The echinocandins represent the first new antifungal drug class introduced for more than 15 years. They inhibit the synthesis of β-D-glucan in fungal cell walls. Their strengths include low toxicity, rapid fungicidal activity against most isolates of Candida spp. and predictable favourable kinetics allowing once a day dosing. In addition to Candida spp., their inhibitory spectrum includes Aspergillus spp. and Pneumocystis carinii, but not Cryptococcus neoformans.

The first licensed echinocandin product is caspofungin acetate (Cancidas; Merck); subsequent members of the class likely to be licensed include micafungin (Fujisawa) and anidulafungin (Versicor). The initial licensure of caspofungin, however, is for the treatment of patients with invasive aspergillosis refractory to amphotericin B (in its various formulations) and/or itraconazole. In fact, the very strength of these data, from incontrovertible cases of invasive aspergillosis with no licensed therapeutic options left, initially enabled the national sceptical Food and Drug Administration, and was originally identified by Eli Lilly (as LY 303366) and subsequently licensed to Versicor as VER-002.

The echinocandins are synthetically modified lipopeptides, originally derived from fermentation broths of various fungi. Different structures have been elucidated, including aculeacin A (from Aspergillus aculeatus), echinocandin B [from Aspergillus rugulovatus (formerly Aspergillus rugulosus, a close relative of Aspergillus nidulans and Coleophoma empedri)], pneumocandin B (from Zalerion arboricola), enfumafungin (from a Hormonema-like fungus) and the papulacandins (from Papularia sphaerosperma). Anidulafungin was originally identified by Eli Lilly (as LY 303366) and subsequently licensed to Versicor as VER-002.

The molecular weight of all three echinocandins is large, and this presumably explains their poor oral absorption (c. 3%); therefore, all three compounds are for intravenous use only. In the course of development, scientists at Eli Lilly spent much time endeavouring to derive a bioavailable analogue, but unsuccessfully. Following single dose intravenous administration, all echinocandins have linear kinetics and a terminal half-life of 8–13 h, so once a day usage is appropriate. The precise degradation pathways are not fully understood, but almost all drug is degraded by non-oxidative pathways in the liver and the metabolites (which have no antifungal activity) are excreted in the bile and faeces. The drugs are concentrated in the liver, spleen and gut, are present in equal concentrations in plasma and lung and in lower concentrations in other tissues. Urine, cerebrospinal fluid (CSF) and vitreous concentrations are probably negligible. Despite the low CSF concentrations, at least two patients with cerebral aspergillosis have responded to caspofungin, mimicking the situation with itraconazole and amphotericin B for fungal meningitis and brain abscess. It will be important to gather data on the response or otherwise of fungal endocarditis to echinocandins, as amphotericin B and the azoles do not have an unblemished record in this respect.

There are very few drug interaction issues with the echinocandins compared with the azoles. Caspofungin is a poor substrate for the major liver cytochrome P450 enzymes. Caspofungin plasma concentrations are increased by ciclosporin (without change in ciclosporin concentrations), and may lead to abnormal liver function tests. This is also true with rifampicin. Tacrolimus concentrations are reduced slightly by caspofungin, with no detectable clinical consequences in 17 patients enrolled in the early aspergillosis treatment protocols. Mycophenolate and caspofungin do not interact. Caspofungin concentrations fall slightly in those patients with HIV receiving efavirenz and possibly other antiretroviral agents.

No appreciable differences in kinetics were observed in patients at the extremes of age, or of different gender or race, although neonates have not yet been carefully studied. No alteration of dose is required in patients with renal impairment. A reduced dose (e.g. half) should probably be given to
patients with significant hepatic impairment, based on small pharmacokinetic studies.

Several clinical studies have been reported fully and many are in progress. Caspofungin, 50 and 70 mg daily, is slightly more effective than amphotericin B deoxycholate 0.5 mg/kg/day for oesophageal candidosis in AIDS.5 It is expected that all three echinocandins will be effective in most serious Candida infections. All are intrinsically less active against Candida parapsilosis and Candida guilliermondii compared with all other common pathogenic species (MCs typically 1–2 mg/L compared with 0.001 mg/L).6 About 10% of isolates of other species of Candida, including Candida albicans, are tolerant to anidulafungin,7 and probably other echinocandins (as is the case with >95% of Candida spp. and azoles). Whether this is clinically relevant needs to be determined, as the majority of isolates of Candida are killed at concentrations similar to the MIC. How the echinocandins will compare with fluconazole and amphotericin B for infections caused by these tolerant pathogens deserves careful scrutiny. The echinocandins are active against fluconazole-resistant Candida.7

The situation with Aspergillus is intriguing. Despite the vast majority of glucan in the fungal cell wall of Aspergillus being β-1,3-D-glucan, synthesized by echinocandins’ target enzyme, glucan synthase, Aspergillus spp. are not killed by the echinocandins.8,9 Inhibition of growth is almost complete and cell wall-deficient, viable colonies are produced in vitro at all concentrations above the MIC. In animal models of aspergillosis, survival is improved by all three echinocandins in an impressive fashion, but organ cultures remain positive.10,11 The compounds are not as effective in persistently neutropenic models of aspergillosis, 12 and this may be predictive of responses in patients. Recent work with quantitative PCR methods has demonstrated that there is a massive reduction in DNA units in the tissue of infected treated mice, which correlated better with improvements in mortality than standard viability counts.13 In vitro, there may be subtle differences in activity against Aspergillus non-fumigatus spp.; the differences require further work.8,9

Clinically, caspofungin has produced impressive results in invasive aspergillosis: a 35% response rate in patients refractory to all licensed drugs.4 Many of these patients had relapsed leukaemia or lymphoma, or were treated after an allogeneic stem-cell transplant—all situations with otherwise poor outcomes from invasive aspergillosis. This may not seem impressive, but this is the response rate for amphotericin B as primary therapy. Persistently neutropenic patients fared less well.

While the echinocandins have activity against Candida and Aspergillus spp., C. neoformans is intrinsically resistant,14 as are Fusarium spp., the Mucorales and Trichosporon spp. Activity against the dimorphic endemic moulds such as Histoplasma capsulatum and Coccidioides immitis is questionable. Other difficult-to-treat fungi, such as Cladophialophora bantiana, Scedosporium apiospermum and Scedosporium prolificans, are apparently moderately susceptible in vitro.9 On the positive side, Saccharomyces cerevisiae and the ‘cyst’ form of Pneumocystis are susceptible,15 and prophylaxis may be a useful role for the echinocandins in the future. Efforts to induce caspofungin resistance in C. albicans by serial passage in the presence of the agent in vitro failed, suggesting that the potential for development of resistance to the echinocandins is low.16

With all new drugs introduced, questions of optimum dose arise, for reasons of efficacy, toxicity and cost.17 In oesophageal candidiasis, 35 mg caspofungin was almost equivalent to 50 and 70 mg daily. Almost all the caspofungin clinical studies have been at 50 mg daily, using loading doses of 70 mg on day 1. The occurrence of abnormal liver function tests with elevated plasma concentrations of caspofungin in combination with ciclosporin suggests a caspofungin dose ceiling of c. 1 mg/kg. The development strategy with micafungin has allowed dose increases to 300 mg daily, so far without apparent toxicity, and higher doses are being explored. A recently completed dose comparison study at the Royal Marsden Hospital in adults showed that micafungin at 8 mg/kg was well tolerated, with no significant adverse events. A dose response is apparent in models of candidosis and invasive aspergillosis. In our animal studies with anidulafungin and micafungin doses of 1 mg/kg were inferior to 2–10 mg/kg, which were equivalently effective.10,11 Establishing the optimum dose for certain indications can take years.

Much debate, to date mostly uninformed, centres around combination therapy with the echinocandins. Given the novel mechanism of action of the echinocandins compared with azoles, amphotericin B and flucytosine, synergic or additive combinations are possible and even likely. Initially it is critical to exclude antagonism. In fact, synergy or additive effects look probable, at least for Aspergillus spp. The low intrinsic toxicity of the echinocandins (phlebitis, fever, nausea, skin rash, abnormal liver function tests) indicate that combinations should not lead to additional or synergic toxicity. Whether it is possible to demonstrate better clinical results with combinations may be difficult, but initially requires careful evaluation of the results of the drugs used alone.

The echinocandins are most welcome—an important place in the treatment of serious fungal infection is assured.

References


