

Caspofungin: the first representative of a new antifungal class

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Caspofungin (MK-0991; L-743,872) belongs to the echinocandin family, a new class of antifungal agents that act on the fungal cell wall by inhibiting glucan synthesis. Data *in vitro*, and experimental studies, have demonstrated that caspofungin has antifungal activity against yeasts of the genus *Candida* (including isolates resistant to azoles and amphotericin B), several species of filamentous fungi, including *Aspergillus*, and certain dimorphic fungi, such as *Histoplasma*, *Blastomyces* and *Coccidioides*. *In vitro* and in animals, caspofungin shows additive or synergic antifungal activity with amphotericin B and triazoles. It also possesses activity against *Pneumocystis carinii*. Clinical trials have shown caspofungin to be well tolerated and effective in invasive aspergillosis in patients refractory or intolerant to standard treatment (45% favourable responses), in oropharyngeal and oesophageal candidiasis (67–93% favourable responses with an efficacy similar to those of amphotericin B and fluconazole), and in invasive candidiasis with efficacy equivalent to that of amphotericin B, and better tolerability. The results of these first clinical trials were promising, and led to the approval of caspofungin for invasive aspergillosis after failure of, or intolerance to, standard therapy. Further studies are required to define the exact role of caspofungin in the antifungal armamentarium.

Keywords: echinocandin, candidaemia, oropharyngeal candidiasis, oesophageal candidiasis, invasive aspergillosis

Introduction

The incidence and diversity of fungal infections have increased considerably over recent decades.^{1–3} This reflects the rising numbers of patients at risk of fungal infection. The AIDS epidemic, the increasing intensity of anticancer chemotherapy, the development of haematopoietic stem cell and organ transplantation, and new developments in surgical and invasive techniques have all increased the number of immunosuppressed and vulnerable patients. Candidiasis and aspergillosis remain the most common fungal infections, but new fungi, previously regarded as saprophytic, are now implicated in human pathology.⁴ The arsenal of antifungal agents is growing. New compounds, more active or better tolerated, are being developed. Some are new members of old families, such as the new triazoles or the lipid formulations of amphotericin B; others belong to new classes of antifungal agents, such as the echinocandins. Caspofungin is the first echinocandin to be approved by a drug regulatory authority.

Pharmacodynamics

Structure

Caspofungin (caspofungin acetate) is a semi-synthetic water-soluble lipopeptide produced from a fermentation product of the fungus *Glarea lozoyensis*. It belongs to the echinocandin family, and is a derivative of pneumocandin B₀. The structural formula of caspofungin is shown in Figure 1.

Mechanism of action

Caspofungin blocks the synthesis of $\beta(1,3)$ -D-glucan of the fungal cell wall, by non-competitive inhibition of the enzyme $\beta(1,3)$ -D-glucan synthase. $\beta(1,3)$ -D-Glucan is an essential component of the cell wall of numerous fungal species. The chains of $\beta(1,3)$ -D-glucan form a solid three-dimensional matrix, which gives the cell wall its shape and mechanical strength.

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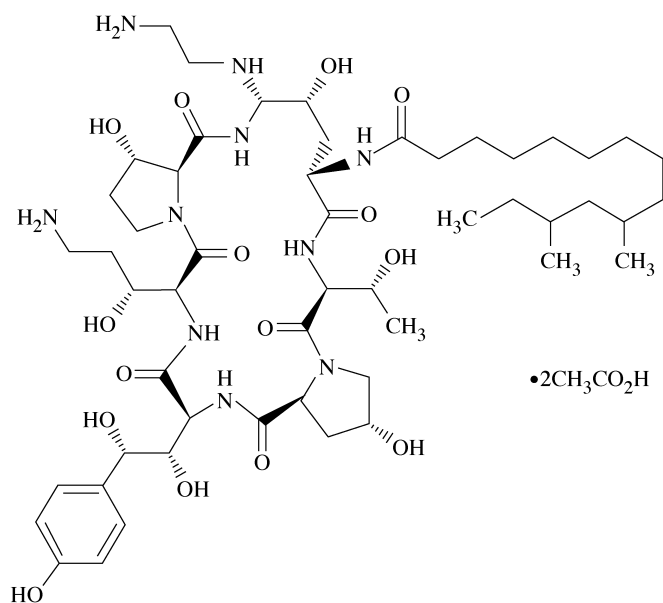


Figure 1. Structure of caspofungin.

Inhibition of the synthesis of $\beta(1,3)$ -D-glucan produces a double effect, both fungistatic and fungicidal. The fungistatic effect results from blockade of the cell wall synthesis, reducing fungal growth. The fungicidal effect results from a change in the integrity of the cell wall, which loses its mechanical strength and becomes unable to resist the intracellular osmotic pressure, leading ultimately to destruction of the fungal cell. This mechanism of action differs from that of other antifungal families, which act on the cell membrane (polyenes, azoles or terbinafine), or inhibit DNA and protein synthesis (5-fluorocytosine).

The fungicidal activity of caspofungin has been demonstrated in *Candida* spp.⁵ Studies *in vitro* have demonstrated that the compound has a fungistatic effect on *Aspergillus* spp. It also has an unconventional fungicidal action, by acting selectively on the extremities of the hyphae, which are the site of cell wall synthesis essential for apical growth of the fungus.⁶ A culture of *Aspergillus fumigatus* treated with caspofungin showed reduced growth and abnormal morphology by electron microscopy.⁶

Mammalian cells do not contain $\beta(1,3)$ -D-glucan, suggesting that the compound should be selectively active against fungal cells.

Studies *in vitro*

The theoretical spectrum of activity of caspofungin extends to all fungi that possess $\beta(1,3)$ -D-glucan. Antifungal susceptibility studies *in vitro* have been conducted using the NCCLS reference method. However, this method has not been standardized for the echinocandins, the breakpoints for MICs have not been defined and the correlation between data *in vitro* and clinical efficacy is unknown. Furthermore, the reference

method appears to be poorly suited to the assessment of the susceptibility of filamentous fungi to caspofungin, since, unlike other compounds, the echinocandins act essentially on the growth zones of hyphae. This effect is difficult to visualize and hence difficult to quantify objectively.

Yeasts. Caspofungin is active against *Candida* spp., including species that are resistant (*Candida krusei*), or isolates that are less susceptible (*Candida dubliniensis*, *Candida glabrata*) to azoles, or resistant to amphotericin B.^{7–12} The lack of cross resistance is a result of the different mechanism of action of caspofungin.

MICs range between 0.015 and 4 mg/L, depending on the species.^{9,12–16} In three comparable studies using the NCCLS microdilution method with an endpoint of 100% growth inhibition, *Candida albicans*, *C. glabrata*, *Candida tropicalis* and *Candida parapsilosis* showed low MIC₉₀s \leq 1 mg/L (range 0.125–1 mg/L) (Table 1). *C. krusei*, *Candida guilliermondii* and *Candida famata* have MICs \geq 1 mg/L (range 1–2 mg/L), and caspofungin does not appear to be fungicidal against any isolate.^{9,12,13}

Caspofungin, like the other echinocandins, is not active against *Cryptococcus neoformans*, with average MICs of 32 mg/L.^{9,14,15,17} Although *C. neoformans* possesses $\beta(1,3)$ -D-glucan synthase, possible explanations for the lack of activity of the echinocandins include: (i) a lower quantity of parietal $\beta(1,3)$ -D-glucan; (ii) the compound's difficulty in accessing its target due to the polysaccharide capsule that surrounds the cell wall; and (iii) lower inhibition of the $\beta(1,3)$ -D-glucan synthase of *C. neoformans*.^{18–20} However, synergy between caspofungin and amphotericin B or fluconazole against *C. neoformans* has been demonstrated *in vitro* and in animals.¹⁷ The combination of caspofungin with fluconazole is also active against strains of *C. neoformans* resistant to fluconazole.¹⁷ The mechanism of this synergy is not known, but it is possible that caspofungin, by weakening the fungal wall, might facilitate the passage and access of amphotericin B and fluconazole to their membrane targets.

Few data have been published on the yeast species less commonly implicated in human pathology. However, other basidiomycetous yeasts also seem to be resistant to caspofungin, with MICs of 16 mg/L or more for *Trichosporon* spp. and 8 mg/L for *Rhodotorula*.^{9,21,22}

Filamentous fungi. Caspofungin has been tested on the most common pathogenic filamentous fungi, and in particular on those responsible for deep infections.

Caspofungin is active against *A. fumigatus*, *Aspergillus flavus*, *Aspergillus niger* and *Aspergillus terreus* (Table 2). Several studies *in vitro* showed MICs frequently <0.5 mg/L, and caspofungin was active against isolates resistant to amphotericin B.^{9,11,15,23–27} The combination of amphotericin B and caspofungin was additive or synergic *in vitro* against

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Table 1. *In vitro* activity of caspofungin against *Candida* species^a

	Bartizal <i>et al.</i> ¹⁵			Marco <i>et al.</i> ¹⁶			Vazquez <i>et al.</i> ¹²		
	<i>n</i>	MIC ₉₀	range	<i>n</i>	MIC ₉₀	range	<i>n</i>	MIC ₉₀	range
<i>C. albicans</i>	40	0.5	0.25–0.5	206	0.125	0.015–0.5	50	0.4	0.05–0.8
<i>C. glabrata</i>	20	1	0.25–2	77	0.25	0.03–0.5	21	0.4	0.1–0.4
<i>C. tropicalis</i>	20	1	0.25–1	54	0.125	0.03–0.25	10	0.4	0.1–0.8
<i>C. parapsilosis</i>	20	0.5	0.25–1	40	1	0.03–2	7	ND	0.1–1.6
<i>C. krusei</i>	20	2	0.5–2	17	1	0.125–1	5	ND	0.4–0.8
<i>C. kefyr</i>	20	0.5	0.125–0.5	ND	ND	ND	5	ND	0.05–0.4
<i>C. lusitaniae</i>	20	0.5	0.125–0.5	ND	ND	ND	5	ND	0.4–0.8
<i>C. guilliermondii</i>	20	2	0.25–2	ND	ND	ND	5	ND	1.6

^aMICs (mg/L) were obtained by the NCCLS reference method (micromethod M27-P) with 100% inhibition of fungal growth. MIC₉₀ corresponds to the MIC that inhibited 90% of the isolates. ND, not determined.

Table 2. *In vitro* activity of caspofungin against *Aspergillus* species

	Arikan <i>et al.</i> ²⁶			Espinel-Ingroff ⁹		
	<i>n</i>	MIC ^a		<i>n</i>	MIC ^a	
		geometric mean	range		geometric mean	range
<i>A. fumigatus</i>	4	0.25	0.25	13 ^b	2.15	0.5–>16
<i>A. flavus</i>	4	12.12	0.5–>16	11	0.50	0.5
<i>A. terreus</i>	3	0.25	0.25	2	ND	0.5
<i>A. niger</i>	3	0.25	0.25	ND	ND	ND

^aMICs (mg/L) were obtained by the NCCLS reference method (micromethod M28-P) with 50% inhibition of fungal growth.

^bIncluding two isolates resistant to itraconazole (MIC > 8 mg/L). ND, not determined.

Aspergillus.^{15,26,28} No antagonistic interaction has been observed. The combination with voriconazole was studied for 48 strains of *Aspergillus* spp.²⁹ The interaction was synergic for 42 strains and additive for the remaining six strains.

The activity of caspofungin against other filamentous fungi varies between species. Caspofungin is active against *Paecilomyces variotii* (MIC ≤ 0.5 mg/L), but not against *Paecilomyces lilacinus* (MIC 3–100 mg/L), and is active against *Scedosporium apiospermum*, but not against *Scedosporium prolificans*.^{24,25} Caspofungin is also active against rarer moulds, such as *Acremonium*, *Curvularia*, *Bipolaris*, *Trichoderma* and *Alternaria*.^{9,24,25}

Caspofungin is inactive *in vitro* against *Fusarium solani* and *Fusarium oxysporum* (MIC > 50 mg/L), and against Mucorales of the genus *Rhizopus* (MIC > 100 mg/L).^{9,24–26} No data are available about other Mucorales. Synergic or additive interactions between caspofungin and amphotericin B have, however, been observed in *Fusarium*.²⁶

Dimorphic fungi. Caspofungin is active against *Blastomyces dermatitidis*, and in a more inconstant manner against *Histoplasma capsulatum*.^{9,30} *Sporothrix schenckii* appears less susceptible, with a mean MIC of 5.4 mg/L.⁹

Pneumocystis carinii. Unlike amphotericin B and the triazoles, caspofungin is active against the cysts of *P. carinii*, since they contain β(1,3)-D-glucan in their walls.³¹ It is not active against the vegetative forms, which do not have this compound. There is no technique for determining the susceptibility *in vitro* of *P. carinii*. Studies have therefore been carried out directly on animals.

Mechanisms of action and resistance

At present, very few data are available on resistance to the echinocandins. The molecular mechanisms of action of β(1,3)-D-glucan synthase have been studied *in vitro* in

Saccharomyces cerevisiae, then in *C. albicans* and more recently in *A. fumigatus*.^{32–35} $\beta(1,3)$ -D-Glucan synthase is a heteromeric enzyme complex bound to the cell membrane. It is formed from a catalytic membrane subunit (Fks p), which binds intracellular UDP-glucose, and a regulatory subunit (Rho 1 p), which binds intracellular GTP. The complex polymerizes UDP-glucose to glucan, which is progressively released on the extracellular side to then be incorporated in the fungal wall. Caspofungin blocks the catalytic Fks p subunit in a non-competitive manner.

It has been demonstrated *in vitro* that strains of *S. cerevisiae* or *C. albicans*, mutated on the *FKS* gene coding for the catalytic subunit, or on the *RHO 01* gene coding for the regulatory subunit of $\beta(1,3)$ -D-glucan synthase, become resistant to caspofungin, and all other echinocandins.^{36–38} These strains remain susceptible to azoles and amphotericin B. Additional studies are required to improve our understanding of these mechanisms of resistance, and to determine whether or not they are inducible by antifungal agents.

Experimental studies

Studies have been carried out in several experimental models of fungal infection. The results usually correlated with the susceptibility data observed *in vitro*.

Candidiasis. Several studies have demonstrated the efficacy of caspofungin in disseminated candidiasis in immunocompetent or immunosuppressed mice.^{39–42} The low MICs of caspofungin observed *in vitro* for species resistant, or poorly susceptible, to fluconazole, suggested that caspofungin might be active against these strains *in vivo*. Experimental data have confirmed its efficacy in immunosuppressed mice infected with *in vitro* fluconazole-resistant or dose-dependent susceptible isolates of *C. krusei*, *C. glabrata* and *C. albicans*.^{40–41} In these experiments, fluconazole (10 mg/kg/day) did not prolong survival or reduce the renal fungal burden, as compared with untreated animals. Caspofungin (0.05–5 mg/kg/day), administered by the intravenous (iv) or intraperitoneal route, significantly prolonged the survival of infected animals and reduced the renal fungal load, although without sterilizing the organs. The minimum effective dose was 0.05 mg/kg/day for *C. albicans* and 0.5 mg/kg/day for *C. glabrata* and *C. krusei*.

Cryptococcosis. Caspofungin, even at high doses of 40 mg/kg/day, did not protect mice against lethal infection with *C. neoformans*.³⁹ These experimental data confirm the resistance of *C. neoformans* observed *in vitro*.

Aspergillosis. Several experimental studies of invasive aspergillosis in immunocompromised rodents have demonstrated the efficacy of caspofungin.

Caspofungin administered by the intraperitoneal route showed dose-dependent efficacy in disseminated aspergillosis in mice deficient in complement fraction C5.³⁹ The survival rates 28 days after infection were 40% for 0.04 mg/kg/day, 80% for 0.16 mg/kg/day and 93% for 2.5 mg/kg/day, as compared with 0% in control animals. Administration by the oral route considerably reduced the compound's efficacy, with ED₅₀ and ED₉₀ values of 20.5 and >50 mg/kg twice daily, respectively, as compared with ED₅₀ and ED₉₀ values of 0.03 and 0.12 mg/kg twice daily, respectively, by the intraperitoneal route.

In neutropenic mice, intraperitoneal caspofungin showed dose-dependent activity on survival, at doses of 0.125 mg/kg/day and above, during short-duration neutropenia (10 days), and 0.5 mg/kg/day and above, during prolonged neutropenia (over 28 days).⁴² In both models, doses of 0.5–1 mg/kg/day of caspofungin were required to obtain at least 70% survival rates; these were comparable to those obtained with amphotericin B at the same dosages.

Caspofungin 2 mg/kg/day and amphotericin B 4 mg/kg/day demonstrated comparable efficacy in invasive pulmonary aspergillosis in rats pre-treated with cortisone, with 100% survival of the animals 7 days after infection, as compared with 30% in control animals.⁴³ In the same model, prophylactic administration of a single dose 2 h before infection protected the animals. Survival rates after 7 days were 90% and 100% with 2 and 8 mg/kg/day of caspofungin, respectively, 100% with amphotericin B 4 mg/kg/day and 40% in the control group.

Combination therapy with caspofungin and amphotericin B was evaluated in disseminated aspergillosis in mice with cyclophosphamide-induced neutropenia.⁴⁴ The animals received daily treatment with caspofungin alone, amphotericin B alone or caspofungin plus amphotericin B at doses of 0.008–0.5 mg/kg/day. Efficacy was evaluated on day 4 post-infection by measurement of the renal fungal load. Caspofungin and amphotericin B alone significantly reduced the fungal load, as compared with untreated animals. The combination of caspofungin and amphotericin B reduced the renal fungal load as much as, or more than, each drug alone. These results suggest additive or synergic interaction *in vivo*.

Dimorphic fungi. One study compared caspofungin and amphotericin B in histoplasmosis.³⁰ Caspofungin was relatively ineffective, with only 20% and 30% survival at doses of 4 and 8 mg/kg/day, respectively, as compared with 100% for amphotericin B 2 mg/kg/every other day. The high MIC of caspofungin (8 mg/L) for the strain of *H. capsulatum* used may explain this therapeutic failure. Another study, using a strain of *H. capsulatum* with a low MIC of 0.25 mg/L, showed a significant effect on survival and on tissue fungal burden at caspofungin doses of ≥ 0.05 mg/kg/day.⁴⁵

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In blastomycosis, despite a high MIC, caspofungin was effective in prolonging survival and reducing fungal load in organs.⁴⁶ Caspofungin 1 mg/kg/day led to 100% survival of mice infected by a strain of *B. dermatitidis*, with an MIC of 8 mg/L. When a second strain with a higher MIC (64 mg/L) was used, only higher caspofungin doses of 5 and 10 mg/kg/day led to 80% and 100% survival, respectively.

Pneumocystosis. Caspofungin, administered by the subcutaneous or oral route, was compared with the reference treatment trimethoprim plus sulfamethoxazole, in mice pretreated with steroids and infected with *P. carinii*.⁴⁷ The results demonstrated that both subcutaneous caspofungin and the reference treatment reduced the number of pulmonary cysts by 90%, and that this effect was achieved more rapidly with caspofungin (4 days) than with the reference treatment (14 days). Caspofungin was always less effective by the oral route. Daily subcutaneous caspofungin administration demonstrated a prophylactic effect in the same models.

Pharmacokinetics

The oral bioavailability of caspofungin is very low, requiring parenteral administration. Protein binding is high, ranging from 96% to 99%, depending on animal species.⁴⁸ After intravenous administration to rats, tissue distribution studies showed high levels in the kidneys, liver, spleen and lungs.⁴⁸ Lower levels were measured in the brain.

Pharmacokinetics are linear in humans after single doses ranging from 5 to 100 mg.⁴⁹ At the end of an infusion of 70 mg, mean plasma concentration measured in six subjects was 12 mg/L. At 24 h the levels still ranged between 1 and 2 mg/L. The β -phase half-life is long (9–11 h), leading to moderate accumulation after administration of multiple doses.

Caspofungin is mainly eliminated in the urine and the faeces as metabolites. Following a 1 h intravenous infusion of 70 mg of caspofungin in healthy subjects, 41% and 35% of the dosed radioactivity was recovered in urine and faeces, respectively, over 27 days.⁵⁰ However, very little caspofungin is excreted unchanged in urine: only 2% of the dose was recovered in urine within 24 h following multiple daily infusions of 70 mg.⁴⁹

Metabolism of caspofungin is thought to be independent of the cytochrome system, and caspofungin does not inhibit the cytochrome P450 isoenzymes. Nevertheless, interaction studies suggest that caspofungin concentrations are reduced during concomitant administration of cytochrome inducers. Caspofungin does not cause any significant change in the pharmacokinetics of amphotericin B, itraconazole, cyclosporin or mycophenolate.⁵¹ However, concentrations of tacrolimus are reduced by ~20% during administration of caspofungin, necessitating closer monitoring of serum tacrolimus concentrations.⁵² In contrast, cyclosporin increases the area

under the curve of caspofungin by ~35%, but these alterations are not sufficient to suggest any dosage modification.⁵¹ However, cases of transient elevation of alanine aminotransferase (but not aspartate aminotransferase) have been noted in healthy volunteers receiving caspofungin and cyclosporin simultaneously. At the present time, this combination is not recommended unless the potential benefit appears to outweigh the risk of hepatotoxicity. Tacrolimus does not influence the pharmacokinetics of caspofungin.⁵²

Studies in special populations suggest that there is no need to reduce dosage in elderly subjects, or in cases of moderate renal insufficiency or mild hepatic insufficiency.^{51,53} In patients with moderate hepatic insufficiency, it is recommended that dosage be reduced to 35 mg/day after a loading dose of 70 mg on day 1.⁵³ Insufficient data are available in patients with severe hepatic failure. Caspofungin is not dialysable.

Clinical trials

Few clinical trials have been carried out to date, insufficient to evaluate the real therapeutic potential of caspofungin.

Efficacy in clinical trials

Five clinical trials have supported the efficacy of caspofungin in *Candida* and *Aspergillus* infections.

Caspofungin (50 or 70 mg daily) was compared with amphotericin B (0.5 mg/kg/day) in oesophageal candidiasis under double-blind conditions.⁵⁴ The duration of treatment was 14 days. One hundred and twenty-eight patients were entered and were all evaluated in the modified intent-to-treat analysis. The majority of the patients suffered from HIV infection. The primary endpoint was the outcome 14 days after end of treatment. A favourable response, defined as a resolution of the symptoms combined with major endoscopic improvement, was observed in 34/46 (74%) of patients treated with caspofungin 50 mg/day, 25/28 (89%) treated with caspofungin 70 mg/day and 34/54 (63%) treated with amphotericin B (Table 3).

A similar trial was carried out in oropharyngeal and oesophageal candidiasis. Patients were treated with caspofungin (35, 50 or 70 mg/day) or amphotericin B (0.5 mg/kg/day).⁵⁵ The minimum duration of treatment was set at 7 days for oropharyngeal disease and 10 days for oesophageal disease, with a maximum of 14 days. The primary endpoint was outcome 3–4 days after the end of therapy. One hundred and forty patients were randomized, and 138 received at least one dose of study drug and could be assessed for efficacy and safety. Success was defined as the complete resolution of symptoms, and either major improvement or complete resolution of oesophageal lesions. The results, shown in Table 3, demonstrate no significant difference in the various therapeutic arms. Mycological eradication was seen in a higher proportion of

Table 3. Efficacy of caspofungin in oropharyngeal and oesophageal candidiasis

	Favourable responses (%)					Reference
	caspofungin			amphotericin B (0.5 mg/kg/day)	fluconazole (200 mg/day)	
	35 mg/day	50 mg/day	70 mg/day			
Oesophageal candidiasis (<i>n</i> = 128)	ND	34/46 (74)	25/28 (89)	34/54 (63)	ND	54
Oropharyngeal or oesophageal candidiasis						55
oropharyngeal only (<i>n</i> = 52)	11/13 (85)	13/14 (93)	12/13 (92)	8/12 (67)	ND	
oesophageal (<i>n</i> = 86)	14/21 (67)	18/20 (90)	17/22 (77)	14/23 (61)	ND	
Oesophageal candidiasis (<i>n</i> = 175)	ND	66/81 (82)	ND	ND	80/94 (85)	56

ND, not determined.

patients treated with caspofungin compared with amphotericin B.

A randomized double-blind trial compared caspofungin and fluconazole in oesophageal candidiasis.⁵⁶ Treatment was randomly allocated to caspofungin (50 mg/day) or fluconazole (200 mg/day intravenously) over a period of 7–21 days. Response was assessed 5–7 days after the end of therapy. A favourable response required both resolution of symptoms and significant endoscopic improvement. One hundred and seventy-five patients were evaluable. Response rates were high, >80%, and similar in the two arms (Table 3).

Results of a randomized double-blind comparison of caspofungin (70 mg on day 1, then 50 mg/day) and amphotericin B deoxycholate (0.6 to 1.0 mg/kg/day) in invasive candidiasis in neutropenic and non-neutropenic patients have recently been presented.⁵⁷ Treatment was continued for at least 14 days after the last positive culture, but could be switched to oral fluconazole after at least 10 days of intravenous initial randomized therapy. Two hundred and thirty-nine patients were enrolled and 224 met the criteria for a modified intent-to-treat analysis, which were clinical evidence of infection and positive culture from blood or from a sterile site and at least one dose of treatment. Most frequent infections were candidaemia (83%) and peritonitis (10%). Caspofungin was equivalent to amphotericin B for the response rate in this modified intent-to-treat population: 73.4% of the caspofungin-treated patients responded favourably, compared with 61.7% of the amphotericin B-treated patients (95% confidence interval for the difference in response: -0.7, 26.0). In a pre-defined analysis of the patients treated for at least 5 days, caspofungin was superior to amphotericin B (80.7% success for caspofungin compared with 64.9% for amphotericin B; 95% confidence interval for the difference: 1.1, 29.7). Survival at 6–8 week follow-up was identical in both arms.

Caspofungin (70 mg on day 1, then 50 mg/day) was evaluated in invasive aspergillosis after failure or intolerance of

amphotericin B (deoxycholate or a lipid formulation) or itraconazole.⁵⁸ Ninety patients were treated in this trial and 83 of them could be assessed for response. The site of infection was the lungs in 64 cases, and another single site in six cases. The infection was disseminated in 13 cases. The principal risk factors were haematological malignancies, allogeneic haematopoietic stem cell transplantation, organ transplantation or steroid treatment. In 71 cases (86%), patients had not responded to prior antifungal therapy. An independent committee of experts evaluated responses to treatment. A favourable response was defined as complete or partial response. The favourable response rate was 45% (37/83). Three of the 13 patients with disseminated disease responded favourably to the treatment with caspofungin.

No prospective studies have evaluated the clinical value of the combination of caspofungin with amphotericin B or a triazole. However, a few recent case reports suggest that these combinations should be highly effective. In children, one case of *C. famata* osteomyelitis, one of *C. albicans* peritonitis and one of cerebral aspergillosis failing on amphotericin B were successfully treated by a combination of voriconazole plus caspofungin.^{59,60} Two immunocompromised adult patients (one leukaemic patient and one lung-transplant patient) with invasive pulmonary aspergillosis were cured with a combination of oral itraconazole and caspofungin.⁶¹

Tolerability

The tolerability profile has been evaluated in 623 patients receiving caspofungin in pharmacological or therapeutic clinical studies.⁶² Of these patients, 295 received 50 mg/day or more for at least 1 week. Caspofungin was generally well tolerated. Serious drug-related adverse effects and discontinuation of therapy because of drug-related adverse events were uncommon. The most commonly encountered drug-related adverse effects were fever (12–39%), phlebitis at the

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infusion site (12–18%), headache (up to 15%) and nausea (up to 9%).^{54,62} Rare cases of skin rashes or pruritis were also reported. Renal tolerability was excellent, even on prolonged treatment. Transient mild-to-moderate elevations in alanine aminotransferase levels were seen in 11–24% of patients.⁶² Aspartate aminotransferase and alkaline phosphatase levels were typically increased, together with alanine aminotransferase levels. In randomized studies, phlebitis at the infusion site and elevation of hepatic enzyme levels were not observed in a higher proportion of patients receiving caspofungin than in patients receiving amphotericin B or fluconazole.^{54,62} Concomitant administration of caspofungin and cyclosporin may increase the frequency of liver function test abnormalities.

Indications and usage

Caspofungin has been approved recently in the USA and Europe for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (i.e. amphotericin B, lipid formulations of amphotericin B and/or itraconazole).

Caspofungin is available as a white lyophilized powder in 50 or 70 mg vials. The powder is reconstituted with physiological 0.9% saline and then diluted in 250 mL of physiological saline. Dextrose solutions should not be used. The dose is given by intravenous infusion over 1 h. No pre-medication is necessary.

Conclusions

Only a very limited number of clinical trials are available so far, and these do not yet demonstrate the true therapeutic potential of caspofungin. Its excellent safety profile can already be confirmed. Additional studies are eagerly awaited, particularly in the first-line treatment of invasive aspergillosis. The hopes raised by the findings *in vitro* of synergy with amphotericin B and the azoles call for such antifungal combination therapies to be evaluated in the context of clinical trials.

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