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Review

The echinocandins: three useful choices or three too many?

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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 (AMB) 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 (L-AmB) 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 μg/mL (The interpretive MIC breakpoint for susceptibility of Candida species to all three echinocandins set by the Clinical and Laboratory Standards Institute is ≤2 μg/mL). However, a significant proportion of such strains have a comparatively lower MIC for ANI and MFG (<2 μg/mL but >0.5 μg/mL). However, when tested in the presence of serum, the MIC of all *FKS1* mutant strains was found to be ≥2 μg/mL for all three echinocandins [1]. The efficacy of these agents is affected by protein binding, and therefore a lower susceptibility breakpoint (≤0.5 μg/mL) might be more appropriate for ANI and MFG compared with CAS (2 μg/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.

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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 patients 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. Serum concentrations of sirolimus and nifedipine may increase 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 associated with human infections. *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 lusitaniae* 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 MIC_{50} (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 MIC_{90} (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 MIC_{90} 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 AMB and itraconazole (ITC) that are fungicidal. Echinocandin monotherapy should not be used for primary 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% of 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 enhances the synergistic effects on *A. terreus* but diminishes 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 L-AmB