

New Antifungal Can Fight *Candida*, *Aspergillus*

BY DAMIAN McNAMARA

Miami Bureau

MIAMI — Approval of micafungin by the Food and Drug Administration in March added another option for combating infections caused by *Candida* or *Aspergillus* species. John R. Perfect, M.D., said at a meeting on fungal infections sponsored by Imedex.

Micafungin (Mycamine), an echinocandin antifungal agent, is indicated for pro-

phylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation and for treatment of esophageal candidiasis. The echinocandin class also includes caspofungin (Cancidas), approved in 2001. Two more drugs in this class, anidulafungin and aminocandin, are in development.

“My suspicion is, [drugs in this class] will have a significant impact on how we manage patients,” said Dr. Perfect, professor of medicine at Duke University Medical Center, Durham, N.C. Yet “candins lack any significantly good data for any fungal infections outside *Candida* or *Aspergillus*.”

A possible drawback is that the echinocandins are available only for intravenous infusion. Other considerations are the low urinary and brain concentrations achieved by these drugs, but “these things are not necessarily bad,” he added.

Dr. Perfect disclosed an affiliation with PLIVA, a company that manufactures

generic fluconazole, ketoconazole, and metronidazole.

Both caspofungin and micafungin are effective in treating esophageal candidiasis. The echinocandins also have a long half-life and low toxicity, and require little dosage adjustment for patients with renal or liver dysfunction. And the agents have

a low potential for drug interactions, which means they can be used in patients taking many other drugs, he said.

Although prevention of *Aspergillus* infections would be an off-label use of micafungin, the drug does

have activity against these organisms, said Dr. Perfect. He predicted that the echinocandins would have a role in preventing *Aspergillus* infections in the future. “Candins for aspergillosis are trendy in combination, but no one has any data to support that today.”

The “paradigm-changing study” for the echinocandins, Dr. Perfect said, was a randomized, double-blind, multicenter com-

parison between caspofungin and amphotericin B for patients with invasive candidiasis (N. Engl. J. Med. 2002;347:2020-9). The patients were stratified by neutropenic status and Apache score, and there was no difference between the two drugs in outcome. The study design was practical, he added, because after 10 days of intravenous therapy, patients were switched to oral fluconazole. Intravenous therapy is very expensive, he noted.

He and his colleagues examined caspofungin efficacy for 109 episodes of invasive candidiasis at Duke University Medical Center. The clinical cure rate was 83% (55/66) for bloodstream infections and 88% (23/26) for intraabdominal infections. “This drug performed very, very well with intraabdominal infections.” The failure rate for invasive candidiasis decreased from 26% in 2001 to 11% in 2003. “In this population, there are few ways you are going to improve on that success rate,” he said.

Some people point out that echinocandins are very expensive, compared with the azoles, which are available as generics in many cases, Dr. Perfect said. “But there are a number of candins coming out, so hopefully the market will help with that.” ■

Ezetimibe: The pharmacokinetics of ezetimibe in adolescents (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with ezetimibe in the pediatric population is limited to 4 patients (9 to 17 years) with homozygous sitosterolemia and 5 patients (11 to 17 years) with HoFH. Treatment with ezetimibe in children (<10 years) is not recommended.

Simvastatin: Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses >40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on therapy with simvastatin (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

Genetic Use: Of the patients who received VYTORIN™ (ezetimibe/simvastatin) in clinical studies, 792 were 65 and older (this included 176 who were 75 and older). The safety of VYTORIN was similar between these patients and younger patients. Greater sensitivity of some older individuals cannot be ruled out. (See CLINICAL PHARMACOLOGY, Special Populations and ADVERSE REACTIONS.)

ADVERSE REACTIONS: VYTORIN has been evaluated for safety in more than 3800 patients in clinical trials. VYTORIN was generally well tolerated.

Table 1 summarizes the frequency of clinical adverse experiences reported in ≥2% of patients treated with VYTORIN (n=1236) and at an incidence greater than placebo regardless of causality assessment from 3 similarly designed, placebo-controlled trials.

Table 1
Clinical Adverse Events Occurring in ≥2% of Patients Treated with VYTORIN and at an Incidence Greater than Placebo, Regardless of Causality

Body System/ Organ Class Adverse Event	Placebo (%) n=311	Ezetimibe 10 mg (%) n=302	Simvastatin** (%) n=1234	VYTORIN** (%) n=1236
Body as a whole – general disorders				
Headache	6.4	6.0	5.9	6.8
Infection and infestations				
Influenza	1.0	1.0	1.9	2.6
Upper respiratory tract infection	2.6	5.0	5.0	3.9
Musculoskeletal and connective tissue disorders				
Myalgia	2.9	2.5	2.6	3.5
Pain in extremity	1.3	3.0	2.0	2.3

* Includes 2 placebo-controlled combination studies in which the active ingredients equivalent to VYTORIN were coadministered and 1 placebo-controlled study in which VYTORIN was administered.

** All doses.

Ezetimibe: Other adverse experiences reported with ezetimibe in placebo-controlled studies, regardless of causality assessment: *Body as a whole – general disorders:* fatigue; *Gastrointestinal system disorders:* abdominal pain, diarrhea; *Infection and infestations:* infection viral, pharyngitis, sinusitis; *Musculoskeletal system disorders:* arthralgia, back pain; *Respiratory system disorders:* coughing.

Post-marketing Experience: The following adverse reactions have been reported in post-marketing experience, regardless of causality assessment:

Hypersensitivity reactions, including angioedema and rash; increased CPK; elevations in liver transaminases; hepatitis; thrombocytopenia; pancreatitis; nausea; cholelithiasis; cholecystitis; and, very rarely in patients taking an HMG-CoA reductase inhibitor with ezetimibe, rhabdomyolysis (see WARNINGS, Myopathy/Rhabdomyolysis).

Simvastatin: Other adverse experiences reported with simvastatin in placebo-controlled clinical studies, regardless of causality assessment: *Body as a whole – general disorders:* asthma; *Eye disorders:* cataract; *Gastrointestinal system disorders:* abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea; *Skin and subcutaneous tissue disorders:* eczema, pruritus, rash.

The following effects have been reported with other HMG-CoA reductase inhibitors. Not all the effects listed below have necessarily been associated with simvastatin therapy.

Musculoskeletal system disorders: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgia.

Nervous system disorders: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial palsy), tremor, dizziness, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances.

Ear and labyrinth disorders: vertigo.

Psychiatric disorders: anxiety, insomnia, depression, loss of libido.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal system disorders: pancreatitis, vomiting.

Hepatobiliary disorders: hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma.

Metabolism and nutrition disorders: anorexia.

Skin and subcutaneous tissue disorders: alopecia, pruritus. A variety of skin changes (eg, nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive system and breast disorders: gynecostasia, erectile dysfunction.

Eye disorders: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ -glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Laboratory Tests:

Marked persistent increases of serum transaminases have been noted (see WARNINGS, Liver Enzymes). About 5% of patients taking simvastatin had elevations of CK levels of 3 or more times the normal value on 1 or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS, Myopathy/Rhabdomyolysis).

Concomitant Lipid-Lowering Therapy:

In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine.

Adolescent Patients (ages 10-17 years)

In a 48-week controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolemia (n=175), the safety and tolerability profile of the group treated with simvastatin (10-40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea (see CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS, Pediatric Use).

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20502352(1)(602)-VYT

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Echinocandins Offer Antifungal Therapy With Low Toxicity, Few Drug-Drug Interactions

BY DAMIAN McNAMARA

Miami Bureau

MIAMI — The echinocandin antifungal agents appear to have little significant toxicity and may prove safer than the azoles or amphotericin B in terms of potential interactions, said Paul O. Gubbins, Pharm.D.

“Echinocandins are an exciting new class. To date, there are few significant drug-drug interactions,” he said at a meeting on fungal infections sponsored by Imedex.

The echinocandin caspofungin (Cancidas) has “no significant interaction” with cytochrome P-450 (CYP450) metabolism or P-glycoprotein, according to product labeling. The most abundant enzyme in the CYP450 system, CYP3A4, metabolizes about 50%-60% of all medicines.

The recently approved echinocandin micafungin (Mycamine) is not a substrate or inhibitor for P-glycoprotein, a transmembrane efflux pump in the liver, intestine, kidneys, and blood-brain barrier.

With a lower potential for interactions, the echinocandins may be ideal for combination therapy, said Dr. Gubbins, chair of the department of pharmacy practice, University of Arkansas, Little Rock.

Traditional formulations of amphotericin B have renal toxicity that can produce additive drug interactions. “We’re all familiar with the toxicities of amphotericin B. They are subtle and, in most cases, unavoidable. Consider renal-sparing alternatives” such as lipid amphotericin B or caspofungin, he suggested.

When prescribing traditional amphotericin B, monitor serum levels of drugs

that have a narrow therapeutic index and are eliminated by the kidneys. Examples include aminoglycosides and 5-flucytosine.

Some patients, such as organ transplant recipients, require closer monitoring. They often must use drugs—such as immunosuppressants—that increase the risk of fungal infections, he noted.

The azoles can interact through multiple mechanisms, including CYP450 metabolism, gastric pH-dependent effects, and P-glycoprotein activity.

“Interactions can be managed with alternative drugs in the affected class or by switching agents,” Dr. Gubbins said.

Itraconazole leads the azole class in terms of potential interactions. The antifungal interacts through the CYP450 system with statins, especially lovastatin, simvastatin, and atorvastatin (Lipitor), and this can lead to skeletal muscle toxicity. Other affected agents include benzodiazepines, anxiolytics, immunosuppressants, and corticosteroids. With corticosteroids, he said, “The key is, it doesn’t matter if you give these orally or IV, or if they’re inhaled, you can get interactions.”

Itraconazole can also have significant pH interactions. Dr. Gubbins suggested that patients take the tablets with a high-fat meal in order to slow gastric emptying or with a meal that contains enough protein to buffer the stomach contents. Other techniques for reducing pH interactions include spacing the administra-

tion of tablets, considering itraconazole oral solution, or switching to another agent.

P-glycoprotein interactions are significant only for itraconazole, not for voriconazole (Vfend), or fluconazole, he said.

Several agents lower serum levels of itraconazole, including phenytoin, phenobarbital, rifampin, and rifabutin (Mycobutin), but “remember that itraconazole affects other medications more than other medications affect itraconazole,” he said. “The ones we’re worried about are the ones with a narrow therapeutic index, such as digoxin.”

Fluconazole affects more CYP450 enzymes than does itraconazole. Interactions depend largely on fluconazole concentration and are typically seen with doses above 200 mg. Of particular concern are interactions between fluconazole and phenytoin or warfarin. “With phenytoin, if you do not see a response, it could be that [phenytoin] is inhibiting fluconazole,” he said.

“We also worry about the anticoagulant warfarin. ... This interaction is almost guaranteed.” Decreasing the warfarin dose might help, but “you almost always need to move to another antifungal.”

Drugs that affect voriconazole include phenytoin, rifampin, and rifabutin. Other potential interactions include carbamazepine, protease inhibitors, nonnucleoside reverse transcriptase inhibitors, benzodiazepines, and statins. ■

Echinocandins—members of ‘an exciting new class’ that appears to have few significant drug-drug interactions—may be ideal for combination therapy.