Voriconazole Treatment of Disseminated Paecilomyces Infection in a Patient with Acquired Immunodeficiency Syndrome

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We describe a patient with poorly controlled, multidrug-resistant human immunodeficiency virus disease who developed >20 skin lesions caused by Paecilomyces lilacinus. The lesions failed to improve during treatment with oral itraconazole, amphotericin B, and amphotericin B lipid complex but improved during treatment with voriconazole.

Paecilomyces species are saprophytic fungi that are found worldwide, often in soil, and function as biodegrading agents. They are uncommon causes of human disease but appear to be pathogens of increasing importance among immunocompromised patients [1]. Documented Paecilomyces infections in such patients include cutaneous disease, onychomycosis, catheter-related fungemia, pneumonia, peritonitis, osteomyelitis, and prosthetic-valve endocarditis [2–9]. Other infections reported in immunocompromised hosts include keratitis associated with use of extended-wear contact lenses, sporothrichosis-like skin infections, chronic maxillary sinusitis, and lung abscesses [10–13]. Paecilomyces species have been shown to survive well on commonly used fabrics and plastics and have been implicated in an outbreak of infection in which contaminated skin lotion was the reservoir [8, 14]. Risk factors for invasive disease are neutropenia, depressed cellular immunity, corticosteroid use, diabetes mellitus, and transplantation [11]. The optimal treatment regimen is unknown, and treatment failure is common. Antifungals that have been helpful or successful include amphotericin B (alone or combined with 5-flucytosine), terbinafine, miconazole, griseofulvin, ketoconazole, and itraconazole [15]. In addition, at least 1 serious case of cutaneous infection due to Paecilomyces lilacinus that was successfully treated with voriconazole has been reported [16].

Voriconazole is a new triazole antifungal agent with in vitro activity against many clinically significant fungi, including Candida, Aspergillus, Fusarium, Scedosporium, and Paecilomyces species and others [15]. The mechanism of voriconazole appears to be efficient inhibition of ergosterol synthesis in susceptible fungi, which results from inhibition of the cytochrome P450-dependent 14α-demethylase enzyme. Voriconazole has been shown to be a more potent inhibitor of this enzyme in Candida species than is fluconazole [17]. Adverse effects of voriconazole therapy reported in clinical trials have included changes in visual acuity, increases in hepatic enzyme levels, and rash [18].

We report a case of treatment-refractory disseminated Paecilomyces infection that improved during therapy with voriconazole, with subsequent worsening on discontinuation of treatment. Appropriate informed consent was obtained and clinical research was conducted in accordance with guidelines for human experimentation as specified by the US Department of Health and Human Services (Washington, DC) and the University of Kentucky (Lexington).

Case history. The patient was a 40-year-old man who had AIDS diagnosed in 1994 after he developed pneumonia caused by Pneumocystis carinii. During the next several years, the HIV infection was refractory to treatment with multiple combinations of antiretrovirals, and his CD4 count remained <20 cells/μL. In February 1998, the patient developed a subcutaneous indurated and nodular lesion on the posterior aspect of his calf. Culture of a biopsy specimen grew P. lilacinus, and histologic examination of the specimen showed no evidence of fungal infection. At this time, treatment with itraconazole capsules was started (200 mg po b.i.d.). The lesion increased in size, and by May 1998 the patient had developed lesions on the right ankle (figure 1), the right anterior tibial region, and the lateral aspect of the right thigh. A biopsy of the thigh lesion was performed and revealed invasive infection with a filamentous fungus. P. lilacinus was again recovered from culture of the biopsy specimen. After advancement of the lesions, the patient was treated with amphotericin B deoxycholate, and his serum creatinine level subsequently increased to 2.4 mg/dL. Therapy was changed to amphotericin B lipid complex (5 mg/kg per day; Abelcet; The Liposome Company). After 2 months of therapy with amphotericin B preparations, during which time lesions continued to appear, the regimen was changed to...
itraconazole oral solution (300 mg po b.i.d.). Again, 2 months passed with no improvement.

Our patient was then enrolled in a phase III, open-label, noncomparative, multicenter trial of the efficacy, safety, and toleration of voriconazole in the primary or secondary treatment of invasive fungal infections (Pfizer trial 604) and, subsequently, in an open-label, noncomparative protocol of the efficacy, safety, and toleration of extended voriconazole treatment of invasive fungal infections (Pfizer trial 607). Voriconazole therapy was initiated on 19 November 1998 with a loading dose of 6 mg/kg iv q12h for the first 24 h, followed by dosages of 4 mg/kg iv q12h for 3 days and then 200 mg po b.i.d. for 30 days. Although the lesions showed some reduction in size, they persisted.

At this time the decision was made to increase the dosage of voriconazole to 300 mg b.i.d. During the eighth month of voriconazole therapy, an elevation in hepatic enzyme levels was detected, and the dosage was decreased to 200 mg b.i.d. The patient’s hepatic enzyme levels returned to normal, and ∼2 weeks later the dosage was once again increased to 300 mg b.i.d. The patient continued this dosage for 10 months, at which time he decided to discontinue all antiretroviral therapy and voriconazole treatment. No new lesions were noted during this 10-month period, and many lesions decreased in size or disappeared. The patient’s total voriconazole exposure was ∼325 g. At a follow-up visit 2 months later, the patient was noted to have more skin lesions and extension of many existing lesions. Biopsies of the lesions were not performed at this time.

After discontinuation of all antiretroviral, antifungal, and antibacterial therapy, the patient died in August 2000.

Medications administered periodically during voriconazole therapy included clarithromycin, ethambutol, sulfamethoxazole/trimethoprim, amantadine, trovafloxacin, vancomycin, azithromycin, cefuroxime, megestrol, ranitidine, morphine, oxandrolone, promethazine, hydrocortisone, famotidine, loperamide, stavudine, saquinavir, indinavir, didanosine, ritonavir, efavirenz, abacavir, amprenavir, and nelfinavir. Table 1 shows voriconazole serum concentrations as related to the concomitant medications and the timing of voriconazole dosages. The reason for the variability in serum concentrations is not obvious. The patient had higher concentrations at the beginning of therapy and while receiving protease inhibitors. Peak values dropped ∼1 month after the initiation of voriconazole therapy. We believe the patient to have been compliant with all medications. We suggest that, for patients receiving complex drug regimens, especially those that contain CYP450-metabolized agents, voriconazole serum concentrations should be monitored.

The following MICs were determined for the *P. lilacinus* isolate: voriconazole, 0.12 μg/mL; itraconazole, 2 μg/mL; and amphotericin B, >8 μg/mL. Maintaining serum concentrations of voriconazole several-fold greater than the MIC would seem to have been critically important for this patient. Adjustment of the voriconazole dosage based on serum concentration might have improved his clinical response to voriconazole treatment; nevertheless, the patient survived the chronic *Paecilomyces* in-

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**Figure 1.** Lesion due to *Paecilomyces lilacinus* on the patient’s right ankle
fection while taking voriconazole, even though he did not have significant numbers of CD4 cells and lacked normal host defenses.

In our patient, the only adverse event attributed to voriconazole was an increase in hepatic enzyme levels. The elevations were mild—the aspartate transaminase level peaked at 183 U/L (normal range, 15–35 U/L) and the alanine transaminase level at 124 U/L (normal range, 11–35 U/L)—and resolved with a reduction of the dose of voriconazole and changes in other medications. The dosage of voriconazole was subsequently restored to 300 mg b.i.d. without resulting in an increase in hepatic enzyme levels. Throughout therapy, the alkaline phosphatase level was consistently elevated, with values ranging from 237 to 419 U/L (normal range, 11–35 U/L) and the alanine transaminase level was mild—the aspartate transaminase level peaked at 183 U/L (normal range, 30–90 U/L). The reason for this elevation is unknown. The patient was hospitalized 4 times during the voriconazole treatment period. The causes for these hospitalizations were (1) fatigue and anorexia attributed to ritonavir, (2) gastro-intestinal symptoms during the concomitant treatment with multiple drugs. Although voriconazole therapy did not resolve the Paecilomyces infection, it altered the course of the illness, resulting in partial resolution of many of the existing cutaneous lesions. The observation that, at times, the patient’s condition seemed to improve more rapidly suggests that treatment efficacy could be related to the level of voriconazole in the blood. After discontinuation of voriconazole therapy, the patient’s lesions worsened, demonstrating that voriconazole had a fungistatic rather than fungicidal effect on Paecilomyces infection in this patient. In addition, voriconazole serum concentrations varied widely during therapy. This variation indicates that monitoring of serum voriconazole levels would be helpful in managing patients at risk of potential drug-drug interactions with antiretroviral agents and other medications.

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