mice with severe combined immunodeficiency (SCID).[32] In addition, the effects of micafungin on histamine release, blood pressure and heart rate have been evaluated in rats.[33]

- Micafungin significantly (all $p < 0.01$ vs control mice) prolonged survival in mice with disseminated candidiasis or aspergillosis, when administered intravenously for 4 days at dosages ≥0.125 and ≥0.5 mg/kg/day, respectively.[25] At a dosage of 1 mg/kg/day, no mice with disseminated candidiasis or aspergillosis died when monitored for 22 days after infection. All control mice died within 13 days of injection with *C. albicans* and within 5 days of injection with *A. fumigatus* conidia.[25]
- In mice with cyclophosphamide- or hydrocortisone-induced immunosuppression, the effective dose in preventing death in 50% of mice (ED_{50}) with micafungin was somewhat higher in immunosuppressed mice than in normal mice (figure 2).[25] The ED_{50} values 15 days after infection with various *Candida* spp. or *Aspergillus* spp. are also presented in figure 2.[25]
- Intravenous micafungin 1 mg/kg for 5 days prevented death in BALB/c mice with disseminated azole-resistant *C. albicans* infection.[24] All untreated mice died within 16 days of inoculation.[24] The number of yeast colonies raised from homogenised kidney tissue (0.33 vs 5.76 $\log_{10}$ colony forming units [cfu]/kidney) and plasma concentrations of β-(1,3)-*D*-glucan (3.7 vs 51.1 ng/L) were significantly ($p < 0.01$) lower in micafungin-treated than in control animals.[24]
- A single dose of micafungin 0.5 or 1 mg/kg administered 1 hour after intravenous infection with *C. albicans* FP633 significantly reduced the viable counts of yeast cells recovered from kidney tissue 24 hours after infection ($p < 0.01$ vs control).[25] In contrast, a single 4 mg/kg intravenous dose of fluconazole was ineffective in this model.
- In rabbits with persistent neutropenia induced by cytarabine, intravenous micafungin 0.25–2 mg/kg/day produced significant ($p < 0.05$ vs untreated neutropenic control rabbits) dose-dependent clearance of *C. albicans* from liver, spleen, kidney, brain, eye, lung and vena cava that reflected the results of *in vitro* time-kill assays.[31]
- Although the drug did not quantitatively reduce growth of *A. fumigatus* in the lung tissue of rabbits, the extent of lung injury was reduced ($p < 0.05$ for micafungin 1 or 2 mg/kg vs control) and the duration of survival increased among rabbits treated with dosages ≥0.5 mg/kg ($p < 0.001$).[31]
- Seven days' treatment with intravenous micafungin (2–10 mg/kg/dose) effectively cleared amphotericin B- and fluconazole-resistant *C. tropi-*

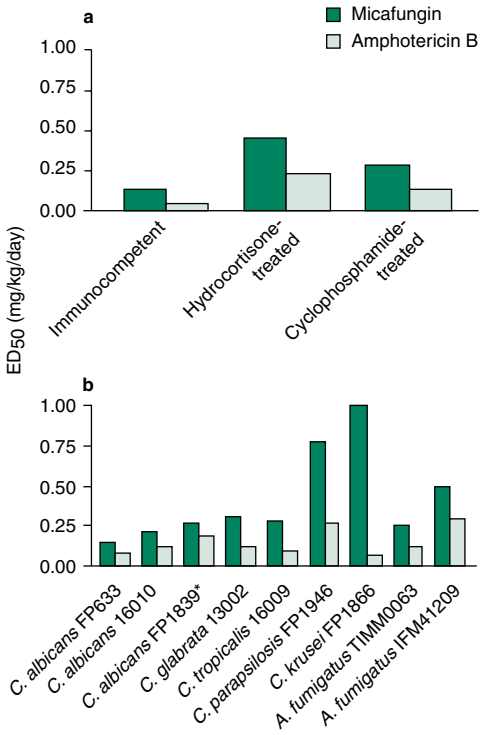


Fig. 2. Efficacy of micafungin in mouse models of disseminated candidiasis or aspergillosis. (**a**) The influence of immunosuppression on disseminated *Candida albicans* FP633 infection was evaluated by comparing the effects of antifungal agents in immunocompetent mice with those treated with intraperitoneal cyclophosphamide 200 mg/kg administered 4 days prior and 1 day after infection, or subcutaneous hydrocortisone 100 mg/kg administered 1 day prior to, and 3, 24 and 48 hours after infection.[25] (**b**) The effective dose at preventing death in 50% (ED_{50}) of mice 15 days after infection with *Candida* spp. or *Aspergillus* spp. was determined by treating mice with micafungin, amphotericin B or fluconazole (not shown) once daily for 4 days starting 1 hour after infection.[25] Disseminated infections were induced by intraperitoneal injection of cyclophosphamide 200 mg/kg 4 days before (*A. fumigatus* TIMM0063), and 1 (*C. albicans*, *C. tropicalis*, *C. krusei*, *C. parapsilosis* and *A. fumigatus* IFM41209) and 6 (*C. glabrata*) days after infection. ED_{50} values for fluconazole are not presented because they were 9.6- to >77-fold greater than those of micafungin. * indicates fluconazole-resistant strain (ED_{50} >20 mg/L for fluconazole).

calis infection in mice with persistent neutropenia.[26] As might be expected, intraperitoneal amphotericin B (0.5–5 mg/kg/dose) or oral fluconazole (50 mg/kg/dose) failed to clear the infection.

- Neutropenic mice infected with *A. fumigatus* showed prolonged survival after 7 days' treatment with intravenous micafungin (2–10 mg/kg/day), intravenous liposomal amphotericin B (5 or 25 mg/kg/day) or intraperitoneal amphotericin B (0.5 or 5 mg/kg/day).[27] The same regimen of micafungin was also effective against *A. terreus* infections in this mouse model, as was itraconazole 25 or 75 mg/kg/day administered by gavage. However, amphotericin B had no effect against *A. terreus* infections.[27]

- In mice with pulmonary aspergillosis induced by intranasal inoculation, micafungin 0.25–1 mg/kg significantly prolonged survival ($p < 0.01$ vs untreated control mice all of which died within 9 days of inoculation).[29] The ED_{50} of micafungin ranged from 0.26–0.51 mg/kg against the three strains of *A. fumigatus* used in the study. Plasma micafungin concentrations ≥0.55 mg/L significantly reduced viable counts of fungal cells in lungs when the drug was administered as a continuous infusion ($p < 0.05$ vs control).[29]

- In a mouse model of systemic aspergillosis caused by *A. fumigatus* infection, subcutaneous micafungin 10 mg/kg twice daily for 12 days significantly prolonged survival compared with untreated or saline-treated control animals (70% vs 20–30% survival 15 days postinfection, $p = 0.011$; values estimated from a graph).[28] Moreover, this micafungin regimen reduced the number of cfu in the brain and kidney compared with both control groups.

- Subcutaneous micafungin 3 mg/kg twice daily plus intravenous amphotericin B 0.8 mg/kg/day also prolonged survival in this model, as did the same regimen of micafungin plus oral itraconazole 100 mg/kg/day.[28]

- Intraperitoneal micafungin in combination with intravenous amphotericin B was more effective than monotherapy with either agent in a mouse model of pulmonary aspergillosis.[30] Thus, a higher percentage of mice survived (no p-value reported) and the fungal burden in the lung was significantly ($p < 0.001$) lower with combination therapy (both dosages 0.5 mg/kg) than with monotherapy treatments (no data reported in abstract).

• Micafungin was effective as prophylaxis against *P. jiroveci* infection in SCID mice.[32] When administered subcutaneously for 6 weeks starting 1 day after intranasal inoculation, micafungin 0.2 or 1.0 mg/kg/day, or pentamidine 4 mg/kg/day suppressed growth of *P. jiroveci* ($p < 0.01$ vs saline-treated mice). Neither *P. jiroveci* cysts, nor pathological changes typical of early stage infection were detectable in the lungs of any micafungin-treated mouse at the end of treatment. Although a pathogen-specific DNA fragment was amplified from the lungs of some micafungin- and pentamidine-treated mice, the amount of material was considerably less than that contained in the lungs of control mice, all of which were positive.[32]

• A single dose of intravenous micafungin 10 mg/kg showed no effect on histamine release, blood pressure or heart rate compared with control (saline vehicle) in rats.[33] However, at higher concentrations of micafungin (32 and 100 mg/kg), there were significant transient increases in the release of histamine; at a dose of 100 mg/kg there was also a significant transient decrease in blood pressure (no p-values were reported in abstract). There were no effects on heart rate with any dose of micafungin.[33]

• In contrast, compared with rats treated with vehicle control, caspofungin 10 mg/kg caused significant prolonged release of histamine, and significant and persistent reductions in blood pressure at concentrations of 3.2 and 10 mg/kg in the same study (no p-values reported).[33] Furthermore, caspofungin treatment caused a persistent decrease in heart rate.[33]

2. Pharmacokinetic Profile

The pharmacokinetic properties of micafungin have been studied in animals[34,35] and in healthy adult volunteers,[36-40] healthy elderly volunteers,[38] in children with neutropenia,[41] in premature infants,[42] in adult haematopoietic stem cell transplant (HSCT) recipients,[24,41,43,44] in patients with severe renal impairment[45] and in those with moderate hepatic impairment.[46] In patients and healthy volunteers, micafungin was administered as a once-daily 1-[34,37-41,44-47] or 2-hour[36] intravenous infusion. Currently, all pharmacokinetic data in humans are available in abstracts.

Absorption and Distribution

• The area under the plasma concentration-time curve (AUC) and peak plasma concentrations (C_{max}) of micafungin increased in a dose-proportional manner after a single infusion of micafungin 2.5–50mg in 27 Japanese volunteers.[36] Steady-state plasma concentrations were obtained by day 4 in six men who received 25 mg/day for 7 days (no data reported).[36]

• Concentrations of micafungin were highest in the lung, liver, spleen and kidney tissue of rabbits treated for 8 days with intravenous micafungin 0.5–2.0 mg/kg/day.[34] Although the drug was present in brain tissue it was not detectable in cerebrospinal fluid.[34]

Metabolism and Elimination

• Sixty-six and 19% of total radioactivity, respectively, was associated with parent drug 1 and 48 hours after a 1-hour infusion of ^{14}C-labelled micafungin (28.3mg) in six men.[37] Between 4 and 48 hours after administration, 3–8% of radioactivity was associated with a ω-1-hydroxy metabolite (M-5). Within 7 days of administration, 43.8% of radioactivity was recovered in faeces and 7.4% in urine; 26% and 10% of recoverable radioactivity in faeces and urine was associated with unchanged micafungin.[37]

• The mean terminal elimination half-life ($t_{1/2}$) of micafungin was 13.6 hours and plasma concentrations of the parent drug were not measurable beyond 72 hours.[37] Radioactivity was still detectable in plasma after 7 days and the mean $t_{1/2}$ of radioactivity was 92.8 hours.

• The mean $t_{1/2}$ of micafungin was similar after single (14.7 hours) and multiple doses (14.6 hours) in 27 Japanese volunteers.[36]

Special Patient Populations

• The single-dose pharmacokinetics of micafungin were similar in young and elderly healthy Japanese

men.[38] After an infusion of micafungin 50mg, mean plasma concentrations were 4.95 and 4.97 mg/L in ten young men aged 20–24 years and ten elderly men aged 66–78 years, respectively.[38] Corresponding mean values for total body clearance (CL_{tot}; 0.011 vs 0.012 L/h/kg), volume of distribution at steady state (V_{ss}; 0.228 vs 0.239 L/kg) and plasma protein binding ratio (both 99.85%) were also similar between men in the two age groups. Consistent with values discussed earlier,[36] the mean $t_{1/2}$ was 15.2 and 14.9 hours, respectively, in young and healthy elderly men.[38]

- Pharmacokinetic parameters in children (aged 2–12 years) with neutropenia were similar to those in adult patients.[41] AUC from zero to 24 hours (AUC_{24}) values were dose proportional and approximately 25–30% higher at steady state in both age groups (no data reported). Mean V_{ss} values in children ranged from 0.266–0.466 L/kg compared with 0.246–0.271 L/kg in adult patients; corresponding mean CL_{tot} values ranged from 0.015–0.025 L/h/kg and 0.012–0.015 L/h/kg.[41]

Children received micafungin 0.5–4 mg/kg/day and adults 12.5–200 mg/day.[41]

- A study in eight children (aged 2–12 years) and eight adolescents (aged 13–17 years) with febrile neutropenia confirmed that pharmacokinetic parameters in children were similar to those in adolescents.[47]

Children and adolescents received a 1-hour infusion of micafungin 0.5–4 mg/kg/day for an average of 8 days (range 1–14 days).[47]

- Mean pharmacokinetic values in eight premature infants who received a single 30-minute intravenous infusion of micafungin 0.75 mg/kg were: C_{max} 2.52 μg/mL, minimum trough concentration (C_{min}) 20 μg/mL, volume of distribution 0.406 L/kg, AUC 20.6 μg • h/mL and $t_{1/2}$ 7.5 hours.[42] Notably, the mean C_{min} value was greater than the MIC for most *Candida* spp. (section 1).

- In patients with moderate hepatic impairment (Child Pugh score 7–9), there were no clinically relevant changes in single-dose pharmacokinetic parameters of micafungin compared with healthy volunteers.[46] Although the mean C_{max} value was reduced by 21% in patients with hepatic impairment, this decrease was not statistically significant. There was a significant ($p < 0.05$) 23% reduction in mean AUC_{24} and AUC from zero to infinity (AUC_{∞}) values; however, no adjustments to the initial dosage of micafungin in patients with moderate hepatic impairment are thought to be necessary.

Eight healthy volunteers and eight patients with hepatic impairment received a single infusion of micafungin 100mg.[46]

- Single-dose pharmacokinetic properties of micafungin in patients with severe renal impairment were similar to those in healthy volunteers.[45] There were no significant differences in the rate (t_{max} 1.2 vs 1.1 hours) and extent (C_{max} 8.68 vs 8.17 mg/L; AUC_{48} 107.8 vs 111.4 mg • h/L; AUC_{∞} 118.8 vs 123.8 mg • h/L) of absorption in those with renal impairment versus healthy volunteers. Elimination parameters were also similar in both groups ($t_{1/2}$ 14.23 vs 14.83 hours; CL 0.011 vs 0.010 L/h/kg).

Nine patients with severe renal impairment (glomerular filtration rate [GFR] <1.8 L/h [<30 mL/min]) and nine healthy volunteers (GFR >4.8 L/h [>80 mL/min]) received a single 1-hour infusion of micafungin 100mg.

Drug Interactions

- Concomitant administration of micafungin and fluconazole had no effect on the pharmacokinetic properties of either agent in 62 adult HSCT recipients.[43,44] C_{max} and AUC values of micafungin were proportional to dose in patients receiving micafungin 12.5–200 mg/day plus oral or intravenous fluconazole 400 mg/day (data not reported).[43,44] AUC values on day 7 were similar to those obtained on day 1.[44] The mean $t_{1/2}$ of micafungin ranged from 11.3 to 13.9 hours on day 1 and from 10.7 to 13.5 hours on day 7.[43] Mean V_{ss} values ranged from 0.246–0.271 L/kg and CL_{tot} values ranged from 0.012 to 0.015 L/h/kg.[44]

Patients were treated for a mean duration of 10 days (range 1–27 days) in this study.[43,44]

- Studies in healthy adult volunteers indicated that micafungin had no clinically relevant effects on the single-dose pharmacokinetic properties of

ciclosporin[40] or tacrolimus,[39] and that single doses of these concomitantly administered agents had no effects on the single-dose or steady-state pharmacokinetic parameters of micafungin.[39,40]

In these two studies (n = 28 volunteers in each study), volunteers received a single dose of oral tacrolimus 5mg[39] or oral ciclosporin 5 mg/kg[40] on days 1, 9 and 16, and a 1-hour infusion of micafungin 100mg[39,40] on days 7, 9 and 12–16.

3. Therapeutic Efficacy

Micafungin has been evaluated in patients with presumed and proven fungal infections due to *Aspergillus* or *Candida* spp.,[48-51] including HIV-positive adults[52-55] or children[55] with oesophageal candidiasis, and has been used as a prophylactic agent in patients with haematological malignancies undergoing HSCT.[50,56,57] Micafungin was administered by intravenous infusion in these noncomparative trials, most of which were multicentred. All studies are currently only available as abstracts.

In HIV-Positive Adults with Oesophageal Candidiasis

- Fourteen to 21 days' treatment with micafungin 100 (n = 62) or 150 mg/day (n = 59) was as effective as fluconazole 200 mg/day (n = 60) in the eradication of oesophageal candidiasis in patients with HIV in a randomised, double-blind, multicentre trial.[52] Endoscopically confirmed oesophageal clearance of infection (primary endpoint) occurred in 77.4%, 89.8% and 86.7% of micafungin 100 or 150 mg/day or fluconazole recipients, respectively, in intent-to-treat (ITT) analyses of all patients who received at least one dose of micafungin. Response rates were significantly lower in the micafungin 50 mg/day group (n = 64) than in the 150 mg/day group (68.8% vs 89.8%; p = 0.007), with the response to micafungin being dose-dependent (p = 0.024; Cochran-Mantel-Haenszel analysis).[52]
- These data were supported by a smaller study in HIV-positive patients with endoscopically-confirmed oesophageal candidiasis (figure 3).[53,54] Clinical responses, defined as clearing or improvement from baseline in dysphagia, odynophagia and retrosternal pain, were observed in virtually all patients treated with dosages ≥50 mg/day, with improvement in endoscopic lesions documented in 35 of 36 patients (97.2%) treated with micafungin 75 or 100 mg/day for ≥10 days.[53,54]

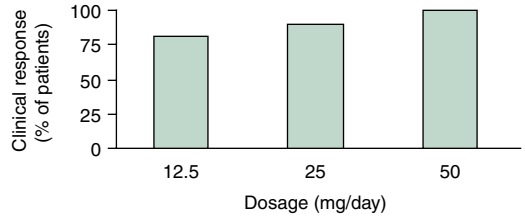


Fig. 3. Efficacy of micafungin in HIV-positive adults with oesophageal candidiasis. Clinical responses, defined as clearing or improvement from baseline in dysphagia, odynophagia and retrosternal pain, in patients treated for ≥8 days with micafungin 12.5 (n = 21), 25 (n = 20) or 50 mg/day (n = 21) in a multicentre, noncomparative study in South Africa.[54] Twelve patients received <8 days' therapy including five who withdrew consent, three who died secondary to progression of AIDS, three who withdrew because of adverse events (not specified) and one who withdrew because of a lack of efficacy.

Patients received a 1-hour intravenous infusion of micafungin 12.5–100 mg/day for 1–23 days (mean 12 days) in this ongoing multicentre, nonblind study in South Africa.[53]

- Ninety-two percent of paediatric (n = 4) and adult (n = 93) patients with endoscopically-confirmed oesophageal candidiasis responded (complete or partial response) to treatment with micafungin in another nonblind trial.[55]

In this multinational trial, 92% of patients were infected with HIV; 88 patients had new infections and nine recipients were refractory to previous treatment (not specified in abstract).[55] Patients with infections caused by *C. albicans* (84% of patients) received an initial dosage of micafungin 50 mg/day (1 mg/kg in those <40kg in weight), whereas those with infections caused by other *Candida* spp. received 100 mg/day (2 mg/kg in those <40kg); dosage escalation was permitted in those who showed an incomplete response. The mean duration of treatment was 22 days (maximum duration 42 days).

In Patients with Cancer and Candidaemia

- Micafungin was effective in cancer patients with candidaemia.[49] In 12 evaluable patients, six of

whom were neutropenic at the time treatment with the drug was initiated, eight and three were deemed to have had complete and partial responses to therapy, respectively. Two non-neutropenic patients, one with an undrained abscess and a second with an infected biliary stent, had relapses; one patient with relapsed leukaemia, neutropenia and *C. krusei* candidaemia failed to respond.[49]

Micafungin was administered intravenously at a dosage of 50–150 mg/day for 4–26 days (median 15 days).[49] Nine patients were infected with non-albicans spp. including *C. glabrata* (n = 6), *C. tropicalis* (2), *C. krusei* (1) or *C. parapsilosis* (1). The most common sources of infection were central venous catheters (9) or intra-abdominal sites (3). Seven patients received either amphotericin B formulations (5) or fluconazole (2) concomitantly.[49]

In Patients with Aspergillosis or Candidiasis

- A complete or partial response (success) was achieved by 88% (60 of 68 patients) of patients with newly diagnosed candidaemia and 76% (39 of 51) of those with refractory candidaemia receiving micafungin treatment in a nonblind, multinational trial.[58] Subgroup analysis indicated that success rates were high in adults (86 of 101 patients; 85%) and paediatric patients (13 of 18 patients; 72%), including neonates (6 of 7 neonates; 86%).
- Micafungin was also effective against several *Candida* spp. in this trial.[58] Success rates based on a per pathogen basis were: *C. albicans* 85% (39 of 46 patients), *C. glabrata* 93% (28 of 30), *C. parapsilosis* 86% (18 of 21), *C. tropicalis* 82% (9 of 11), *C. krusei* 67% (6 of 9), *C. pelliculosa* 100% (2 of 2), *C. inconspicua* 100% (1 of 1) and *C. lusitaniae* 100% (1 of 1). Infections persisted in 6% (4 of 68 patients) of recipients with newly diagnosed candidaemia and 18% (9 of 51) of those with refractory infections.[58]

The initial dosage of micafungin was 50 mg/day (1 mg/kg in those weighing <40kg) in patients with infections caused by *C. albicans* and 100 mg/day (2 mg/kg in those <40kg in weight) in recipients with infections caused by other *Candida* spp. in this trial.[58] Dose escalation was permitted in those who showed an incomplete response, with 41% of patients requiring dose escalation. The mean duration of treatment was 20 days, with a maximum duration of 42 days.[58]

- In a randomised, nonblind, multinational trial, micafungin proved effective in the treatment of invasive aspergillosis in paediatric and adult patients who had undergone HSCT or had leukaemia.[50] A complete or partial response was experienced by 27 of 38 patients (71%) receiving micafungin versus 50 of 141 micafungin-combination therapy recipients (35%). With the exception of *A. terreus* (0 of 7 infections), complete or partial responses were seen against all *Aspergillus* spp.[50]

In this trial, patients (aged 9 weeks to 84 years; mean age 37 years) with probable or proven invasive aspergillosis failing, likely to fail or intolerant of existing antifungal therapy received micafungin 75 mg/day (1.5 mg/kg in those weighing ≤40kg) or a combination of previous therapy (not specified) plus micafungin.[50] The median duration of treatment was 34 days in adults and 37 days in children. Dosage escalation was permitted, with 60% of adults having their dosage escalated (25% received micafungin ≥200 mg/day).

- Another nonblind, multinational study supported the efficacy of micafungin-containing antifungal regimens in patients with aspergillosis unresponsive to previous treatment, with 39% of 85 recipients responding.[51] A complete or partial response (success) was achieved by 40% (30 of 75 recipients) of allogenic transplant patients and 30% (3 of 10) of autologous transplant recipients. Success rates in paediatric patients (six of 16 recipients) were similar to those reported in adults (27 of 69). Survival rates at the end of therapy and at study-end were 89 and 33%; 54% of deaths were probably related to the fungal infection.[51]

Participants received one of the following regimens: micafungin plus amphotericin B; micafungin plus an azole (not specified); micafungin plus an azole (not specified) plus amphotericin B.[51] Sixteen paediatric and 69 adult patients received an initial dosage of micafungin 75 mg/day (1.5 mg/kg in those weighing <40kg), with dose escalation per-

mitted. Patients were treated for 7–638 days (mean duration 63 days); the average daily dosage of micafungin was 112 mg/day (range 11–292 mg/day). Dosages of the other agents in these combination regimens were not specified.[51]

• Micafungin was effective in the majority of patients with presumed aspergillosis or candidiasis in a Japanese noncomparative, multicentre study.[48] Overall clinical responses were experienced by six of ten patients with invasive pulmonary aspergillosis, six of nine recipients with chronic necrotising pulmonary aspergillosis and 12 of 22 patients with pulmonary aspergilloma. In those with candidal infections, clinical responses were achieved by all six patients with candidaemia and five of seven patients with oesophageal candidiasis. Mycological eradication was documented in 12 of 19 patients infected with *A. fumigatus*, *A. flavus*, *A. niger* or *A. terreus* and four of eight patients with infections caused by *C. albicans*, *C. glabrata* or *C. krusei*.[48]

In this Japanese study, received micafungin 12.5–150 mg/day for 7–56 days.[48]

Prophylaxis in Bone Marrow Transplant Recipients

• Micafungin provided significantly better antifungal prophylaxis than fluconazole in HSCT recipients (aged ≥6 months).[59] The overall success rates (defined as the absence of fungal infection throughout the 4 weeks following treatment) in micafungin (n = 425) and fluconazole (n = 457) groups were 80% and 73.5% (95% CI 0.9%, 12%) in this large, randomised, double-blind, multicentre trial. Furthermore, there was a trend (p = 0.07) for fewer micafungin recipients to experience aspergillosis than fluconazole recipients (one vs seven patients), with no between-group difference in the rate of candidiasis (0.9% vs 0.4% of recipients).[59]

Patients received micafungin 50 mg/day (1 mg/kg in those <50kg in weight) or fluconazole 400 mg/day (8 mg/kg in those weighing <50kg; route of administration not reported).[59] Treatment was initiated within 48 hours of transplantation and continued until up to 5 days following engraftment to ≥500 cells/mm^3, development of a fungal infection, unacceptable toxicity, death or day 42 following HSCT. The median duration of treatment was 18 days.[59]

• Similarly, in a small noncomparative trial, micafungin provided effective antifungal prophylaxis in 36 patients undergoing HSCT.[56,57] No patients developed a proven or probable fungal infection, as defined by the European Organisation for Research and Treatment of Cancer criteria, during 8–28 days' (median 18 days) treatment. Micafungin was stopped after 8–25 days (median 14 days) and empirical antifungal therapy introduced in 11 of these patients for suspicion of fungal infection because of persistent fever despite 96 hours of antibiotic therapy.[56,57]

In this study, sequential groups of ten, ten, eight and eight patients (aged 19–62 years) with haematological malignancies received micafungin 3, 4, 6 and 8 mg/kg/day, respectively, starting 2 or 3 days before transplantation.[56,57] Patients received median dosages of 245, 294, 420 and 578 mg/day, respectively, for a median of 16.5, 18.5, 22.5 and 20 days. Although dosages as high as 900 mg/day were given, the maximum tolerated dose was not achieved. Micafungin was given for at least 7 days or until the absolute neutrophil count exceeded 0.5×10^9/L, but for no longer than 28 days. Engraftment rates did not differ from those of age- and procedure-matched historical controls.[56,57]

4. Tolerability

• Based on limited data derived from abstracts, intravenous micafungin appears to be generally well tolerated in trials discussed in section 3.[47,48,50,52,53,56,59] Adverse events were not dose-related over the range of 12.5–900 mg/day, with the maximum tolerated dosage not reached over this range (i.e. the highest dose of micafungin that did not cause the same grade 3 or 4 adverse event in at least three individual patients).[48,53,56] Infusion-related or histamine-like reactions have not been observed in studies to date.[43,47,53,56,59]

• In a double-blind study in 882 HSCT recipients, micafungin prophylaxis was as well tolerated as fluconazole.[59] The most commonly reported adverse events during treatment were bilirubinaemia,

nausea and diarrhoea (treatment group not specified). Adverse events considered to be related to the study drug occurred with a similar incidence in the micafungin and fluconazole groups (15.1% vs 16.8% of recipients) [see section 3 for dosage details]. There was a trend ($p = 0.058$) for fewer micafungin than fluconazole recipients to discontinue treatment because of an adverse event (4.2% vs 7.2% of patients).[59]

- Micafungin 12.5–100 mg/day was well tolerated in a noncomparative, multicentre study in 119 HIV-positive adults with endoscopically confirmed oesophageal candidiasis.[53,54] One patient (a recipient of 50 mg/day) experienced a serious adverse event (diarrhoea and dehydration)[53] and three patients withdrew because of adverse events.[54]

- Although there were no infusion-related adverse events (fever, chills, rigors), phlebitis was documented in three of 36 HSCT recipients treated with intravenous micafungin 3–8 mg/kg/day.[57] When each recipient was compared with two historical controls matched for age, type of malignancy and type of transplant (autologous or allogenic), there was no evidence of renal or hepatic adverse events attributable to the drug. Adverse events were considered to be disease related and no drug-related grade 3 or 4 adverse events were documented.[56,57]

- The incidence of nephrotoxicity after 6 months' treatment was appreciably lower in HSCT recipients who received micafungin (16.6% of patients) than in those treated with amphotericin B (100%).[60]

Nephrotoxicity was defined as a decline of ≥50% in creatinine clearance from baseline levels. No dosages were reported in the abstract presentation.[60]

- Renal failure was documented in one of 14 cancer patients treated with micafungin 50–150 mg/day for a median of 15 days.[49] Importantly, seven patients received treatment with intravenous amphotericin formulations during this study, although the authors did not indicate whether this patient was one of them.

5. Dosage and Administration

In clinical trials, the dosage of micafungin ranged from 12.5 to 900 mg/day, with the drug administered once daily as an intravenous infusion. The initial dosages of micafungin for the treatment of fungal infections were: for invasive aspergillosis 75 mg/day (1.5 mg/kg/day in those weighing <40kg); for *C. albicans* 50 mg/day (1 mg/kg/day in those weighing <40kg); for non-albicans *Candida* spp. 100 mg/day (2 mg/kg/day in those weighing <40kg); and for prophylaxis of fungal infections 50 mg/day (1 mg/kg/day in those weighing <40kg). Further clinical studies investigating the minimal effective dose and the maximum tolerated dose used dosages ranging from 12 mg/day to 8 mg/kg/day.

In Japan, the recommended initial dosage of micafungin for the treatment of invasive aspergillosis is 50–150 mg/day (dosage escalation permitted to 300 mg/day) and for the treatment of invasive candidiasis is 50 mg/day (dosage escalation permitted to 300 mg/day).[61]

6. Micafungin: Current Status

In the majority of recipients, intravenous micafungin effectively eradicated endoscopically-confirmed oesophageal candidiasis in HIV-positive adults in a double-blind, controlled trial, and in several nonblind trials, resulted in a complete or partial response in adult and paediatric patients with candidiasis or aspergillosis. In addition, the drug has been used as prophylaxis or treatment in patients undergoing HSCT for haematological malignancy. Micafungin was generally well tolerated in these trials.

Micafungin is approved in Japan for the treatment of a range of opportunistic systemic *Aspergillus* spp. and *Candida* spp. infections.[62] A new drug application for micafungin is currently under review by the US FDA.[63] The indications under review include use of micafungin alone or in combination with other systemic antifungal agents in patients refractory to ongoing antifungal therapy, in patients in whom toxicity precludes the use of other agents, and as prophylaxis in patients undergoing HSCT.[63]

Approval is also being sought in Europe for the use of micafungin in the treatment of invasive fungal infections.[64]

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