Drug Class Review: Echinocandins

By Jackie Schneider, Pharm.D. and Bambi Ogren, Pharm.D Candidate May 2007

P&T Action

The Antimicrobial Subcommittee reviewed this class and recommended the addition of micafungin and the removal of caspofungin from the inpatient formulary. In December, the P&T Committee accepted the Subcommittee's recommendation. Effective February 1st, 2007, micafungin is the formulary echinocandin at The Nebraska Medical Center.

Introduction

The incidence of fungal infections is steadily rising in immunocompromised patients. Current treatment options for these infections include amphotericin B (conventional and lipid formulations), the azoles (ketoconazole, itraconazole, fluconazole, voriconazole, and posaconazole), and the echinocandins (caspofungin, micafungin, and anidulafungin). Caspofungin, micafungin, and anidulafungin are available only as intravenous formulations and have been found to be rapidly fungicidal against most *Candida* spp. and fungistatic against *Aspergillus* spp. Along with their fungal spectrum of activity, having few adverse effects and drug interactions make the echinocandins an attractive option in the treatment of systemic fungal infections.

Pharmacology/Pharmacodynamics

Echinocandins are noncompetitive inhibitors of 1,3-β-D-glucan synthase, an enzyme needed for the formation of 1,3-β-D-glucan. Glucan synthase is not found in mammalian cells, making it an ideal target for antifungal agents. Glucan is essential for fungal cell wall structure and growth, maintaining cell shape and rigidity, and resistance to osmotic pressure. The different fungal species have varying amounts of chitin, glucans, mannoproteins, and other cell wall constituents making some species more susceptible to the echinocandins than others. 1,3-β-D-glucan is a major cell wall component of *Candida* and *Aspergillus* species, rendering them more vulnerable to agents found in this drug class.

Micafungin exhibits *in vitro* activity against:

- *Aspergillus* species
- *Candida* species (including *C.albicans, glabrata, krusei, parapsilosis, and tropicalis)*

Caspofungin exhibits *in vitro* activity against:

- *Aspergillus* species (including *A. fumigatus, flavus, and terreus*)
- *Candida* species (including C.*albicans, glabrata, guilliermondii, krusei, parapsilosis, and tropicalis*)

Anidulafungin exhibits *in vitro* activity against:

- *Candida* species (including *C.albicans, glabrata, parapsilosis, tropicalis, famata, rugosa, and stellatoidea*)
- *Aspergillus* species (*A. fumigatus)*
- Other molds
    - *Bipolaris spicifera*
    - *Exophiala jeanselmei*

- *Fonsecaea pedrosoi*
- *Madurella spp.*
- *Penicillium marneffei*
- *Phialophora verrucosa*
- *Pseudallescheria boydii*
- *Wangiella dermatitidis*

Micafungin, caspofungin and anidulafungin are not active at clinically relevant concentrations against Zygomycetes, *Cryptococcus neoformans, Fusarium* spp., or *Trichosporon spp.*

It is important to note that the echinocandins are concentration-dependent agents, meaning that the rate and extent of antifungal activity are related to the concentration of the agent (i.e., increased concentration leads to increased kill). This characteristic is different from the azoles, which display time-dependent activity or increased antifungal activity with increased exposure to the drug.

Clinical Efficacy

FDA Approved Indications

- Micafungin
  - Treatment of esophageal candidiasis
  - Prophylaxis of *Candida* infections in hematopoietic stem cell transplant (HSCT) recipients
- Caspofungin
  - Empirical treatment for presumed fungal infections in febrile, neutropenic patients
  - Treatment of candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis, and pleural space infections
  - Treatment of esophageal candidiasis
  - 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)
- Anidulafungin
  - Treatment of candidemia and other forms of *Candida* infections such as intra-abdominal abscess and peritonitis.
    - Anidulafungin has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida*, and has not been studied in sufficient numbers of neutropenic patients to determine efficacy in this group.
  - Treatment of esophageal candidiasis.

*****No agent within this class is FDA approved for use in the pediatric population. For each agent, there is limited clinical data on use of the agent in pediatric patients.

Adverse Effects

The common adverse effects for any of agents within this class include headache, fever, liver toxic effects, phlebitis, histamine-mediated symptoms, nausea/vomiting, rash and diarrhea.

Drug Interactions

Micafungin is not an inhibitor of P-glycoprotein and therefore would not be expected to alter P-glycoprotein-mediated drug transport activity. Caspofungin is not a substrate for P-glycoprotein. Anidulafungin is not a clinically relevant substrate, inducer, or inhibitor of cytochrome P450 enzymes.

	Micafungin	Caspofungin	Anidulafungin
Mycophenolate mofetil	No effect	No effect	No effect
Cyclosporine	No effect	Cyclosporine (one 4 mg/kg dose or two 3 mg/kg doses) increased the AUC of caspofungin by ~35%. Increased risk of hepatic enzyme elevations.	Concurrent use of anidulafungin and cyclosporine may result in increased anidulafungin exposure. No dosage adjustment of either drug necessary
Tacrolimus	No effect	Tacrolimus AUC_{0-12} was reduced by ~20%, C_{max} by 16%, and 12-hr blood concentration by 26% when 2 doses of 0.1 mg/kg were administered 12 hours apart on the 10^{th} day of caspofungin 70 mg daily	No dosage adjustment of either drug necessary
Prednisolone	No effect	No information	No effect
Sirolimus	Sirolimus AUC was increased by 21% with no effect on C_{max}	No information	No effect
Nifedipine	Nifedipine AUC and C_{max} were increased by 18% and 42%, respectively	No information	No effect
Fluconazole	No effect	No effect	No effect
Amphotericin B	No effect	No effect	No effect
Rifampin	No information	Caspofungin trough concentration decreased by 30%	No dosage adjustment of either drug necessary
Efavirenz, Nevirapine, Phenytoin, Dexamethasone, Carbamazepine, Nelfinavir	No information	Caspofungin plasma concentration reduced	No effect

Dosing and Administration

Micafungin and caspofungin should be administered as an IV infusion over 1 hour. The rate of infusion for anidulafungin should not exceed 1.1 mg/minute. Anidulafungin is reconstituted with a diluent containing 20% alcohol.

Micafungin	
Indication	**Recommended Adult Dose**
Treatment of Esophageal Candidiasis	150 mg/day
Treatment of invasive aspergillosis	150 mg/day (under investigation)
Treatment of systemic candidiasis	100 mg/day (under investigation)
Prophylaxis of *Candida* Infections in HSCT Recipients	50 mg/day
Caspofungin	
Indication	**Recommended Adult Dose**
Empirical treatment for presumed fungal infections in febrile, neutropenic patients	70 mg loading dose on Day 1 followed by 50 mg daily thereafter
Treatment of Candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis, and pleural space infections.	70 mg loading dose on Day 1 followed by 50 mg daily thereafter
Treatment of Esophageal Candidiasis	50 mg/day
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)	70 mg loading dose on Day 1 followed by 50 mg daily thereafter
Anidulafungin	
Indication	**Recommended Adult Dose**
Treatment of candidemia and other forms of *Candida* infections such as intra-abdominal abscess and peritonitis	Single 200 mg loading dose on Day 1, followed by 100 mg daily dose thereafter. Antifungal therapy should continue for at least 14 days after the last positive culture.
Treatment of esophageal candidiasis	Single 100 mg loading dose on Day 1, followed by 50 mg daily dose thereafter. Duration of treatment should be for a minimum of 14 days and for at least 7 days following resolution of symptoms.

*HSCT = Hematopoietic Stem Cell Transplant