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Voriconazole Use for Endemic Fungal Infections▽

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In a retrospective review of 24 patients with histoplasmosis, blastomycosis, or coccidioidomycosis treated with voriconazole (most for salvage therapy), the outcome was favorable (improved or stable) for 22 (95.8%) within 2 months of starting voriconazole and for 20 (83.3%) at the last follow-up. Prospective studies are required to determine its role in the treatment of endemic mycoses.

Endemic fungal infections in the United States due to *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis* are generally treated with amphotericin B formulations, itraconazole, or fluconazole (6, 9, 27). Each of these standard antifungals has limitations that preclude its use by some patients. Renal and infusional toxicities associated with amphotericin B formulations and gastrointestinal absorption and intolerance difficulties with oral itraconazole are the most notable. Voriconazole is a well-tolerated, orally bioavailable newer triazole antifungal with a broad range of activity against a variety of yeasts and molds (22). Although primarily indicated for the treatment of *Aspergillus* infections, voriconazole is also active in vitro against *H. capsulatum*, *B. dermatitidis*, and *Coccidioides* species (10, 13, 20, 26). However, except for a few case reports, clinical studies evaluating voriconazole for the treatment of endemic mycoses in humans have not been performed.

We undertook a retrospective chart review of 24 patients with endemic fungal infections who were treated with voriconazole between 1 January 2001 and 30 May 2005 at eight tertiary care centers. Five of the cases were previously reported (8, 12, 19). The study was approved by the institutional review committee at each institution.

Fifteen of the 24 patients were male, and the mean age was 45 years. Nine were solid organ transplant recipients, one was an allogeneic stem cell transplant recipient, six had other chronic diseases, and eight had no underlying disease (Table 1). Diagnostic criteria were modifications of previously published definitions of fungal infection in immunocompromised hosts (3, 17). The diagnosis of endemic fungal infection was considered "proven" for 18 patients based upon positive cultures or characteristic histopathologic features and "probable" for 6 patients, 2 with histoplasmosis based upon positive blood and urine *Histoplasma* antigen tests in the setting of pulmonary nodules and 4 with coccidioidomycosis based upon *Coccidioides*-positive serologic tests of cerebrospinal fluid and/or serum in the setting of compatible symptoms. Localized pulmonary infection occurred in 6 patients, and disseminated disease occurred in 18, defined by clinical or laboratory findings (including a positive serum antigen test) of extrapulmonary involvement. Central nervous system (CNS) involvement was diagnosed in seven patients, based on neuroimaging studies and/or positive spinal fluid serology.

Voriconazole was given as primary therapy to two patients (no. 8 in conjunction with amphotericin B), to three following the failure of another antifungal agent, to 16 due to toxicity or intolerance of prior antifungals, and to 3 according to the attending physician's clinical decision. Voriconazole was given for a median of 236 days (range, 22 to 1,797 days). Responses to voriconazole, within 2 months of initiation, were characterized as favorable if there was clinical improvement (decreasing signs and symptoms of infection) or stable disease (no change in stable clinical status with some persistent signs and symptoms). Table 1 shows the cases and responses to voriconazole according to the underlying endemic fungal infections. Overall, the outcome was favorable (improved or stable) in 22 cases (95.8%) within 2 months of starting voriconazole and in 20 (83.3%) at the last follow-up. Reasons for subsequently stopping voriconazole for 19 patients included completion of treatment for 12 (range, 31 to 640 days), death for 2, high drug cost for 2, and hepatotoxicity and low drug levels for 1 each (both judged important by the reporting physician), and clinical failure, defined as worsening signs and symptoms after at least 4 weeks of other antifungal therapy, for 1. Five patients remained on long-term chronic voriconazole suppression. No information regarding the safety or tolerability of voriconazole was systematically collected in this study, which is a significant limitation. However, in 2 of the 24 cases, liver function test (LFT) elevations were noted during voriconazole treatment, although specific values were not provided by reporting clinicians. In one of these cases, the decision was made to switch from voriconazole to fluconazole. Thus, in the absence of concrete data from this study, no definitive comment can be made about the safety or tolerability of voriconazole in the treatment of endemic fungal infections, but this issue should be addressed in a prospective study.

In vitro, voriconazole may be as active as, or perhaps slightly

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TABLE 1. Characteristics, treatments, and outcomes of the patients described in this report[a]

Disease and case no. (reference)	Age (yr), sex, underlying condition	Classification based on diagnostic criteria	Prior antifungal treatment (no. of days)	Reason for Vori treatment	Response to Vori within first 2 mo	Reason Vori stopped (total no. of days given)	Survival (total no. of days from diagnosis)
Histoplasmosis							
1 (8)	18, F, kidney Tx	Disseminated proven	Itra, Flu (44)	Failure (increasing antigenuria)	Improved	Completed therapy (315)	Alive (478)
2 (8)	54, F, liver Tx	Disseminated probable (positive for blood and urine antigen, pulmonary lesions)	AmB, Itra (25)	Intolerance (gastrointestinal with Itra)	Stable	Completed therapy (293)	Alive (322)
3 (8)	52, F, kidney Tx	Disseminated proven	AmB (1)	Intolerance (chills with AmB)	Stable	Cost (22)	Alive (360)
4	15, F, kidney Tx	Disseminated probable (positive for blood and urine antigen, pulmonary lesions)	Itra (459)	Intolerance (noncompliance)	Improved	Completed therapy (559)	Alive (1,104)
5	59, M, SLE, RA on inflixamab	Disseminated proven	Flu, L-AmB, Itra (28)	Clinician decision (low serum Itra level)	Stable (but persistent antigenuria despite clinical stability)	Persistent antigenuria, switched to Itra solution (151)	Alive (561)
6	41, M, kidney Tx	Disseminated proven	Itra (30)	Intolerance (gastrointestinal with Itra)	Stable	Cost (243)	Alive (535)
7	22, F, none	Pulmonary proven	Itra, L-AmB (91)	Failure (persistent signs and symptoms on Itra), toxicity (nephrotoxicity with L-AmB)	Stable	Completed therapy (31)	Alive (150)
8	71, M, renal failure	Disseminated CNS proven		Primary (combined with AmB for 6 wk)	Improved	Completed therapy (640)	Alive (697)
9	37, F, MS	Pulmonary proven	Itra (123)	Toxicity (alopecia and fatigue with Itra)	Stable	Completed therapy (91)	Alive (578)
Blastomycosis							
10	61, M, heart Tx	Pulmonary proven	ABLC, AmB (4)	Toxicity (nephrotoxicity with AmB)	Stable	Completed therapy (234)	Alive (243)
11	42, M, kidney Tx	Disseminated proven	ABLC (1)	Toxicity (nephrotoxicity with ABLC)	Stable	Clinician decision to switch back to Itra (45)	Alive (413)
12	54, M, liver Tx	Pulmonary proven	L-AmB, Flu, Caspo, ABLC, Itra (104)	Clinician decision: low serum Itra level)	Improved	Completed therapy, relapsed 90 days after stopping Vori (234)	Death unrelated to mycosis (486)
13	59, M, none	Disseminated proven	ABLC, Itra (138)	Intolerance (gastrointestinal with Itra)	Stable	Continued Vori chronic suppressive therapy (238)	Alive (376)
14	68, M, kidney Tx	Pulmonary proven		Primary	Improved	Completed therapy (147), relapsed 36 days after stopping Vori (147)	Death related to mycosis (budding yeast compatible with blastomycosis in lung at autopsy) (183)
15 (12)	44, M, none	Disseminated CNS proven	AmB(12)	Toxicity (ototoxicity with AmB)	Stable	Completed therapy (179)	Alive (317)
16	39, F, none	Disseminated proven	L-AmB (29)	Toxicity (nephrotoxicity with L-AmB)	Stable	Completed therapy (366)	Alive (426)
17	31, M, malignant thymoma on chemotherapy	Disseminated meningitis proven	L-AmB (40)	Toxicity (nephrotoxicity with L-AmB)	Improved	Death (84)	Death unrelated to mycosis (124)
Coccidioidomycosis							
18	46, M, allergic aspergillosis on prednisone	Disseminated meningitis probable (positive CSF serology)	Itra, Flu (532)	Failure (worsening CNS symptoms on high-dose Flu)	Improved	Toxicity (elevated LFTs) (53)	Death related to mycosis (293)
19	35, F, anorexia nervosa	Disseminated probable (positive serum serology)	Flu (Unk)	Intolerance (gastrointestinal, rash)	Stable	Continued Vori, chronic suppressive therapy (553)	Alive (602)
20	66, F, bone marrow Tx	Pulmonary proven	L-AmB (48)	Toxicity (nephrotoxicity with L-AmB)	Stable	Continued Vori, chronic suppressive therapy (649)	Alive (712)
21	67, M, none	Disseminated meningitis probable (positive CSF serology)	Flu (395)	Failure (progressive CNS symptoms on high-dose Flu)	Improved	Completed therapy (355)	Alive (753)
22	32, M, diabetes	Disseminated meningitis proven	Flu (14)	Toxicity (elevated LFTs with Flu)	Failure (also received AmB intracisternally)	Death (22)	Death related to mycosis (33)
23	44, M, none	Disseminated proven	Flu, AmB, ABLC (40)	Clinician decision	Stable	Continued Vori (1,120), chronic suppressive therapy	Alive (1,711)
24 (19)	30, M, none	Disseminated meningitis probable (positive CSF and serum serology)	Flu, AmB, ABLC, Flu, L-AmB + Flu, intrathecal AmB (588)	Toxicity (tinnitus, diplopia, headache, nausea with intrathecal AmB)	Improved	Continued Vori, chronic suppressive therapy (1,797)	Alive (2,163)

[a] Abbreviations: M, male; F, female; Caspo, caspofungin; Vori, voriconazole; Tx, transplant; Itra, itraconazole; L-AmB, liposomal amphotericin B; ABLC, amphotericin B lipid complex; MS, multiple sclerosis; AmB, amphotericin B-desoxycholate; SLE, systemic lupus erythematosus; Flu, fluconazole; RA, rheumatoid arthritis.

less active than, itraconazole or posaconazole against *H. capsulatum* (10, 15, 26), but the in vivo correlation of this observation is unknown. Voriconazole has not been studied in animal models of histoplasmosis. The in vitro inhibitory effects of the drug on *H. capsulatum* and its high bioavailability suggest its utility for treating clinical histoplasmosis. As shown in Table 1, all of the nine patients with histoplasmosis treated with voriconazole either primarily (no. 8, plus amphotericin B) or due to failure or intolerance of other antifungals (no. 1 to 7 and 9) either improved or remained clinically stable following initiation of voriconazole. One patient who improved clinically on voriconazole was later switched back to itraconazole when his *Histoplasma* antigenuria failed to decline. A number of others have reported successful treatment of histoplasmosis (1, 11, 23–25) with voriconazole, although failure has also been reported, with subsequent response to posaconazole (21). Cross-resistance between fluconazole and voriconazole has been described in *H. capsulatum* isolates from patients infected with human immunodeficiency virus (26).

Voriconazole is also active in vitro against *B. dermatitidis*, exhibiting a susceptibility pattern similar to that of itraconazole (16). It has not been studied in an animal model of blastomycosis. Among the eight patients with blastomycosis in this series, all either improved or remained stable after starting voriconazole, although two relapsed after stopping long courses of the drug. One renal transplant patient (no. 14) who received voriconazole as initial therapy for pulmonary blastomycosis improved clinically and completed a 4-month course of therapy but relapsed 36 days after stopping therapy and died shortly thereafter, with pulmonary blastomycosis identified at autopsy. Another immunosuppressed patient (no. 12, with a liver transplant) responded to voriconazole rapidly after multiple antifungals failed to control his recurrent pulmonary blastomycosis. After achieving 10 months of stable disease on voriconazole, he died as a consequence of sepsis and multiorgan failure with evidence of recurrent blastomycosis in the lungs. This case illustrates the critical importance of host immunologic competence in containing and eradicating endemic fungal infections. An antifungal agent cannot alone cure deep invasive mycoses without some level of host immune defense. Two other patients with CNS blastomycosis (no. 15 with no underlying disease, no. 17 with cancer) were switched to voriconazole after developing intolerance to amphotericin products (after 12 and 40 days, respectively), and both responded favorably. Others have reported successful voriconazole treatment of patients with CNS blastomycosis failing other azoles (4, 5, 12, 16). Good penetration of the brain and cerebrospinal fluid by voriconazole has been documented in animals and immunocompromised patients (14). It should be emphasized, however, that Infectious Diseases Society of America guidelines strongly advocate amphotericin B or its lipid formulations as the initial treatment for CNS blastomycosis, as well as for CNS histoplasmosis; azoles should be reserved for salvage therapy, as in the cases reported herein (6, 27).

Voriconazole is active in vitro against *Coccidioides* spp. exhibiting susceptibility patterns comparable to those of *B. dermatitidis* and *H. capsulatum* (13). Furthermore, in vitro susceptibility to voriconazole was somewhat better than to itraconazole. Voriconazole has not been studied in an animal model of coccidioidomycosis, but it has been used successfully in a few patients (2, 18, 19).

In this report, six of the seven patients with coccidioidomycosis who were treated with voriconazole, after other antifungal toxicity/intolerance or for physician preference, responded to the drug favorably. Three of the four patients with *C. immitis* meningitis unresponsive to a variety of other antifungals improved after switching to voriconazole. One patient (no. 18) with meningitis initially improved on voriconazole but died of recurrent disease when switched back to long-term fluconazole (which had previously failed to contain his infection). There are a few other case reports of successful treatment of coccidioidomycosis with voriconazole (2, 7, 18), including meningitis (7).

Combining all of the results from this limited case series, there is evidence that patients with endemic fungal infections who received voriconazole for toxicity, intolerance, or failure of other antifungals are likely to remain stable or be improved clinically after starting the drug. Only 1 of the 24 patients reported here died of the endemic fungal infection while receiving voriconazole, although two relapses of blastomycosis (one fatal) occurred within 1 to 3 months after stopping long courses of the drug. It is notable that the duration of voriconazole therapy varied significantly according to the underlying disease, the location of the infection, and the degree of immunocompromise. These management variations highlight the gaps in knowledge about treating endemic fungal infections. Several caveats should be considered in applying the findings of this report to the management of patients with endemic mycoses. First, assessment of effectiveness and tolerability is difficult in a retrospective review, and the accuracy of retrospective observations is not verifiable. The lack of tolerability data in this report is, in part, due to this constraint. Second, the follow-up period was short, less than 1 year in many of the patients. Third, the number of patients receiving voriconazole for initial treatment or "salvage" treatment after failure of another agent was small. Fourth, adherence and drug exposure were not evaluated. Fifth, effectiveness cannot be adequately assessed in patients who received voriconazole because of intolerance or toxicity of other agents. Recognizing the limitations, our findings still suggest that voriconazole can be useful in some patients with endemic mycoses, particularly those who have demonstrated intolerance to other antifungal agents. However, prospective studies are needed to fully assess the utility of voriconazole in this setting.

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