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A.M. Bal

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The echinocandins: three useful choices or three too many?

A.M. Bal *

Department of Medical Microbiology, Crosshouse Hospital, NHS Ayrshire and Arran, Kilmarnock KA2 0BE, UK

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* Tel.: +44 1563 827 422.

E-mail address: abhijit.bal@nhs.net

ABSTRACT

Echinocandins act by inhibiting 1,3- β -D-glucan synthesis in the fungal cell wall. The three licensed agents in this class, namely anidulafungin, caspofungin and micafungin, have a favourable pharmacological profile. These agents are narrow spectrum with clinically relevant activity against *Candida* and *Aspergillus* spp. Several trials have established the non-inferiority of these agents over existing agents in the treatment of invasive fungal infections. Caspofungin is also licensed for empirical antifungal therapy of presumed fungal infections in patients with febrile neutropenia. This paper reviews the literature on echinocandins.

1. Introduction

For many years, amphotericin B deoxycholate was the only systemic antifungal agent for the treatment of severe invasive fungal infections.

Development of the triazoles in the 1990s and the availability of liposomal amphotericin provided alternative options for treating systemic fungal sepsis.

In the last few years, the echinocandins have added to the armamentarium of antifungal agents. Caspofungin (CAS), the first echinocandin, was approved in 2002. Two more agents in this group, namely anidulafungin (ANI) and micafungin (MFG), are now licensed.

The spectrum of all three echinocandins is similar, although their activity against individual fungal species is somewhat variable. Agents of this class are narrow spectrum and their clinical utility is largely restricted to the treatment of candidiasis and aspergillosis. They possess very limited activity against fungi such as *Fusarium*, *Scedosporium*, *Coccidioides*, *Blastomyces* and *Histoplasma*; the zygomycetes are resistant. *Cryptococcus* and *Trichosporon* spp. are also resistant to echinocandins.

2. Mechanism of action of echinocandins and the development of resistance

1,3- β -D-glucan is an integral part of the fungal cell wall. Echinocandins inhibit 1,3- β -D-glucan synthesis by inhibiting 1,3- β -D-glucan synthase, an enzyme with two subunits, Fksp and Rho1p. Fksp is encoded by three genes, *FKS1*, *FKS2* and *FKS3*. Fksp is the active site of the enzyme [1]. Yeasts such as

Cryptococcus neoformans contain α -(1,3) or α -(1,6) glucan in their cell wall and are therefore resistant to the echinocandins [2].

Mutations of the *FKS* gene can lead to echinocandin resistance in fungi. Several such mutations have been identified. Mutation at Ser645 within the *FKS1* region was found to be associated with a profound decrease in susceptibility to echinocandins. Almost all *FKS1* mutants have a CAS minimum inhibitory concentration (MIC) of ≥ 2 $\mu\text{g/mL}$, which is the breakpoint set by the Clinical and Laboratory Standards Institute. However, a significant proportion of such strains have a comparatively lower MIC for ANI and MFG (< 2 $\mu\text{g/mL}$ but > 0.5 $\mu\text{g/mL}$). However, when tested in the presence of serum, the MIC of all *FKS1* mutant strains was found to be ≥ 2 $\mu\text{g/mL}$ for all three echinocandins [1]. The efficacy of these agents is affected by protein binding, and therefore a lower susceptibility breakpoint (≤ 0.5 $\mu\text{g/mL}$) might be more appropriate for ANI and MFG compared with CAS (2 $\mu\text{g/mL}$). Selection of mutant strains has been reported during CAS treatment. Thompson et al. [3] described a patient who had previously undergone a transplant and subsequently developed *Candida glabrata* bloodstream infection (BSI). A strain of *C. glabrata* recovered from peritoneal fluid on Day 40 of CAS treatment was found to have a mutation in the *FKS2* region [3]. Although such reports are rare, clinicians must remain alert to the possibility of secondary resistance on treatment. More work is needed to establish the extent of cross-resistance amongst echinocandins and to determine the clinical relevance of the MIC.

3. Pharmacological properties

ANI is highly protein bound (99%) and displays linear pharmacokinetics. It undergoes slow biotransformation and is excreted in bile without undergoing metabolism in the liver, with small amounts of unchanged drug appearing in the faeces and urine. Dose adjustments are not required in patients on medications that induce the cytochrome P450 enzymes [4] or in patients with any degree of liver or renal failure [5]. ANI has a long half-life (24 h) and animal studies indicate that the tissue concentrations are roughly ten times that of plasma [6]. ANI has no drug interactions with tacrolimus, but cyclosporin may cause an increase in ANI levels although this does not appear to be clinically relevant [7]. The manufacturer-supplied diluent that is used to prepare the drug before intravenous (i.v.) injection contains 20% alcohol but ANI is well tolerated in patients receiving metronidazole [8].

CAS is also highly protein bound and displays non-linear pharmacokinetics [9]. It undergoes spontaneous disintegration to an open-ring compound that subsequently undergoes peptide hydrolysis and *N*-acetylation [10]. The dose of CAS should be reduced in patients with moderate hepatic insufficiency. CAS should be used with caution in patients with severe liver failure. Dose adjustment is not necessary in patient with renal failure. CAS is not dialysable [9]. A transient increase in liver enzymes has been reported in patients on CAS and cyclosporin. It is recommended that CAS should be used in patients on cyclosporin only when benefits outweigh the risk. However, the clinical relevance of elevation of liver enzymes is uncertain [11]. CAS reduces serum levels of tacrolimus, therefore tacrolimus levels should be measured in

patients on both these medications [12]. Rifampicin (RIF) has a bimodal effect on the CAS concentration in plasma. Administration of RIF with CAS when both are initiated together increases the concentration of CAS, but this effect appears to be transient and is possibly related to inhibition of CAS uptake into tissues by RIF. With continued co-administration or if RIF is started prior to CAS, the trough concentration of CAS is reduced because of an induction effect mediated by RIF [13].

MFG shares many of the features of ANI in relation to protein binding and linear kinetics. It does not undergo any significant metabolism by the cytochrome P450 system and its half-life is 14 h. MFG has very few drug interactions. Levels of sirolimus and nifedipine should be monitored in patients receiving MFG [14]. Similar to ANI, dose adjustment is not required for either hepatic or renal impairment.

None of the echinocandins reliably penetrate the central nervous system or the eye and they are consequently not recommended for meningitis or endophthalmitis [15].

4. Activity against *Candida*

Candida is the most common yeast causing infections in human. *Candida albicans* accounts for roughly one-half of all *Candida* infections in the bloodstream [16]. Amongst the non-*albicans* species, *C. glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida guilliermondii*, *Candida krusei*, *Candida lusitanae* and *Candida kefyr* account for almost all of the remaining

Candida BSIs. Invasive infections due to *Candida sake*, *Candida famata* and *Candida utilis* have occasionally been reported.

Echinocandins are very active against *Candida* spp. Against *C. albicans*, the MIC₅₀ (MIC for 50% of organisms) of CAS and ANI ranges from <0.01 µg/mL to >8 µg/mL, whilst that of MFG ranges from ≤0.01 µg/mL to 0.5 µg/mL. Some species such as *C. parapsilosis* and *C. guilliermondii* have a relatively higher echinocandin MIC. There may be differences between the activities of the three available echinocandins against individual species. The MIC₉₀ (MIC for 90% of organisms) of ANI and MFG against *C. albicans* ranges from 0.01 µg/mL to 0.5 µg/mL and 0.01 µg/mL to 0.25 µg/mL, respectively, when data from several reports are examined in a cumulative manner, whilst the MIC₉₀ for CAS is somewhat higher ranging from 0.12 µg/mL to 1 µg/mL. The difference between the fungicidal activities of these agents is more striking. The minimum fungicidal concentration (MFC) of MFG against *C. glabrata* ranges between 0.01 µg/mL and 0.03 µg/mL compared with 0.12–2 µg/mL for ANI and 0.5–8 µg/mL for CAS. It is uncertain whether these differences translate into therapeutic efficacy. The MFC of echinocandins against *C. parapsilosis* and *C. guilliermondii* is high (4–8 µg/mL and 8 µg/mL, respectively) [17] and breakthrough BSIs with both *C. parapsilosis* and *C. guilliermondii* have been reported in patients receiving CAS [18,19]. An increase in CAS usage has also been reported to have caused a shift in yeast epidemiology, with selection of *C. parapsilosis* [20]. ANI may have slightly better activity against *C. parapsilosis*. Scanning electron microscopy of the fungal cell reveals that strains of *C. parapsilosis* that are non-susceptible to

CAS undergo distortion of their cell morphology at comparatively lower concentrations of ANI (1 µg/mL) compared with CAS (16 µg/mL). Mutation of the *FKS1* gene apparently does not account for the observed differences in the relative efficacy of these two agents. Ghannoum et al. [21] found that the corresponding amino acid sequences in the 493-bp region of the *FKS1* gene were identical. On the other hand, three species have now been identified within the *C. parapsilosis* complex. Data suggest that *Candida orthopsilosis* and *Candida metapsilosis* have significantly lower echinocandin MICs compared with *C. parapsilosis* [22].

5. Activity against moulds and other fungi

The echinocandins are fungistatic against *Aspergillus* spp., unlike amphotericin B (AMB) and itraconazole (ITC) that are fungicidal. Echinocandin monotherapy should not be used for the treatment of invasive aspergillosis as these agents do not lead to tissue sterilisation, which is an important objective in neutropenic patients. However, there are some data to indicate that the combination of an echinocandin with a polyene or an azole may have a synergistic effect on *Aspergillus* spp. because the combination targets different sites on the fungal cell. Combination therapy with CAS and voriconazole (VCZ) is widely used for the treatment of primary invasive aspergillosis and may reduce mortality [23]. MFG and ITC have been shown to be synergistic in vitro against ≥50% strains of *Aspergillus fumigatus*, *Aspergillus flavus* and *Aspergillus terreus* [24]. Experimental studies on rabbits also suggest a synergistic effect of ANI and VCZ in invasive pulmonary

aspergillosis [25]. Triple combination therapy (azole, polyene and echinocandin) has also been used successfully for the treatment of invasive aspergillosis [26]. Addition of AMB to the combination of VCZ and CAS enhanced the synergistic effects on *A. terreus* but diminished the effect on *A. fumigatus* and *A. flavus* [27]. Clinical evidence of benefit from triple combination therapy is lacking.

The echinocandins are active against some strains of *Penicillium* spp. and *Paecilomyces*. They are only moderately active against dematiaceous fungi such as *Cladosporium*, *Exophiala* and *Fonsecaea*. They are poorly active against zygomycetes. Their activity against *Fusarium* and *Pseudallescheria* and against yeast forms of *Histoplasma capsulatum*, *Blastocystis dermatitidis* and *Coccidioides immitis* is also poor. Echinocandins may still have a useful role as part of combination therapy in the treatment of infections caused by fungi typically resistant to this class. Experimental data suggest that synergistic effects are seen when CAS is combined with terbinafine for the treatment of fusariosis [28], and 1% topical CAS has been shown to be effective for experimental *Fusarium* keratitis in rabbits [29]. Occasional case reports in the medical literature do point to a clinically useful synergistic effect when CAS is combined with AMB for systemic fusariosis in immunocompromised patients [30]. Data are sparse for the other two echinocandins, but the combination of ANI or MFG with VCZ is reported to have a synergistic effect both against *Fusarium* and *Scedosporium* spp. [31,32]. CAS has also been combined with AMB for rhinocerebral zygomycosis unresponsive to monotherapy with the latter [33]. CAS has also

been clinically used to treat *Pneumocystis jiroveci* pneumonia and it may even have some synergy with trimethoprim/sulfamethoxazole [34]. MFG is active against the mycelial forms of *H. capsulatum*, *B. dermatitidis* and *C. immitis* but it is very weakly active against their yeast forms. MFG is also active against the mycelial forms of *Paracoccidioides brasiliensis*, *Penicillium marneffeii* and *Sporothrix schenckii* [14].

Generally, echinocandins have a limited role in the treatment of mould infections. Whilst the experimental data and the individual case reports are important sources of information to clinicians when deciding on individual cases, the existing literature is bound to suffer from reporting bias. Some cases may have improved on account of the natural history of the disease process, and many cases where clinical benefit was not seen might not have been reported.

6. Activity against biofilms

Candidaemia is often associated with intravascular catheters. Catheter infection is associated with biofilms, where sessile cells are embedded in an extracellular matrix (ECM). Biofilms are often refractory to treatment. Traditionally, the ECM has been thought to contribute to the resistance of biofilms, but recent data suggest that ECM-free sessile cells are also resistant [35]. Factors that are implicated in biofilm resistance include efflux pumps and diminished sterol synthesis [36,37]. Removal of intravascular catheters is strongly recommended in non-neutropenic patients and should also be considered in neutropenic patients [15].

Choi et al. [38] demonstrated that fluconazole (FLC) was ineffective against *Candida* biofilms. In contrast, the CAS MIC₈₀ (MIC for 80% of organisms) for sessile cells of *C. albicans* and *C. glabrata* was 0.5 µg/mL and 1 µg/mL, respectively. MFG was also active against sessile cells (MIC₈₀ = 0.5 µg/mL and 0.25 µg/mL for *C. albicans* and *C. glabrata*, respectively). Neither was effective against *C. tropicalis* or *C. parapsilosis* in biofilms [38]. In vitro models of antifungal lock therapy show that both CAS and MFG reduce the metabolic activity of *C. albicans* in biofilm [39]. Data from animal studies also indicate that the use of CAS line locks reduces the incidence of disseminated disease in mice with central venous catheters infected with *Candida* biofilms [40]. ANI also appears to be effective against biofilms [41]. There are data that suggest overexpression of drug targets for echinocandins on sessile cells [42].

7. Data from clinical trials

7.1. Anidulafungin

In a multicentre trial on the treatment of invasive candidiasis, ANI was shown to be non-inferior to FLC [43]. Most patients in the trial were candidaemic and a vast majority were non-neutropenic. Patients were randomised to receive either drug intravenously [127 in the ANI group and 118 in the FLC group in the modified intention-to-treat population (mITT)] and after 10 days of i.v. therapy all patients could receive oral FLC. The success rate was 75.6% in the ANI group and 60.2% in FLC group. One of the 47 participating centres enrolled 10% of the patient population and had a disproportionate number of

successful responses in favour of ANI. On removing the data for this centre, the success rates for ANI and FLC were 73.2% and 61.1%, respectively, and there was no evidence of a centre effect. In the subset analysis, 81.2% of patients with an Acute Physiology and Chronic Health Evaluation (APACHE) score of ≤ 20 had a successful response with ANI compared with 61.2% for FLC. The success rate was similar in those with an APACHE score > 20 . The global success rate with ANI was statistically significant in patients with *C. albicans* (81.1% in the ANI group compared with 62.3% in the FLC group; $P = 0.02$), whilst the global response rate in patients with *C. glabrata* was similar (56.3% in the ANI group and 50.0% in the FLC group) although FLC is generally believed to be less effective for the treatment of infection caused by *C. glabrata*. Indeed, the microbiological success rates (negative follow-up cultures) in the *C. glabrata* group were 75% and 60% for ANI and FLC, respectively. These data demonstrate that microbiological response does not necessarily predict global response. On the other hand, most *C. glabrata* isolates in this study were sensitive to FLC and the difference in microbiological success rate may therefore be related to the rapidly fungicidal activity of ANI compared with FLC that is fungistatic. There was a lower rate of persistent candidaemia in the ANI group (6.3% vs. 14.4%) [43]. ANI was also found to be statistically non-inferior to FLC for the treatment of oesophageal candidiasis (success rates 97.2% and 98.8%, respectively) and both agents had a comparable safety profile [44].

7.2. Caspofungin

CAS has been extensively studied in the setting of invasive candidiasis, oesophageal candidiasis, invasive aspergillosis and empirical therapy of febrile neutropenia. A trial comparing CAS with AMB for invasive candidiasis showed that CAS was better tolerated with significantly fewer adverse reactions while being equally effective (73.4% vs. 61.7% in the mITT analysis; $n = 224$). When subsets were analysed on the basis of *Candida* species, the efficacy of CAS was 64% and 80% and that of AMB was 58% and 62% for *C. albicans* and non-*albicans* species, respectively [45]. In the treatment of candidal oesophagitis, clinical success with CAS 50 mg/day, CAS 70 mg/day and AMB was 74%, 89% and 63%, respectively, and while as many as one-quarter of the patients had to discontinue AMB, CAS was extremely well tolerated [46]. In immunosuppressed patients with oesophageal candidiasis, CAS was as efficacious as FLC (response rate 81% vs. 85%) but the relapse rate was higher in patients who received CAS, although the difference was not statistically significant (28% vs. 17%) [47]. CAS is the only echinocandin that has been compared with standard antifungal therapy under randomised controlled trial (RCT) conditions in patients with persistent febrile neutropenia [48]. A total of 556 patients received CAS and 539 patients received liposomal amphotericin B (L-AmB). The overall success rates were 33.9% in the CAS arm and 33.7% in the L-AmB arm. CAS met the pre-specified criteria for non-inferiority. The most dramatic effect was seen in patients with proven baseline fungal infections (27 in each group). The rate of successful outcome in patients with baseline fungal infection was significantly higher in the CAS group (51.9% vs. 25.9%). The incidence of breakthrough fungal infections was

similar in the two arms. Fewer patients on CAS had nephrotoxic effects, infusion-related effects or other side effects leading to drug discontinuation. Overall mortality was 10.8% in the CAS group and 13.7% in the L-AmB group [48]. A systematic review of RCTs for the treatment of fungal infections showed that CAS was superior to AMB in terms of clinical response and was better tolerated. However, there was no difference in overall mortality [49].

7.3. Micafungin

MFG has been compared with CAS in the only RCT so far directly comparing two echinocandins [50]. The trial compared MFG in doses of 100 mg ($n = 191$) and 150 mg ($n = 199$) with CAS ($n = 188$) in patients with invasive candidiasis. The success rate was comparable in all three groups (76.4%, 71.4% and 72.3%, respectively) with no significant difference in mortality, relapse or adverse effects [50]. A phase III trial comparing MFG (100 mg/day) with L-AmB (3 mg/kg/day) in the treatment of invasive candidiasis and candidaemia showed similar overall success rates (complete and partial response) in the two study arms of both the per-protocol group (89.6% in the MFG group and 89.5% in the L-AmB group) and the mITT population (74.1% vs. 69.6%, respectively) but there were fewer adverse events in patients receiving the echinocandin and the median time for culture sterility was shorter in the MFG group (3 days vs. 4 days). There was no difference between the subsets comprising *C. albicans* and non-*albicans Candida* spp. [51]. A randomised trial in paediatric patients with invasive candidiasis also showed that the success rate was comparable (72.9% with MFG and 76% with L-AmB) and, while both treatments were generally well tolerated, the incidence of

discontinuation of the study agent was higher in the L-AmB group (16.7%) than in the MFG group (3.8%) [52].

8. Summary of clinical data and future perspectives

What do the results of these trials tell us? Minor differences between the trials notwithstanding (e.g. the trial that compared ANI with FLC excluded patients with *C. krusei* infection and patients with *Candida* endocarditis, meningitis or osteomyelitis [43], and the empirical antifungal therapy trial comparing CAS with L-AmB excluded patients receiving RIF or cyclosporin [48]), the clinical utility of all three echinocandins appears to be similar if not identical. Notably, all three agents are safe and they are as effective as standard treatment.

They offer a more acceptable safety profile than agents such as amphotericin B deoxycholate (ABD). On the other hand, the data from these trials also raise several questions. First, the efficacy of the standard agents (e.g. L-AmB) appears to vary significantly if the results of some of the trials are compared with one another [53]. Successful outcome with L-AmB was seen in only a small proportion (25.9%) of patients with baseline fungal infection in the CAS trial [48] but the same agent had a very high success rate (66.7%) in a similar trial that compared it with VCZ [54] and a success rate >80% when compared with ABD [55]. A high variability in success rates between trials separated by only a few years raises significant questions, although the absolute numbers were small. Second, concerns have been raised that prior azole prophylaxis might have diminished the response to L-AmB [56] in some studies because of interference of the former with ergosterol synthesis [57] and might have enhanced the activity of CAS against *Aspergillus* [58]. Third, components of

the study design may also influence the outcome. For example, the dose of L-AmB in the febrile neutropenia trial comparing it with CAS [48] was possibly suboptimal [59] at 3 mg/kg/day when higher doses have been used for the treatment of invasive aspergillosis [60]. Fourth, correlation between clinical efficacy of the agents and their predicted microbiological activity is disappointingly absent. For example, ANI would be expected to be superior to FLC against many of the non-*albicans* *Candida* spp., but such an effect was not seen in the subset analysis [43]. Finally, several other confounding variables could influence the outcome of the abovementioned studies. In the trial comparing ANI with FLC [43], patients on ANI received i.v. drug for a longer duration (14 days vs. 11 days) and more patients on ANI had their central venous catheters removed [61].

Despite the above arguments, the echinocandins do offer a viable alternative to conventional treatment particularly in well defined clinical settings such as invasive candidiasis and candidaemia. Future studies should focus on invasive aspergillosis (as combination therapy for primary invasive aspergillosis or as salvage therapy) and on early empirical treatment and pre-emptive therapy because the mortality of proven fungal infections continues to be high. In the 12-week follow up period in the trial comparing MFG with L-AmB for invasive candidiasis, as many as 40% of patients died in each group [51], and results from a meta-analysis comparing CAS with AMB did not show any benefit in terms of survival, which is disappointing [49]. However, empirical treatment might also treat many patients unnecessarily and better patient selection is essential to ensure that those most likely to have invasive

fungal infections get early treatment. There are sparse data comparing L-AmB or VCZ monotherapy and combination therapy that includes echinocandins for the treatment of invasive mould infections other than aspergillosis. Whilst randomised trials might be impractical in many such settings (e.g. fusariosis) owing to the rarity of infections, a meta-analysis of short case series reports might shed some light on the therapeutic utility of echinocandins.

9. Echinocandins as agents for antifungal prophylaxis

Fungal infections are reported to occur in roughly 14% of patients undergoing chemotherapy for acute leukaemia [62]. There has been a growing interest in prophylactic use of antifungal agents because established fungal infection is associated with high mortality despite adequate therapy. The fatality rate is between 20% and 40% for invasive candidiasis and between 50% and 90% for aspergillosis. Moreover, antifungal treatment may lead to a delay in therapy of the underlying malignancy. The main risk groups for which antifungal prophylaxis might prove to be useful are patients with acute leukaemia and prolonged neutropenia (neutrophil count $<0.5 \times 10^9/L$ for >10 days) or allogeneic stem cell transplantation. ITC is widely used for primary prophylaxis because it has been shown to reduce mortality and has an acceptable safety profile [63]. Posaconazole (PCZ) has been found to be more effective than FLC or ITC as a prophylactic agent in patients with neutropenia (7/304 patients in the PCZ group and 25/298 patients in the FLC and ITC group suffered from proven or probable fungal infection) [64].

Among the echinocandins, only MFG is currently licensed for prophylactic use. In a large randomised phase III trial, MFG was found to be superior to FLC for prevention of fungal infection during the neutropenic phase in patients undergoing haematopoietic stem cell transplantation (HSCT). At the onset of the neutropenic phase or pre-engraftment phase of HSCT, 425 patients in the MFG group and 457 patients in the FLC group received at least one dose of study drug. The overall success rate was significantly higher in the MFG arm (80% vs. 73.5%; $P = 0.03$) and fewer patients discontinued MFG compared with FLC (4.2% vs. 7.2%). A significantly higher proportion of patients in the FLC group was found to be colonised with *C. glabrata* [65].

10. Economic analysis

Drugs contribute substantially towards a hospital's budget. Newer antifungal agents are expensive and prolonged therapy is often required in order to achieve a successful outcome particularly in patients with prolonged neutropenia. Consequently, cost of treatment is one of the most relevant issues when comparing one antifungal agent with another. Bruynesteyn et al. [66] developed an economic model that included successful fever resolution, cure of baseline infection, absence of breakthrough infection, and survival and quality-adjusted life-years as parameters to demonstrate the effectiveness of CAS (70 mg on Day 1 followed by 50 mg/day for an average weight of 77 kg) over L-AmB (3 mg/kg/day). The average total direct cost favoured the use of CAS (£9763 vs. £11 795) [66]. However, the total cost would depend upon the dose of L-AmB (1 mg/kg/day vs. 3 mg/kg/day) and also higher doses of CAS as indicated for patients weighing more than 80 kg (70 mg/day instead of 50

mg/day). Moreover, published prices could vary from local prices making a generalised economic analysis difficult. A direct cost comparison between MFG and CAS showed that while MFG was more cost effective compared with CAS, this difference was not significant [67]. At the existing prices, cost of treatment is likely to remain an important parameter but unless substantially subsidised no single agent is likely to have a decisive advantage over others.

11. Choice of individual agents

Finally, what factors should guide us in choosing one echinocandin over another? Clinical experience favours CAS and this agent is now widely used for the empirical treatment of febrile neutropenia and invasive candidiasis and also as salvage therapy or as part of combination therapy for invasive aspergillosis. In certain settings it might be useful to consider an alternative echinocandin. The choice of an agent within the same class other than CAS may be dictated by the patient's clinical condition, previous history of echinocandin treatment, clinical context, laboratory data and cost. For example, patients on medications that have a significant interaction with CAS (e.g. cyclosporin or tacrolimus) or those with severe hepatic insufficiency may benefit from an alternative agent such as ANI. Other factors that might be taken into account include frequency of administration and the need for dose adjustments depending upon the patient's weight. In particularly recalcitrant infections, laboratory data might support the use of one echinocandin over another (e.g. better in vitro fungicidal activity of MFG against *C. glabrata*) [17], although in many such cases drugs belonging to another class of antifungal agent might also be used. As facilities for carrying out antifungal susceptibility

testing become more widely available, the laboratory input into the therapeutic decision may become more significant in the future. Finally, older agents such as FLC continue to be clinically relevant in many common settings such as BSIs due to *C. albicans*. Also, echinocandins have some obvious limitations such as poor penetration into the meninges, and experience with echinocandins in the treatment of complicated infections is still limited.

12. Conclusion

Echinocandins are attractive therapeutic options for the treatment of invasive fungal infections. Although these agents have a narrow spectrum, they cover the two most common invasive fungal infections, candidiasis and aspergillosis. Clinical trials have shown that the echinocandins are non-inferior to many standard antifungal agents. They all have an excellent safety profile. The availability of three echinocandins has increased the number of agents in the existing antifungal pool. It is unlikely that one agent within this class would be found to be clearly superior to the other agents. Given the high mortality rate from fungal sepsis, therapy in future could be guided by laboratory data in relation to the identity of the fungi and antifungal susceptibility. Concomitant medications and patient factors such as liver failure may also have to be taken into account before therapeutic choices are made. Whilst new antifungal agents are welcome addition, new strategies need to be developed to tackle fungal sepsis. Novel treatment options such as monoclonal antibodies (e.g. efungumab) [68] may offer some benefit particularly if combined with conventional agents.

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