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Salvage treatment of histoplasmosis with posaconazole☆

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Summary Six patients received salvage treatment with posaconazole oral suspension (800 mg/day in divided doses) for severe forms of histoplasmosis. One patient had pulmonary disease and 5 had disseminated disease. Previous antifungal therapy consisted of amphotericin B, itraconazole, fluconazole, or voriconazole. Posaconazole treatment duration for individual patients ranged from 6 weeks to 34 weeks. All patients had successful clinical outcomes with significant clinical improvements noted during the first month of therapy. Although the number of patients evaluated in this case series is small, the findings are encouraging and provide preliminary evidence that posaconazole may be a useful salvage treatment option for histoplasmosis involving a variety of infected tissues and organs.

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Introduction

Histoplasmosis is an endemic mycosis caused by the dimorphic fungus *Histoplasma capsulatum*. *H. capsulatum* is ubiquitous in soils worldwide; its endemicity is high in localized areas of North and Latin America and low in Europe.[1,2] In the United States, histoplasmosis is the most common endemic mycotic infection as shown by the high proportion (>80%) of positive histoplasmin skin reactions occurring in healthy persons living in the Ohio, Mississippi, and St. Lawrence River valleys and in other highly endemic areas.[1,2] Histoplasmosis is a major opportunistic pathogen in patients infected with human immunodeficiency virus (HIV) who reside in endemic areas.[2,3] Additionally, it is a ''traveler's disease'', based on outbreaks in those who travel from nonendemic to endemic regions.[3,4] Most cases are acquired by inhalation of *H. capsulatum* microconidia (spores), after the soil they inhabit becomes disturbed by human activity.[5]

Clinical manifestations of disease following infection with *H. capsulatum* depend, in part, on fungal burden and host immune function. Children, the elderly, and immunocompromised individuals are at risk for severe pulmonary infection and/or progressive disseminated histoplasmosis, even after low-level exposure to the fungus.[6] Progressive disseminated histoplasmosis is manifested by lesions in numerous nonpulmonary sites, including the larynx,[7] bone/joints,[8,9] central nervous system,[10] skin,[11,12] cervical and thoracic spine,[13,14] liver,[15–17] colon,[18] oral mucosa,[19] adrenal glands,[20] spleen,[21] and cardiac valves, the latter presenting as endocarditis.[22]

Current treatment recommendations for severe acute or chronic pulmonary histoplasmosis and for disseminated disease include amphotericin B therapy followed by step-down maintenance therapy with itraconazole or fluconazole (on rare occasions if itraconazole is contraindicated).[6] Itraconazole is recommended as first-line therapy only for histoplasmosis of mild to moderate severity in patients who do not require hospitalization,[6] although it has been used successfully to treat children with disseminated histoplasmosis.[23] Despite documented effectiveness, the clinical usefulness of itraconazole and amphotericin B as recommended standard consolidation and maintenance therapies for histoplasmosis is limited by erratic absorption,[24] dose-limiting toxicity, drug–drug interactions, and poor long-term tolerability.[25] As such, a strong impetus exists for the development of novel antifungal agents with activity against histoplasmosis.

Posaconazole is an extended-spectrum triazole antifungal agent with excellent in vitro activity against clinical isolates of *H. capsulatum* (minimum fungicidal concentration [MFC] 0.5–2.0 μg/mL)[26,27] and activity in murine models of intratracheally induced histoplasmosis.[27,28] This paper describes the use of posaconazole oral suspension (800 mg/day, in divided doses) as salvage treatment in 6 patients with histoplasmosis.

Patients and methods

Six patients with proven histoplasmosis were identified from a large open-label, multicenter trial of posaconazole for the salvage treatment of patients with invasive fungal infections. Patients were eligible for salvage therapy if they were intolerant of standard therapy by virtue of organ toxicity (grade 3 or greater by Common Toxicity Criteria[29]) or nephrotoxicity (persistent serum creatinine >2 times the upper limit of normal [ULN] or recurrent serum creatinine >2 times the ULN following resumed amphotericin B therapy) or had refractory disease (disease progression, or failure to improve clinically, despite previous treatment with itraconazole, amphotericin B, or ketoconazole given for at least 30 days).

All patients were at least 13 years of age and were able to take oral medication. The classification of proven histoplasmosis was made based on the demonstration of: (1) *H. capsulatum* in cultures of infected tissues, sputum, or bronchial washing, (2) silver methenamine-stained biopsy sections showing appropriate morphological form of the fungus, or (3) presence of *H. capsulatum* antigen in blood and/or urine (in the United States only). Because the antigen test is not available in Latin America, diagnosis of histoplasmosis was made only by culture or by histopathologic demonstration of yeast-like organisms in the tissue of patients in that geographic region who had symptoms consistent with histoplasmosis. No patient was taking any concomitant systemic antifungal drug or any other agent known to interact with azoles.

Treatment

Patients received 800 mg/day of posaconazole oral suspension (40 mg/mL) in divided doses given as 200 mg 4 times daily while hospitalized, followed by 400 mg posaconazole twice daily after discharge. Doses were taken with food, when possible. The actual treatment duration was at the discretion of the physician investigator and was based on clinical diagnosis, severity of infection and underlying illness, degree of recovery from immunosuppression, and rapidity of clinical response. Treatment was initiated between years 1999 and 2001.

Outcome measures, evaluation, and definitions

Clinical responses were evaluated at week 2, week 4, monthly, and at the end of treatment. A 30-day post-therapy follow-up evaluation was performed, when possible. The primary efficacy end point was clinical response to posaconazole at the end of treatment. A complete response was resolution of all attributable symptoms, signs, and radiographic or bronchoscopic abnormalities. A partial response was clinically meaningful improvement in attributable symptoms, signs, and radiographic or bronchoscopic abnormalities. Stable disease was defined as no major improvement in attributable symptoms, signs, and radiographic or bronchoscopic abnormalities. Failure was defined as deterioration in attributable clinical or radiographic abnormalities. Complete or partial responses were considered successes; stable disease and failure were considered nonsuccesses.

Safety analysis

Adverse events were recorded and categorized using the National Institute of Allergy and Infectious Diseases AIDS