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CLINICAL THERAPEUTICS

# Isavuconazole in the Treatment of Coccidioidal Meningitis

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**ABSTRACT** Patients with coccidioidal meningitis require lifelong antifungal therapy. Cumulative toxicity and lack of antifungal efficacy require salvage therapy in the treatment of some patients. In a retrospective review of nine patients with coccidioidal meningitis treated with isavuconazole, successful therapy was seen in three patients and stable disease was confirmed in six patients. Isavuconazole may be a useful addition to the therapeutic choices currently available for coccidioidal meningitis.

**KEYWORDS** coccidioides, isavuconazole, meningitis

*Coccidioides immitis* and *posadasii* are dimorphic fungi endemic to the southwestern United States (1). The spectrum of disease ranges from asymptomatic acquisition with resultant immunity to severe and life-threatening disseminated infection. Disseminated infection is uncommon, occurring in only 1% to 3% of infected individuals, and is more frequent in immunocompromised individuals, women during the third trimester of pregnancy or the immediate postpartum period, or individuals of Filipino or African ancestry. Dissemination may occur to any site, although the skin, musculoskeletal system, and central nervous system (CNS) are the most frequently encountered sites (2).

CNS involvement that causes meningitis is the most serious complication and carries significant morbidity and mortality (3). Current guidelines recommend high-dose fluconazole or itraconazole in the treatment of coccidioidal meningitis (1). Limited data are available describing the efficacy of other triazoles, including voriconazole and posaconazole (4, 5). Despite the availability of these agents and the utility of polyenes or combination therapy in select cases requiring salvage therapy (6, 7), toxicity and/or lack of efficacy requires investigation of alternative agents.

Isavuconazole is a novel triazole with a broad spectrum of antifungal activity. Administered as a water-soluble prodrug, i.e., isavuconazonium sulfate, it undergoes cleavage by plasma esterases to the active moiety isavuconazole (8). Clinical trials demonstrated efficacy in the treatment of invasive aspergillosis (9), candidiasis (10), and mucormycosis (11) and in the treatment of endemic mycoses without evidence of CNS involvement (12). However, efficacy in the treatment of coccidioidal meningitis has not previously been described.

Patients with coccidioidal meningitis who received isavuconazole were identified by review of the ICD-9 and ICD-10 codes cross-referenced with pharmacy databases. Abstracted data included demographic and clinical information; results of laboratory and radiographic studies; microbiologic, pathologic, and serologic results; outcomes;

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**TABLE 1** Clinical characteristics, treatment, and outcomes of patients with coccidioidal meningitis treated with isavuconazole

| Patient by age (yr), sex, ethnicity, underlying condition | Prior antifungal[a] (days) | Reason for ISAV[b] treatment | Response to ISAV and change in MSG[c] score at 3 mo | Clinician assessment at 3 mo | Outcome, duration of ISAV therapy (days) |
|---|---|---|---|---|---|
| 46, M, African American, none | FLU (734)→POS (2,920)→VOR (607) | FLU, failure; POS, nausea/vomiting; VOR, photopsia, headache confusion | Success (7→3) | Success | Alive, no relapses (621) |
| 49, F, Caucasian, none | FLU (2,079)→VOR (1,455) | VOR, failure | Success (2→0) | Success | Alive, no relapses (441) |
| 44, M, Hispanic, none | FLU (549) | FLU, failure | Success (7→5) | Success | Alive, no relapses (518) |
| 33, M, Hispanic, none | FLU (3,205)→VOR (1,694) | VOR, photodermatitis | Stable (1→1) | Success | Alive, no relapses (637) |
| 55, M, Indian, none | FLU (811)→VOR (148) | VOR, dyspepsia | Stable (8→7) | Success | Alive, no relapses[d] (138) |
| 51, M, Hispanic, none | FLU (560)→VOR (1,560) | VOR, xerosis, photodermatitis | Stable (4→4) | Stable | Alive, no relapses (708) |
| 41, M, Hispanic, none | FLU (915)→VOR (3,071) | VOR, photodermatitis | Stable (0→0) | Stable | Alive, no relapses (274) |
| 43, M, Hispanic, none | FLU (361)→VOR (3,319) | VOR, squamous cell carcinoma | Stable (0→0) | Stable | Alive, no relapses (385) |
| 59, M, Caucasian, none | FLU (1,252)→VOR (410)→FLU (941) | FLU, failure; VOR, hepatic injury; FLU, nausea/vomiting | Stable (10→8) | Stable | Alive, no relapses (810) |

[a]FLU, fluconazole; VOR, voriconazole.
[b]ISAV, isavuconazole.
[c]MSG, Mycoses Study Group scoring system (13).
[d]ISAV discontinued because of worsening dyspepsia and transitioned back to voriconazole.

and prior treatment regimens. Responses to therapy were measured with a previously validated scoring system used in clinical trials of coccidioidal meningitis (13). This scoring system combines clinical, radiographic, and cerebrospinal fluid (CSF) data to evaluate a therapeutic response, defined as a ≥40% reduction in abnormalities. Each patient was assigned a composite score at the time of isavuconazole initiation and after 3 months of therapy. The treating clinician's assessment was also abstracted from patient medical records, and defined as success, stable, or failure.

Nine patients met criteria for inclusion (Table 1). The median patient age was 46 years, and eight of the patients were male. No comorbidities were present in this patient cohort. All patients were initiated on fluconazole as primary therapy for coccidioidal meningitis, and eight were transitioned to voriconazole, although the reasons for this change were not always identifiable on chart review. Treatment failure was found in only one patient treated with voriconazole. All other patients were transitioned from voriconazole to isavuconazole secondary to adverse effects, including photodermatitis ($n = 3$), photopsia ($n = 1$), squamous cell carcinoma ($n = 1$), dyspepsia ($n = 1$), and hepatic injury ($n = 1$).

Patient outcomes assessed with Mycosis Study Group (MSG) scoring criteria showed successful therapy in three of nine patients and stable disease in six patients. Mean time on isavuconazole therapy at last assessment was 504 days (range, 274 to 810 days) per patient. The abstracting treating clinician assessment revealed success in five of nine patients and stable disease in four patients. Discrepancies between the assessment by the treating clinician and MSG scores were seen in two patients. These differences in patient assessments were secondary to MSG criteria requiring a decrease in CSF protein to <100 mg/dL for a change in point assignment, whereas patient 4 had a decline in CSF protein from 599 to only 469 mg/dL. The second discrepant patient had a significant improvement in CSF glucose level (from 22 to 45 mg/dL) with only a moderate change in CSF white blood cell count (from 470 to 450 cells/mm$^3$; protein values, from 2,325 to 2,006 mg/dL). No isavuconazole clinical failures were identified in this retrospective evaluation, although one patient was transitioned back to voriconazole because of worsening dyspepsia after a change to isavuconazole.

Morbidity and mortality associated with coccidioidal meningitis remain unacceptably high, and, in an attempt to prevent relapse(s), patients are maintained on lifelong antifungal therapy (14). The commitment to lifelong therapy subjects patients to cumulative toxicity, ranging from benign but irritating (e.g., xerosis, cheilitis, alopecia) (15) to more serious (e.g., fluorosis, cutaneous malignancy) (16–18) manifestations. These adverse reactions may require the use of alternative agents in attempts to improve patient compliance and tolerability.

Furthermore, despite medication compliance, relapse/breakthrough may occur (19, 20). The reasons for relapse remain unclear, and a data-driven approach to management decisions for these patients has not been presented. In cases of breakthrough fungal infection, a change in class or a change of agent is typically recommended, pending further investigation (e.g., assessment of compliance, determination of possible resistance) (21).

Cumulative toxicity and/or drug efficacy failure have necessitated the evaluation of newer antifungals. Isavuconazole is an attractive new triazole for coccidioidomycosis because of the availability of both oral and intravenous formulations, a favorable side-effect profile when directly compared with voriconazole in the treatment of invasive aspergillosis (9), and low isavuconazole MICs when evaluated against *Coccidioides* isolates (8, 12, 22). However, few patients with coccidioidomycosis have been treated with isavuconazole, and data have been limited to primary pulmonary infections, none with dissemination or severe manifestations of disease (12).

Despite the lack of demonstrated clinical efficacy in cases of disseminated or meningeal coccidioidomycosis, animal models of other mycoses have demonstrated the potential efficacy of isavuconazole in CNS infections (23), and early experience in human cryptococcal meningitis cases has been favorable (12). The current study establishes precedence for use in coccidioidomycosis meningitis cases with a history of treatment failure or adverse reactions to front-line antifungals.

We observed successful or stable disease in all patients included in this study, although the retrospective nature, limited duration of follow-up, and number of patients studied limit implications for wide-scale adoption. Evaluation of isavuconazole in the treatment of coccidioidomycosis would benefit from use of animal models and prospective clinical trials. The response rates observed were favorable, and isavuconazole may be a useful agent in the salvage setting for this morbid disease.

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