Oral Terbinafine for Treatment of Pulmonary *Pseudallescheria boydii* Infection Refractory to Itraconazole Therapy

Pseudallescheria boydii, apparently distributed worldwide, has been isolated from soil (1), polluted streams, and sewage sludge (2). It may cause a wide range of clinical syndromes in humans, including mycetoma, osteomyelitis, brain abscesses, and invasive pulmonary and disseminated infections in both immunocompetent (3) and immunocompromised patients (4). In most cases treatment of pseudallescheriasis includes surgical debridement and excision of necrotic tissue combined with systemic administration of antifungal azole therapy. Of the imidazoles, miconazole appears to be more active in vitro than ketoconazole (5), and parenteral administration should be considered in patients with compromised host defenses. Overall, however, the antifungal azoles have been used with variable success (6), and at present the optimal choice and duration of chemotherapy are unknown.

We have reported previously a case of pulmonary pseudallescheriasis in an immunocompetent host due to preceding trauma. The patient initially responded to treatment with itraconazole (7); however, after nearly two years of treatment with itraconazole, the infection relapsed. We report here the successful treatment of the relapsed infection with oral terbinafine.

In 1984 the 28-year-old man was admitted to hospital with a perforating chest wound after having fallen on a metal bicycle spoke. The course of disease was complicated by hematothorax, hemoptysis, and several bacterial infections with empyema for which he underwent four thoracic surgeries. Finally, a right-sided pneumonectomy was performed. The patient was discharged in good condition and recovery was uneventful until the summer of 1991, when the patient presented with expectoration of small mucus plugs that smelled like "French cheese"; this occurred approximately once every six weeks. The patient was afebrile; laboratory tests revealed a hemoglobin level of 9.2 mmol/l and a leukocyte count of 7.8×10^9/l. Bronchoscopy was unrevealing, but computed tomography scan of the chest showed swelling around the right hilar stump and several collections of air. Microscopic examination of the expectorated mucus plugs showed hyphal elements, and cultures grew *Pseudallescheria boydii*.

Treatment with oral itraconazole (400 mg/day) was initiated, and after three months the patient was symptom free and mycological cultures were negative. However, after 20 months of therapy, the patient relapsed again and began expectorating mucus plugs every two months.

Pseudallescheria boydii was again isolated from culture. At that time the itraconazole serum concentration was 5421 μg/l. Magnetic resonance imaging showed a small, high-signal lesion surrounding the bronchial stump, but no evidence of cavities. Bronchoscopy revealed the presence of a small mucus plug and a loose stitch in the bronchial stump. Both were removed, but cultures were not performed. Itraconazole therapy was continued until June 1994, but, since symptoms and positive cultures persisted, therapy was changed to oral terbinafine (500 mg/day; Sandoz, Switzerland) on compassionate treatment basis.

After four months of therapy, bronchoscopy showed no evidence of fungal infection, and cultures were negative. Treatment was continued for a total of nine months. No adverse events, including liver function abnormalities, were apparent during therapy. At present, more than one year after discontinuation of terbinafine therapy, the patient is free of symptoms.

The MIC for the six isolates of *Pseudallescheria boydii* cultured from the mucus plugs between 1984 and 1994 was determined in Sabouraud broth at 30°C and in RPMI 1640 medium at 37°C (Dr. N.S. Ryder, Sandoz Forschungsinstitut, Vienna). All isolates were found to be resistant in vitro to itraconazole (MIC > 100 μg/ml) and terbinafine (MIC > 100 μg/ml).

Infections caused by *Pseudallescheria boydii* are often refractory to antifungal chemotherapy, including treatment with antifungal azoles. New therapeutic approaches are clearly needed for the treatment of infections by this organism. Itraconazole has been suggested as a good alternative to miconazole for treatment (6, 8), but monitoring of serum levels is required since absorption from the gastrointestinal tract after oral administration may be variable. It causes only minor gastrointestinal side effects but should be avoided in patients with liver disease because it has been reported to induce elevations of serum aminotransferases and, in sporadic cases, severe hepatitis.

Relapse of infection during treatment with itraconazole occurred in our patient despite adequate serum concentrations. The presence of a loose stitch could have contributed to the relapse of infection, but symptoms persisted after the

stitch had been removed and cultures remained positive despite continuous therapy with itraconazole.

Terbinafine is an allylamine antifungal agent that displays a primary fungicidal action against a broad range of dermatophytes, moulds, and yeasts (9). However, MICs of terbinafine for *Pseudallescheria boydii* are relatively high, ranging from 10 to > 64 μg/ml (10). Indeed, in our patient neither itraconazole nor terbinafine showed significant in vitro activity against the *Pseudallescheria boydii* isolates, but these results did not correlate with the successful clinical response to treatment with terbinafine.

A poor correlation between susceptibility results and in vivo response has been reported for *Pseudallescheria boydii* (11). Furthermore, since residual serum and tissue levels of itraconazole may have been present in our patient directly after switching therapy to terbinafine, simultaneous exposure of *Pseudallescheria boydii* to both agents may have enhanced the killing of the fungus. The in vitro antifungal activity of amphotericin B in combination with antifungal azoles against *Pseudallescheria boydii* has been studied (12), but little is known about the activity of terbinafine combined with azoles. Although both the azole and allyamine antifungal agents are potent inhibitors of fungal ergosterol synthesis, their modes of action are different and the combination of these agents may provide an important therapeutic option.

Although terbinafine is commonly used for the treatment of dermatophytic infections of the skin and nails, there is some evidence that it may be effective for the treatment of systemic fungal infections (13). Marked improvement or cure was noted in two patients with invasive pulmonary aspergillosis, one patient with *Aspergillus fumigatus* osteomyelitis and one kidney transplant recipient with a wound infection due to *Rhizopus* spp. (13). All four patients had failed to respond to therapy with amphotericin B. Furthermore, one patient with bronchopneumonia due to *Aspergillus fumigatus* and *Pseudallescheria boydii* was treated with terbinafine (G.F. Shiraldi et al., International Society for Human and Animal Mycology, Adelaide, 1994, Abstract no. 139). Cure of clinical signs and symptoms was achieved after eight months of therapy, but relapse of *Pseudallescheria boydii* infection occurred five months after discontinuation of terbinafine therapy. Complete recovery was achieved after a second treatment course of eight months.

The present case suggests that terbinafine may be useful in difficult-to-treat infections, but this agent should be considered investigational in the treatment of systemic fungal infections until the therapeutic outcome has been assessed in more patients. Terbinafine is well tolerated, even during long-term treatment, and side effects are generally mild to moderate, and transient. The most common are intestinal discomfort, erythema of the skin, and mild elevation of liver enzymes. However, isolated cases of severe skin reactions, including Stevens-Johnsons syndrome and toxic epidermal necrolysis, and serious hepatic dysfunction, including jaundice, cholestasis, and hepatitis, have been reported.

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