New Drugs Could Slow Rise in Fungal Infections

BY ERIK L. GOLDMAN
Contributing Writer

SAN DIEGO — The incidence of cutaneous fungal infections is on the rise in the United States, and the old standby antifungal drugs aren't working as well as they used to, Dr. Ted Rosen said at the American Academy of Dermatology's Academy 2006 conference.

Fortunately, new antifungals are emerging that could stem the mycologic mayhem, at least for a while.

The rise in fungal infections can be partly attributed to an increase in the number of immunosuppressed people living ever-longer lives. HIV-positive people on highly active antiretroviral therapy (HAART), survivors of cancer chemotherapy, and organ transplant recipients on immunosuppressive drugs are all highly susceptible to systemic mycoses, said Dr. Rosen of the department of dermatology at Baylor College of Medicine, Houston.

Another key factor is the unprecedented mobility of the population. More people travel more often and farther than at any other time in history. Immigrants come to the United States from regions that are endemic for fungi seldom seen here in the past.

Tertiary care centers like Baylor are reporting increases in fungi such as *Cryptococcus, Histoplasma capsulatum, Sporothrix, Fusarium, Rhizopus,* and *Fonsecaea,* which often go unrecognized or misdiagnosed for a long time. Given the high numbers of military and oil-industry personnel in Texas, Baylor clinicians are seeing a rise in strange fungal infections in troops and oil workers returning from Iraq, the Persian Gulf, and South America.

Moreover, mainstay drugs like fluconazole, itraconazole, ketoconazole, terbinafine, and griseofulvin are more widely used than ever, applying plenty of selective pressure on the fungi to develop resistance.

Which is just what is happening.

Dr. Rosen cited a recent report of terbinafine-resistant *Trichophyton rubrum* in a patient with onychomycosis who had never before been treated with an antifungal. "We're seeing innate resistance in a garden-variety form of *T. rubrum*. This old 'friend' is suddenly nonresponsive to a very powerful antifungal drug. This is problematic," he said.

Fortunately, he noted, a passel of new antifungals is making its way into clinical practice, including a new class of cell wall–smashing echinocandins.

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All of the azoles, including new ones like voriconazole (Vfend) and posaconazole (Noxafil)—as well as ravuconazole, which is not yet approved—attack fungal cell membranes.

Voriconazole has a broad spectrum and is highly effective against all species of *Candida*. It also works against *Aspergillus* and *Fusarium,* which generally won't yield to fluconazole. In vitro, voriconazole bests griseofulvin and ketoconazole, and it equals terbinafine in killing dermatophytes. It is also extremely bioavailable in oral dosing forms, Dr. Rosen said.

This new drug does have its downside, mainly its strong potential for adverse effects. It is metabolized via two cytochrome P450 enzymes, so it is capable of interacting with other drugs, at least in theory. It induces liver enzyme elevations, which are reversible, and it can also trigger morbilliform eruptions.

The most common adverse effect of voriconazole, though, is visual disturbances. Dr. Rosen said that a number of patients experience photophobia or a very specific visual disturbance characterized by bluish purple halos around objects.

Purple haze aside, Dr. Rosen said he's used this drug a lot, and in his experience, it is reasonably problem free. "I've used it off-label to treat patients who've failed everything else."

Posaconazole was approved in September under the brand name Noxafil for the treatment of aspergillosis. (See story below.) Metabolism of posaconazole involves only one CYP 450 enzyme, so this drug is less likely to cause interactions. Side effects are "pretty reasonable," Dr. Rosen said, the most common being headache and nausea.

"What really makes this drug stand out, aside from its ability to deal with weird fungi, is that it really works for zygomycetes—those deep fungi that really penetrate the nasopharynx in diabetes patients and transplant recipients. It's also great for everything refractory, and it does this orally," he said.

Ravuconazole initially looked quite promising, with excellent in vitro efficacy against dermatophytes, but further development seems to have stalled for reasons that are not clear, he said.

Albaconazole, the newest triazole, is still in an early developmental stage, but "it is better than itraconazole, fluconazole, or voriconazole for almost all of the common dermatophytes and saprophytes, and at least as good as or better than all the existing triazoles," Dr. Rosen said. Albaconazole will be initially formulated as a nail lacquer along with oral and intravenous forms.

The echinocandins bring a new therapeutic mechanism into the antifungal picture: They break down the fungal cell walls by attacking the glucan building blocks and inhibiting the enzyme complexes involved in synthesizing glucans.

According to Dr. Rosen, the candins are strong medicine for "seriously sick patients with really bad bugs." Basically, the candins make it impossible for the fungi to build their cell walls, and the current trend among fungal infection specialists is to combine an echinocandin with one of the new triazoles.

He noted that he has worked with caspofungin (Cancidas) quite a bit and has found that it greatly extends *Candida* coverage. In HIV-positive patients, it can quickly clear refractory esophageal candidiasis.

Micafungin (Mycamine) is the other hot candin these days. It is excellent for *Candida* and *Aspergillus,* but it does not work as well against Zygomycetes or *Fusarium*.

The main drawback to the candins as a class is that they are available only in intravenous forms. "All these drugs are cyclic hexapeptides, and all are destroyed by acids. Therefore, oral formulations are not possible," Dr. Rosen said.

There are a few other antifungals in the offing. PLD-118, also known as icofungipen, is neither an azole nor a candin. It is a tiny molecule that binds to fungal isoleucyl transfer RNA, thus affecting a wide range of *Candida* species. PLD-118 is being developed as topical as well as systemic therapy.

Milbemycin, derived from *Streptomyces,* trips up the fungal gene that enables resistant fungi to "spit out" other antifungals, he said. When it eventually comes to market, it will probably find its place as an adjunct for many of the more conventional antifungals, potentiating their effects against resistant pathogens.

Finally, there's the yet-to-be properly named P-113, the world's first "swish and spit" antifungal. This drug, which is being developed as a therapeutic mouthwash, is a 12-amino acid fragment of histatin 5, a compound produced by the body that has fungistatic effects, especially against *Candida*. Histatin 5 is "basically what prevents most of us from getting thrush. So this drug is essentially a duplication of the natural mechanism for controlling yeasts," Dr. Rosen said. ■

Noxafil Wins Approval for the Prevention Of Invasive *Aspergillus, Candida* Infections

BY JOHN R. BELL
Associate Editor

The Food and Drug Administration has approved a new drug intended for the prevention of *Aspergillus* and *Candida* fungal infections in immunocompromised patients.

Posaconazole, which will be marketed as Noxafil by Schering-Plough, was approved on the basis of two randomized controlled trials that showed greater efficacy than fluconazole in preventing infections in patients aged 13-82 years.

In a study of patients with graft-versus-host disease who had undergone hematopoietic stem cell transplantation, 2% of patients experienced clinical failure due to proven or probable invasive fungal infection (IFI) after 7 days' treatment, versus 7% of patients on fluconazole; after 16 weeks' treatment, these figures were 5% for those on posaconazole and with 9% for those on fluconazole.

In a separate study of patients with hematologic malignancy or prolonged neutropenia, 2% of those on posaconazole had clinical failure due to proven/probable IFI after 7 days, versus 8% of those on fluconazole/itraconazole. After 100 days, these figures were 5% for the posaconazole group and 11% for the fluconazole/itraconazole group.

Reported side effects of posaconazole include nausea, vomiting, diarrhea, changes in QTc interval, and hepatic impairment.

Posaconazole should be given only with a full meal or liquid nutritional supplement, according to the FDA-approved label. No dose adjustment is required for those with mild to moderate renal impairment or for pediatric or geriatric patients.

Coadministration is contraindicated for ergot alkaloids, terfenadine, astemizole, cisapride, pimozide, halofantrine, and quinidine.

The drug works by blocking fungal cells' synthesis of the membrane component ergosterol.

Noxafil was approved in Europe by the European Medicines Agency in October 2005, based on complete or partial resolution of invasive aspergillosis in 42% of patients, compared with 26% of control patients. ■

Bacterial Contamination Prompts Recall of Perineal Washcloths

Certain lots of Comfort Shield Perineal Care Washcloths have been recalled because of contamination with *Burkholderia cepacia*.

The bacteria can cause serious infections including pneumonia and bacterial sepsis in immunocompromised individuals, those with cystic fibrosis, and hospitalized patients in general, as well as certain other patient groups.

The product was distributed to hospitals, medical centers, and long-term care facilities in the United States and Canada. The affected codes/lots include: 7403/1301, 7403/1312, 7403/1457, 7403/1677, 7408/1848, 7503/1999, 7524/2070, 7524/2086, 7905/1766, 7503-M/1702, and 7503-M/1995. There have been no reports of patient injury to date.

Customers with affected lots of the product should stop usage and contact Sage Products Inc. to return and replace the items. For more information or to arrange return and replacement, contact the company at 800-323-2220.

—Kerri Wachter