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Successful use of the novel antifungal olorofim in the treatment of disseminated coccioidomycosis

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Background: Infection due to *Coccidioides* spp. ranges from asymptomatic acquisition with resultant immunity, to severe, multifocal, life-threatening disease. There is a high failure rate with currently approved antifungals and new therapeutic options are needed. Olorofim, a novel antifungal, has potent anti-*Coccidioides* activity in a murine model of infection.

Materials/methods: An open-label Phase 2 study of olorofim in patients with Invasive Fungal Disease lacking alternative treatment options is ongoing.

Results: A 45 y/o African-American man with insulin-dependent diabetes mellitus developed disseminated coccidioidomycosis with severe lung disease and concurrent meningitis. He was treated with fluconazole 800 mg daily, however four weeks later exhibited continued progression of disease and changed to voriconazole 200 mg twice daily. His pulmonary disease continued to worsen and therapy changed to itraconazole 200 mg twice daily due to voriconazole intolerance.

The patient continued to deteriorate and therapy was changed to liposomal amphotericin B (L-AMB) (5 mg/kg/day) and posaconazole 300 mg daily (tablet). His serum *Coccidioides* complement fixation titer (CF) was 1:128. One month later he was significantly hypokalemic, L-AMB was stopped, and salvage posaconazole and micafungin 150 mg IV initiated. He continued to deteriorate, was unable to work, was dependent on supplementary oxygen, and required a walking frame.

Eight months after his initial infection therapy was changed to posaconazole 300 mg daily plus olorofim 120 mg twice daily. The patient noted rapid improvement of his cough and malaise within a week with resolution of all other symtpoms in this time frame.

After three months of posaconazole plus olorofim he returned to his normal activity level without use of oxygen or a walking frame. CSF examination showed complete normalization of his CSF indices and negative coccidioidomycosis serology from spinal fluid. The serum *Coccidioides* CF titer declined to 1:64. Repeat pulmonary CT scan showed improvement in multifocal infiltrates.

After 5 months of therapy he returned to work and the *Coccidioides* CF titer had declined to 1:32. He has tolerated all medications.

Conclusions: Adding olorofim to a failing regimen for severe, disseminated coccidioidomycosis resulted in significant clinical, serologic, and radiologic improvement. Olorofim should be further evaluated in coccidioidomycosis.

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