New Drugs Could Slow Rise in Fungal Infections

BY ERIK L. GOLDMAN
Contributing Writer

SAN DIEGO — The incidence of cuta- neous fungal infections is on the rise in the United States, and the old standby anti- fungal drugs aren’t working as well as they used to, Dr. Ted Rosen said at the Ameri- can Academy of Dermatology’s Academy 2006 conference.

Fortunately, new antifungals are emerg- ing that could stem the mycologic may- hem, at least for a while.

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

Another key factor is the unprecedent- ed mobility of the population. More peo- ple 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 re- porting increases in fungi such as Cryptococcus, Histoplasma capsulatum, Sproehnle, Fusarium, Mucoraceae, and Sternu- fria, 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 flucona- zole, itraconazole, ketoconazole, terbina- fine, and griseofulvin are more widely used than ever, applying plenty of selective pres- sure 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 antifun- gal. Were it to become a common resistance in a gar- den-variety form of T. rubrum. This old ‘friend’ is suddenly nonresponsive to a very powerful antifungal drug. This is prob- lematic,” he said.

Fortunately, he noted, a passel of new antifungals is making its way into clinical practice, including a new class of cell w a l l – s m a sh i n g echinocandins.

All of the azoles, including new ones like voriconazole (Vendio) and posaconazole (Noxafil)—as well as racemic terbinafine, which has not yet approved—attack fungal cell membranes.

Voriconazole has a broad spectrum and is highly effective against all species of Can- dida. 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 dermato- phytes. 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 ef- fects. Patients experience photosensitivity 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 Septem- ber under the brand name Noxafil for the treatment of aspergillosis. (See story be- low.) 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 nau- sea.

“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 immuno- compromised patients and transplant recipients. It’s also great for everything refractory, and it does this orally,” he said.

Racemic terbinafine, which initially looked quite promising, with excellent in vitro efficacy against dermatophytes, but further develop- ment seems to have stalled for reasons that are not clear, he said.

Albacaonazole, 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 exist- ing triazoles,” Dr. Rosen said. Albacaonazole will be initially formulated as a nail lacquer along with oral and intravenous forms.

The echinocandins bring a new thera- peutic mechanism into the antifungal pic- ture: They break down the fungal cell walls by attacking the glucan building blocks and inhibiting the enzyme com- plex involved in synthesizing glucans. According to Dr. Rosen, the canids are strong medicine for “seriously sick pa- tients with really bad bugs.” Basically, the canids 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 caspo- fungin (Cancidas) quite a bit and has found that it generally extends Candida coverage. In HIV-positive patients, it can quickly clear refractory esophageal candidiasis.

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

“The main drawback to the canid as a class is that they are available only in in- travenous 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 antifunginals in the offering. PDA 118, also known as sco- fungin, is neither an azole nor a canid. It is a tiny molecule that binds to fungal iso- enzyme transfer RNA, thus affecting a wide range of Candida species. PDA 118 is being developed as topical as well as sys- temic therapy.

Milbemycin, derived from Stereomyces, trips up the fungal gene that enables resistant fungi to ‘spit out’ other antifun- gals, he said. When it eventually comes to market, it will probably find its place as an adjunct for many of the more conven- tional antifungals, postponing 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 Can- dida. Histatin 5 is “basically what prevents most of us from getting thrush. So this drug is essentially a duplication of the nat- ural mechanism for controlling yeast,” 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 Candia fungal infections in immunocompromised patients.

Posaconazole, which will be marketed as Noxafil by Schering-Plough, was approved on the basis of two ran- domized 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 trans- plantation, 2% of patients experienced clinical infection due to proven or probable invasive fungal infection (IFI) after 7 days’ treatment, versus 7% of patients on flucona- zole; after 16 weeks’ treatment, these figures were 9% on posaconazole and with 9% for those on fluconazole.

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

Posaconazole should be given only with a full meal or liquid nutritional supplement, according to the FDA-ap- proved 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 alka- lids, tetrabenazine, astemizole, cisapride, pimozide, halo- fanidine, and quinidine.

The drug works by blocking fungal cell syntheses of the membrane component ergosterol.

Noxafil will be introduced in the European Med- ical Sciences Agency in October 2005, based on complete or par- tial 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 Barbara curraea. The bacteria can cause serious infections including pneumonia and bacterial sepsis in immunocompro- mised individuals, those with cystic fibrosis, and hospi- tialized patients in general, as well as certain other pa- tient 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, 7504/2070, 7504/1702, and 7503/M-1995. There have been no reports of patient injury to date.

Customers with affected lots of the product should stop using the contaminated Sani-Sponge cloth and replace the items. For more information or to arrange return and replacement, contact the company at 800-323-2220.