Management of systemic fungal infections: alternatives to itraconazole

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For many years, amphotericin B and flucytosine have been the only antifungal agents for invasive fungal infections. Amphotericin B was the standard of care for most of these infections. However, its use was often associated with low efficacy and poor tolerance. Fortunately, the antifungal armamentarium has increased during the past two decades with the addition of several new agents. In addition to itraconazole and fluconazole, lipid formulations of amphotericin B, voriconazole, caspofungin and micafungin have arrived on the market. Other agents are expected to be licensed shortly (anidulafungin, posaconazole). These various antifungal agents differ in their spectrum, pharmacokinetic profile, route of administration, indications, safety profile and, importantly, their cost. There is no longer a unique standard agent for all or nearly all invasive fungal infections but a real choice among several agents. The characteristics of these new agents are reviewed to help clinicians in their decision to select an antifungal agent for their patients.

Keywords: antifungals, azoles, amphotericin B

Introduction

Twenty years ago, the critical decision in invasive fungal infection was whether or not to start therapy. Amphotericin B deoxycholate (AmB-D), a macrocyclic polyene, was the only compound potentially active against most of the fungal pathogens. However, the toxicity of its intravenous form largely precluded its use in prophylaxis or in empirical treatment of invasive infections. The antifungal armamentarium has gradually increased during the past two decades with several new agents available for the treatment of invasive infections.

Itraconazole was developed in the late 1980s and early 1990s. It was the first broad-spectrum azole active against various dermatophytes, yeast, dimorphic fungi and filamentous fungi including those involved in most frequent human invasive fungal infections. Many clinical trials have been conducted and have demonstrated the efficacy of itraconazole in aspergillosis, superficial and systemic candidiasis, endemic mycoses, and prophyllaxis of invasive fungal infection in haematopoietic stem cell transplant recipients.²–⁸

In addition to itraconazole and fluconazole, lipid formulations of amphotericin B, voriconazole, caspofungin and micafungin have arrived on the market. Other agents are expected to be licensed shortly (anidulafungin, posaconazole). These various antifungal agents differ in their spectrum, pharmacokinetic profile, route of administration, indications, safety profile and, importantly, their cost. There is no longer a unique standard agent for all or nearly all invasive fungal infections but a real choice among several agents.

Amphotericin B

Amphotericin B (AmB) is a macrocyclic polyene. Its in vitro antifungal activity covers most of the fungal pathogens involved in human disease including Aspergillus spp. (with the exception of Aspergillus terreus), Candida spp. (some strains of Candida lusitaniae may be less susceptible or resistant), Cryptococcus neoformans and Zygomycetes. However, some fungal species including Trichosporon spp., Geotrichum spp. and Scedosporium spp. are resistant or poorly susceptible to AmB.²⁵ AmB has strong affinity for ergosterol, the principal sterol of fungal membranes, while it shows less affinity for cholesterol, the principal sterol of mammalian cell membranes. AmB modifies the permeability of the fungal membrane, leading to leakage of ions and other cellular components.

Amphotericin B deoxycholate

Amphotericin B deoxycholate (AmB-D; Fungizone®) has been on the market for 40 years. Based on its in vitro activity, AmB-D appears suitable for the treatment of several invasive fungal...
infections. Its clinical efficacy is however reduced by a poor safety profile. More than half of the patients treated with AmB-D experience infusion-related events such as fever, chills, nausea, dyspnoea, or hypotension. Most of these events can be lowered by lowering the infusion rate and by premedication (with paracetamol or antihistamines rather than corticosteroids which can have a deleterious effect on the fungal infection). Renal toxicity (decrease in glomerular filtration, potassium and magnesium wasting, tubular acidosis) of AmB-D limits its prolonged use at therapeutic doses. Up to half of the patients given AmB-D therapy for invasive aspergillosis double their serum creatinine level and more than 10% of the patients may need haemodialysis for severe nephrotoxicity.18

Use of AmB-D has been considerably reduced by the development of more effective and better tolerated agents. Remaining indications may be empirical therapy of persistent fevers in neutropenic patients although a liposomal formulation may be preferred and in neumeningeal cryptococcosis for which AmB-D combined with flucytosine remains the standard of care.19

**Lipid formulations of amphotericin B**

There are three lipid formulations of AmB commercially available: a liposomal preparation, a lipid complex, and a colloidal dispersion. These formulations differ in several respects, especially in their lipid composition, their shape, their pharmacokinetic behaviour and more importantly their clinical effects.20,21 A recently published meta-analysis of all randomized studies comparing any of the lipid formulations of AmB to AmB-D confirmed their better renal tolerability and suggested an improved survival of patients receiving a lipid formulation.22 Lipid formulations of AmB are much more expensive than their parent compound (Table 1).

**Liposomal amphotericin B.** Liposomal AmB (L-AmB) (AmBisome®, Gilead Sciences Inc.) is a formulation of AmB encapsulated in unilamellar liposomes. The liposomes are composed of hydrogenated soya phosphatidylcholine, cholesterol and distearoylphosphatidylglycerol at a ratio of 10:5:4.23 They have a

<table>
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<tr>
<th>Antifungal agent</th>
<th>Route</th>
<th>Unit size</th>
<th>Unit price (£)</th>
<th>Range of typical daily doses</th>
<th>Estimated weekly cost (£)*</th>
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<td>501.25</td>
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<td>Flucytosineb</td>
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<td>30.33</td>
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<td>Caspofungin</td>
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<td>327.67</td>
<td>70 mg on day 1 then 50 mg</td>
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<td>70 mg</td>
<td>416.78</td>
<td>100 mg/kg</td>
<td>636.93</td>
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Prices apply for March 2005 in UK and are subject to variation including contracts with individual hospital pharmacies to provide drugs at a reduced cost.
*aBased on a 70 kg weight. Prices are rounded to nearest whole vial for iv preparations. Lowest price is considered when generic drug is available.
*bFlucytosine should not be given as monotherapy.
Alternatives to itraconazole

The recommended dose for empirical and fungal infections is 4 mg/kg day. Suggestions to increase the daily dosage to 6 mg/kg have been removed from the labelling.

Amphotericin B colloidal dispersion. Amphotericin B colloidal dispersion (ABCD) is marketed under the name Amphotec® in Europe (Cambridge Laboratories) and Amphotec® in the USA (InterMune Inc.). ABCD is composed of cholesteryl sulphate bilayers in which the AmB molecule inserts itself at an equimolar ratio. The particles have a disc-like structure and are 120–140 nm in diameter and 4 nm thick.

ABCD is rapidly taken up by the reticuloendothelial system, explaining why the maximal plasma concentration is low and the volume of distribution high, and also why tissue concentrations (determined in animals) are high in the liver, spleen and bone marrow. In contrast, tissue concentrations of AmB are 7–30 times lower in the kidney, lung and brain after ABCD administration than after AmB-D.

The therapeutic potential of ABCD has been assessed in several settings. Minimal efficacy was observed in coccidioidomycosis, with a clinical improvement in only 13% of patients. However, the dose of ABCD was very low (1 or 2 mg/kg, three times a week). Open label studies included a large number of patients with various invasive mycosis in whom AmB-D had failed or who had renal impairment contraindicating AmB-D. These patients were treated with ABCD doses ranging from 0.5 to 8 mg/kg per day. The response rates were 49% in aspergillosis, 70% in invasive candidiasis and 67% in mucormycosis. There was no evidence that doses over 4 mg/kg per day are more effective than doses of 3–4 mg/kg per day.

The same studies served as the basis for a comparison with a historical aspergillosis control group treated with AmB-D. The response rates were better among patients treated with ABCD (49% versus 23% with AmB-D), but the non-randomized nature of the study undermines the reliability of the data and rules out formal conclusions. A prospective randomized trial comparing ABCD (6 mg/kg per day) and AmB-D (1 to 1.5 mg/kg per day) in invasive aspergillosis showed the identical efficacy of the two treatments. Favourable response rates however were low in both arms with a complete or partial response in only 18% and 23%, respectively.

ABCD (4 mg/kg per day) and AmB-D (0.8 mg/kg per day) had identical efficacy in neutropenic patients with persistent fever. The infusion-related effects are equivalent or even more frequent than with AmB-D.44,46 Daily doses over 4 mg/kg are associated with more adverse events.41 Renal tolerability is far better than with AmB-D. Administration of high cumulative doses (exceeding 10 g and up to 70 g or more) is possible, without significant nephrotoxicity.47

ABCD is indicated in the treatment of severe systemic or deep mycosis where toxicity or renal failure preclude use of AmB-D.47 The recommended dose regimen is 3–4 mg/kg per day. Suggestions to increase the daily dosage to 6 mg/kg have been removed from the labelling.

Amphotericin B lipid complex. ABCD is produced by Zeneus Pharma and marketed under the name of Abelcet®. It is a suspension of AmB complexed to dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol. The particles are ribbon-shaped and 1600–6000 nm long.48

After injection, ABCD is taken up by the macrophage and mononuclear cells of the reticuloendothelial system in complex form which explains why ABCD concentrates mainly in the liver, spleen and lungs and, to a lesser extent, bone marrow.21,49–51 The lipid complexes are disorganized by the action of fungal or host cell-derived phospholipases, thus releasing AmB.52

Open non-comparative trials have involved children and adults in whom AmB-D had failed or was contraindicated.53 They showed a favourable response in 67% of 42 cases of disseminated
candidiasis, 42% in 130 cases of aspergillosis, 82% of 11 cases of fusariosis and 71% of 24 cases of mucormycosis. The mean dose regimen used in these studies was 4.9 mg/kg per day. ABLC (5 mg/kg per day) was compared with AmB-D (0.6–1.0 mg/kg per day) in 231 episodes of haematogenous and invasive Candida infection. No difference in efficacy was shown between the two therapeutic arms.44

ABLC has also been assessed in cryptococcal neuronecrosis with an 86% favourable response rate in 21 patients treated with 5 mg/kg per day.55

The adverse effects of ABLC are similar in nature to those of AmB-D, but their frequency is far lower. Chills, fever, nausea and fatigue were the most frequent. Nephrotoxicity is reduced relative to AmB-D. A doubling of the serum creatinine was reported in only 28% of patients treated with ABLC and in 48% of patients receiving AmB-D.54 The weak nephrotoxicity was also shown by a retrospective study in children, including children with previous renal impairment.56

According to the BNF,37 ABLC is approved, at a dose of 5 mg/kg per day, for the treatment of: severe invasive candidiasis; severe invasive fungal infections, including aspergillosis and cryptococcal meningitis and disseminated cryptococcosis in HIV-positive patients, in patients not responding to AmB-D or to other antifungal drugs or where renal impairment precludes AmB-D.

Flucytosine

Flucytosine (5-fluorocytosine, Ancotil®; Valeant) acts as an antimetabolite. It is activated by deamination within the fungal cells to 5-fluorouracil resulting in an inhibition of fungal DNA and protein synthesis. Flucytosine is available in an oral form and as an intravenous (iv) preparation.

Its spectrum is restricted to Candida species and Cryptococcus neoformans with evidence of primary and acquired resistance in some strains. Flucytosine is also active against some of the dematiaceous fungi.57

Flucytosine should not be used as monotherapy with the exception of the treatment of urinary tract infections due to non-albicans Candida species.58 Resistance may develop rapidly during therapy. Flucytosine has been recommended by expert panels for severe Candida infections in combination with AmB.56 It is also used in combination with AmB-D as the standard of care for the initial therapy of Cryptococcus neoformans neuronecrosis and disseminated infections, especially in AIDS patients.59

In this later indication, flucytosine is given at a daily dose of 100 mg/kg per day concomitantly with AmB-D (0.7–1.0 mg/kg per day) for 2 weeks. The most common toxicities are haematopoietic, occurring mainly in patients with renal impairment, and liver toxicity.57

According to the BNF,37 flucytosine is indicated for: systemic yeast and fungal infections; adjunct to amphotericin B or fluconazole in cryptococcal meningitis; adjunct to AmB in severe systemic candidiasis or in other severe or long-standing infections. The recommended daily dose ranges from 100 to 200 mg/kg.

Triazoles

Triazoles inhibit ergosterol synthesis. They differ considerably in their spectrum, which is restricted to yeasts for fluconazole and extended to filamentous fungi for itraconazole and the newer azoles, their water or lipid solubility and their pharmacokinetic profile.

All triazoles inhibit to varying degrees the cytochrome P3A4, the primary oxidative drug-metabolizing enzyme in humans. Voriconazole also inhibits CYP 2C9/19. These inhibitions lead to numerous drug–drug interactions representing absolute contra-indications of concomitant use or requiring cautious monitoring (Table 2).37,60–81

Fluconazole

Fluconazole (Diflucan®, Pfizer) has been on the market since the late 1980s. Its spectrum of activity covers most yeasts with the notable exception of Candida krusei and, to a lesser extent, of Candida glabrata. Unlike the other triazoles, fluconazole is not active against filamentous fungi. Fluconazole is water-soluble and offers a good pharmacokinetic profile with excellent oral bioavailability, a long half-life (22–37 h), and urinary excretion as an active drug.82

Numerous clinical studies have assessed efficacy and safety of fluconazole in various clinical settings. Efficacy similar to AmB-D has been demonstrated in candidaemia with a better tolerance.53

Fluconazole is active against Cryptococcus neoformans. Fluconazole is recommended for isolated pulmonary, cutaneous or urinary tract cryptococcal infections provided careful assessment has excluded asymptomatic meningeal or cerebral involvement. Combination of fluconazole and flucytosine has been suggested for the most severe of these non-neurological infections. First line standard treatment of cryptococcal neuronecrosis infections is still the combination of AmB-D and flucytosine.19,84 Superiority of fluconazole over itraconazole in consolidation and maintenance therapy of cryptococcal meningitis has been shown in a randomized study: patients who received fluconazole were more likely to have a negative CSF culture at week 10.19

Effective prophylaxis of superficial and invasive fungal infections in neutropenic patients has been convincingly demonstrated with fluconazole (400 mg/day) in the setting of bone marrow transplantation.95,96 Results are more controversial in leukemic patients receiving lower doses of fluconazole (150 and 200 mg/day) with no differences in fungal colonization, superficial and invasive fungal infections in two large trials comparing fluconazole with oral AmB or nystatin.87,88 Whether or not fluconazole promotes the emergence of non-albicans Candida species remains controversial. Wingard et al. first reported a shift toward Candida glabrata and Candida krusei infections in patients receiving fluconazole.89,90 The epidemiology of non-albicans Candida strains is, however, variable as some centres using fluconazole have reported no increase in infections due to such species whereas others have observed this emergence before the use of fluconazole.91

Fluconazole has been compared with itraconazole for the prophylaxis of fungal infections in neutropenic patients as well as in liver transplant patients.92–94 Both drugs prevent Candida infections. With respect to prevention of aspergillosis, there are strong suggestions that itraconazole oral solution is more effective than fluconazole.94 Itraconazole oral solution may thus be preferred to fluconazole for the prophylaxis of fungal infections in high-risk patients.95
Table 2. Major potential or confirmed drug interactions with fluconazole, itraconazole and voriconazole

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
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<tbody>
<tr>
<td>Cisapride</td>
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<tr>
<td>Astemizole, terfenadine</td>
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<td>Quinidine</td>
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<td>Pimozide</td>
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<td>Rifabutin</td>
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<td>Vinca alkaloids</td>
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Effect on drug exposure (main clinical consequence of the interaction)

- **of drug exposure (QT interval prolongation with risk of torsade de pointe)**

Colour code:
- **contra-indication**: avoid concomitant use unless benefit overcomes risk;
- **monitoring or dose adjustment required**: monitoring or dose adjustment required;
- **no shading, no clinically relevant interaction**: no shading, no clinically relevant interaction.

*Where torsade de pointe has been reported for one azole, the contra-indication has been extended to all others. Contra-indication includes also co-administration of azoles and drugs known to prolong the QT interval and to be metabolized by CYP3A4 that is inhibited by all three azoles.*
In addition to skin and mucosal infections, labelling of fluconazole includes treatment of: invasive candidiasis (including candidaemia and disseminated candidiasis); cryptococcal infections (including meningitis); prevention of relapse of cryptococcal meningitis; prevention of fungal infections in immunocompromised patients following cytotoxic chemotherapy or radiotherapy.

Recommended daily doses range from 50 mg in mild mucosal infections to 400 mg in cryptococcal meningitis, in invasive Candida infections and for prevention of infection in high-risk patients. Experts have suggested an increase in the daily dose to 800 mg when fluconazole is given to patients with a Candida glabrata candidaemia or disseminated infection.

**Voriconazole**

Voriconazole (Viendi®, Pfizer) has been marketed in several countries since 2002. The spectrum of this new triazole covers most pathogenic yeasts and also a variety of filamentous fungi including Aspergillus spp., and, to a certain extent, Scedosporium spp. and Fusarium spp. Voriconazole is not active against Zygomycetes. Voriconazole can be given by either the intravenous or the oral route. Oral bioavailability is excellent, greater than 90%. Voriconazole (200 mg twice daily) is as effective as fluconazole (400 mg on day 1 then 200 mg/day) in oesophageal candidiasis. A trial assessing the efficacy of voriconazole in candidaemia in non-neutropenic patients has been recently completed. Results have been presented orally but not yet published. In this trial, voriconazole was compared with a strategy of initial treatment with AmB-D followed by fluconazole once the isolate had been found to be likely to be susceptible. Voriconazole demonstrated better tolerance and similar efficacy to the comparator arm in terms of sustained favourable response rate at week 12, of rapidity of clearance of blood cultures and of survival at day 98.

Efficacy of voriconazole in acute invasive aspergillosis was first demonstrated in an open label study. Voriconazole was given as primary or salvage therapy. Overall, 48% of the patients responded favourably. This open label study served as basis for the design of a large randomized trial comparing voriconazole and AmB-D as primary therapy of invasive aspergillosis. Voriconazole was more effective than AmB-D with a higher response rate (53% compared to 32%) and better survival (71% compared to 58%) at week 12. Voriconazole was superior to AmB-D irrespective of the underlying disease, the site of infection, the neutrophil status and the degree of certainty of the infection.

In addition to its anti-Candida and anti-Aspergillus activity, voriconazole has shown some efficacy in Scedosporium and in Fusarium infections with response rates of 30% and 45%, respectively.

The most frequent adverse events are visual disturbances occurring in 30% of the patients. These events are always transient and seldom lead to discontinuation of the treatment. Other adverse events include skin rashes, hallucinations and abnormal liver function tests.

Voriconazole has been approved in Europe for the treatment of invasive aspergillosis and serious infections caused by Scedosporium spp., Fusarium spp., or invasive fluconazole-resistant Candida spp. (including Candida krusei). The indications approved by the FDA do not include infections caused by fluconazole-resistant Candida. For Scedosporium and Fusarium infection, the indications approved in the USA are restricted to infections in patients intolerant of, or refractory to, other therapy.

**Posaconazole**

Posaconazole (Noxafil®, Schering-Plough) is a broad-spectrum investigational triazole active in vitro against a wide array of yeasts and moulds, including Aspergillus, Fusarium and to a certain extent Zygomycetes. Currently, posaconazole is only available as an oral suspension. Best oral absorption is obtained when the daily dose is divided into two to four doses and administered with food. Preliminary efficacy data from clinical trials are promising.

As salvage therapy, posaconazole provided a complete or partial response in 46% of patients with invasive aspergillosis. Favourable responses have been reported in fusariosis and various other filamentous fungal infections including mucormycosis.

Posaconazole is not yet commercially available. Comparative studies are required to specify the place of posaconazole in the antifungal armamentarium.

**Echinocandins**

Echinocandins form a new family of antifungal agents acting on a different pathway. They inhibit β(1,3)-d-glucan synthesis. β(1,3)-d-Glucan is an essential component of the fungal cell wall. Inhibition of its synthesis has a fungistatic as well as fungicidal effect. The fungistatic effect results from blockade of cell wall synthesis reducing fungal growth. The fungicidal effects result from a change in cell wall integrity causing loss of mechanical strength. Echinocandins have very poor oral bioavailability and must thus be given intravenously.

**Caspofungin**

Caspofungin (Caspofungin®, MSD) is to date the first echinocandin commercially available. In vitro data and experimental studies demonstrated that caspofungin has antifungal activity against yeasts of the genus Candida including isolates resistant to azoles and amphotericin B and several species of filamentous fungi including Aspergillus. Caspofungin has little or no activity against Cryptococcus, Trichosporon, Fusarium and Zygomycetes. Caspofungin also possesses activity against Pneumocystis carinii cysts.

Metabolism of caspofungin is independent of the cytochrome system and caspofungin does not inhibit cytochrome P450. Caspofungin is mainly eliminated in the urine and the faeces as metabolites. Very little caspofungin is excreted unchanged in the urine. No dose adaptation is required in patients with moderate renal insufficiency. Caspofungin is not dialysable.

Caspofungin has few drug–drug interactions. Concentrations of tacrolimus are reduced by 20% during administration of caspofungin. Cyclosporin increases the exposure to caspofungin by 35%. Increase in serum alanine transferases has been observed in 5 of 12 healthy volunteers concomitantly receiving cyclosporin and caspofungin. Interactions between these two drugs are being further investigated. At the present time, co-administration of caspofungin and cyclosporin is not recommended unless the potential benefit exceeds the risk of hepatotoxicity.

Efficacy of caspofungin in invasive aspergillosis has been assessed in 90 patients refractory to or intolerant of standard treatment. Most of the patients failed previous therapy with AmB, lipid formulations of AmB or itraconazole. Thirty-seven (45%) of the 83 evaluable patients responded favourably to caspofungin therapy. Three of the 13 patients with disseminated disease responded favourably.
Alternatives to itraconazole

Caspofungin is similar in efficacy to fluconazole or to AmB-D in oropharyngeal and oesophageal candidiasis with a 67–93% favourable response rate.111–113 A large randomized trial compared caspofungin and AmB-D in invasive candidiasis.114 Two hundred and thirty-nine patients were enrolled of whom 224 met the criteria for a modified intent-to-treat (MITT) analysis. Most frequent infections were candidaemia (83%) and peritonitis (10%). Caspofungin was equivalent to AmB-D for the response rate in this MITT population: 73% of the caspofungin-treated patients responded favourably compared with 62% of the AmB-D-treated patients (95% confidence interval for the difference in response: –0.7, 26.0). Survival at 6–8 weeks follow-up was identical in both arms. Patients receiving caspofungin experienced fewer drug-related adverse events.

Caspofungin also demonstrated similar efficacy to L-AmB in empirical therapy of patients with persistent fever and neutropenia.115 Caspofungin was better tolerated with less nephrotoxicity, infusion-related events and discontinuation of therapy because of adverse events than L-AmB.

Further studies, especially in first-line therapy in invasive aspergillosis, are required to define the exact role of caspofungin in the antifungal armamentarium. As in vitro and experimental studies have shown a potential synergy between caspofungin and either AmB or azoles, great expectations have been raised for combination therapy with caspofungin. Case reports and short series have been published and seem encouraging. Well-conducted trials are required before combination therapy can be recommended. The clinical significance of the anti-Pneumocystis activity has not been assessed.

Caspofungin is well tolerated.114,116 The most common clinical adverse events are fever, nausea, headache and phlebitis at the infusion site. Rare cases of skin rash or pruritis have also been reported. Renal tolerability is excellent, even on prolonged administration. Transient mild-to-moderate elevations in transaminases were seen in 11–24% of the patients.116

Caspofungin has been approved for invasive aspergillosis either unresponsive to AmB or to itraconazole or in patients intolerant of AmB or itraconazole, for invasive candidiasis and for empirical therapy of febrile neutropenia.37 The recommended dose is 70 mg on day 1 then 50 mg once daily. In patients with a body weight over 80 kg, the recommended dose is 70 mg once daily.

Micafungin

Micafungin is also a broad-spectrum echinocandin. Like caspofungin, micafungin is only available as an intravenous form.

Efficacy of micafungin in the treatment of oesophageal candidiasis has been established in a comparative study versus fluconazole.117 Micafungin has also been compared with fluconazole for the prophylaxis of invasive fungal infections in haematopoietic stem cell transplant recipients.118 Micafungin reduced the incidence of invasive fungal infections more effectively than fluconazole with no difference for candidiasis but a trend toward reduction in aspergillosis. Adverse events considered related to study drug were comparable in both arms. The most common events included hyperbilirubinaemia, nausea and diarrhoea. Phase III trials in therapy of documented infections are ongoing.

Micafungin has been approved by the FDA for the therapy of oesophageal candidiasis and for the prophylaxis of Candida infection in haematopoietic stem cell transplant recipients.

Anidulafungin

Anidulafungin is another echinocandin with a similar spectrum and activity to caspofungin. Anidulafungin has been assessed in Candida infections.119 Results have not yet been published. A Phase II combination study (anidulafungin plus L-AmB) has recently been performed. Safety analysis did not demonstrate any unexpected toxicity.120 Efficacy analysis is pending.

Conclusion

Several antifungal agents are now available and this number will continue to increase in the near future. Selection of an agent will not only be based on its in vitro spectrum, its pharmacokinetic and pharmacodynamic profiles, or suggestion of efficacy in open label trials or in case reports. Randomized trials clearly demonstrating efficacy in specific settings as well as tolerability are required for all new agents and these results will be the most important criteria. In addition, cost will certainly be critical in this decision when no major difference appears in the other characteristics.

Transparency declarations

R. H. has served within the last 3 years as a consultant or member of the speakers bureau for Pfizer, Gilead Sciences, Schering-Plough, Zeneus Pharma and Merck Sharp and Dohme. The remaining authors have declared that they have no relevant conflicts of interest.

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