Refractory Coccidioidomycosis Treated with Posaconazole

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Background. Disseminated coccidioidomycosis (which is caused by the endemic fungi of the genus Coccidioides) can be a life-threatening systemic fungal infection. Although conventional antifungal therapies have activity against Coccidioides, the disease can be refractory to standard therapies. Drug-associated toxicities also may limit the clinical utility of the standard antifungal drugs. In addition, relapses in patients with disseminated coccidioidomycosis are common, making long-term management of this disease challenging.

Methods. We report the outcomes of 6 patients with coccidioidomycosis who were treated with posaconazole salvage therapy after treatment with conventional antifungal therapies failed to produce sustained clinical improvement. Patients were administered posaconazole oral suspension 800 mg/day in divided doses as part of an open-label clinical trial. A modified version of the Mycoses Study Group Coccidioides scoring system was used to evaluate the burden of disease. Posaconazole therapy resulted in rapid clinical improvements in the signs and symptoms of coccidioidomycosis.

Results. At the end of therapy, 5 of 6 patients had successful outcomes. Posaconazole was well tolerated despite long-term administration (1–2 years), and 2 patients continued to receive posaconazole maintenance therapy at the time of writing.

Conclusions. The successful outcomes observed in this case series suggest that posaconazole is an effective therapy for coccidioidomycosis.

Coccidioidomycosis is a systemic fungal infection caused by inhalation of arthroconidia from fungi of the genus Coccidioides. (The genus Coccidioides has recently been subdivided on the basis of genomic analyses into Coccidioides immitis, comprised of isolates from California, and Coccidioides posadasii, comprised of isolates from outside of California. There is no apparent difference in the diseases produced by these 2 species [1].) Despite the use of amphotericin B, fluconazole, and itraconazole therapy, disseminated coccidioidomycosis remains difficult to treat, and treatment is often characterized by frequent failure and relapse [2–4].

Posaconazole is an investigational, extended-spectrum triazole that has shown promising activity against Coccidioides in vitro [5], in animal models of coccidioidomycosis [6], and in an early clinical study [7]. Results of the clinical study, which was limited to 6 months of therapy for 20 patients, were presented at an international meeting but have not yet been published in full. However, of the 15 patients who completed ≥23 weeks of posaconazole therapy, median standardized disease severity scores (based on the Mycoses Study Group scoring system [4]) were reduced to 40% of baseline scores at 16 weeks and to 22% of baseline scores at 24 weeks [7]. This response rate suggests to us that posaconazole may be an effective therapy for use in patients who do not benefit from treatment with other drugs. On the basis of this observation, we used posaconazole to treat 6 patients with disseminated disease who previously had not benefited from treatment with traditional antifungal therapies [8].

PATIENTS AND METHODS

Six patients were admitted to the University Hospital in San Antonio, Texas, with culture-documented coccidioidomycosis. All patients had disease refractory to conventional antifungal therapies. Oral therapy was
initiated with posaconazole (200 mg t.i.d. or 400 mg b.i.d. for up to 394 days) in an open-label clinical trial. Patients who required additional treatment could extend posaconazole therapy as part of a treatment-extension use protocol. To evaluate the burden of disease, we used the Coccidioides scoring system from the Mycoses Study Group [4]. Because of the limitations of this scoring system, we also used a modified version of the scoring system that gives a more accurate assessment of response to antifungal treatment (see Discussion). In accordance with the Declaration of Helsinki, written informed consent from patients and approval by the institutional review board at the University of Texas Health Science Center at San Antonio were obtained before initiation of any study-related activities.

Patient demographic characteristics and disease history are presented in table 1. All patients had at least 1 risk factor for dissemination of C. posadasii. Past medical histories of 3 patients (patients 2, 3, and 6) provided evidence of compromised immune function; the other 3 patients were apparently immunocompetent. Patients 1–5 were HIV negative, whereas patient 6 had AIDS. Before posaconazole therapy was initiated, all patients were treated with appropriate antifungal drugs for coccidioidomycosis. All had progressing disease despite previous receipt of ≥40 days of therapy (table 2).

**CASE REPORTS**

**Case 1.** A 20-year-old African American male airman stationed in Las Vegas, Nevada, with no significant past medical history sought treatment for fever, night sweats, myalgias, cough, and multiple skin lesions on his nose, cheek, and jaw. Biopsy specimens of the skin lesions grew C. posadasii. Fluconazole (800 mg) was given once daily. One month later, the dose was reduced to 400 mg/day because of nausea and elevated transaminase concentrations.

After initial clinical improvement that occurred over 7 months, the patient experienced relapse with a new sternal mass, left knee pain, and a small nodule in the right upper lobe of the lung; bronchoalveolar lavage fluid was positive for C. posadasii. After another 2 months of fluconazole treatment, the skin and bony lesions persisted, and bilateral choroidal lesions developed. Treatment was changed to amphotericin B (0.7 mg/kg per day). During amphotericin B treatment given for 28 days, cultures of specimens collected from 4 different cutaneous and bony sites had positive results. Itraconazole was added to the treatment regimen. Because of renal failure, amphotericin B was changed to amphotericin B lipid complex injection (5 mg/kg daily). After a 1-month course of amphotericin B lipid complex injections, results of culture of a biopsy specimen obtained from the distal femur of the left leg were positive.

Congestive heart failure attributed to amphotericin B use then developed [9]. During month 13, the congestive heart failure worsened. A transthoracic echocardiogram showed an ejection fraction of 10%–15%. With continued deterioration of cardiac function and the lack of a microbiologic response, the treatment regimen was changed to posaconazole after a total of 422 days of antifungal therapy.

After 2 weeks of posaconazole therapy, fever, chills, night sweats, and myalgia resolved, and the patient began to gain weight. After 6 weeks of posaconazole therapy, a second transthoracic echocardiogram showed resolution of the congestive heart failure; the ejection fraction improved to 50%–55%, and the size of all 4 heart chambers normalized. Left knee pain improved, and the knee effusion and sternal mass resolved after 2 months of posaconazole therapy. Skin lesions showed continual improvement throughout 62 days of surveillance on posaconazole. The patient was subsequently discharged from the military and was lost to follow-up. This case is described in more detail in the article by Danaher et al. [9].

**Case 2.** A 21-year-old Hispanic woman from Laredo, Texas, with a 3-year history of chronic cough, hemoptysis, and pleuritic chest pain sought treatment at the University Hospital.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, sex</th>
<th>Ethnicity</th>
<th>Risk factor(s)</th>
<th>Underlying disease(s)</th>
<th>Site(s) of infection</th>
<th>Infection duration before receiving posaconazole, months*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20, M</td>
<td>Black</td>
<td>Ethnicity</td>
<td>None</td>
<td>Skin, bone, lung</td>
<td>~13</td>
</tr>
<tr>
<td>2</td>
<td>21, F</td>
<td>Hispanic</td>
<td>Immunosuppressed</td>
<td>Bronchiectasis</td>
<td>Lung</td>
<td>~35</td>
</tr>
<tr>
<td>3</td>
<td>56, M</td>
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<td>Lung</td>
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<tr>
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</tr>
<tr>
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<td>24, F</td>
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<td>Ethnicity, pregnancy</td>
<td>None</td>
<td>Lung, skin</td>
<td>~1</td>
</tr>
<tr>
<td>6</td>
<td>28, M</td>
<td>Hispanic</td>
<td>Immunosuppressed</td>
<td>HIV and Mycobacterium avium complex infection</td>
<td>Lung</td>
<td>2</td>
</tr>
</tbody>
</table>

* Duration includes relapses and remissions.
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Table 2. Summary of clinical findings for 6 patients at the University Hospital (San Antonio, TX) who received posaconazole for treatment of coccidioidomycosis.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Previous antifungal therapy</th>
<th>Posaconazole therapy</th>
<th>NIAID MSG scorea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Duration, days</td>
<td>Dosage</td>
<td>Reason used</td>
</tr>
<tr>
<td>1</td>
<td>Flu</td>
<td>322</td>
<td>400–800 mg/day</td>
</tr>
<tr>
<td></td>
<td>AmB</td>
<td>28</td>
<td>0.7 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Itzb</td>
<td>63</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>2</td>
<td>AmB-LC</td>
<td>58</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Itz</td>
<td>212</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>3</td>
<td>Flu</td>
<td>26</td>
<td>100 mg/day</td>
</tr>
<tr>
<td>4</td>
<td>L-AmB</td>
<td>14</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td></td>
<td>L-AmB</td>
<td>40</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td>5</td>
<td>AmB</td>
<td>6</td>
<td>1 mg/kg</td>
</tr>
<tr>
<td></td>
<td>L-AmBb</td>
<td>29</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Itz</td>
<td>11</td>
<td>200 mg/day iv</td>
</tr>
<tr>
<td>6</td>
<td>AmB</td>
<td>14</td>
<td>0.7 mg/kg</td>
</tr>
</tbody>
</table>

NOTE. AmB, amphotericin B; AmB-LC, amphotericin B lipid complex; CHF, congestive heart failure; Flu, fluconazole; Itz, itraconazole; L-AmB, liposomal amphotericin B.

Data were calculated using the National Institute of Allergy and Infectious Diseases Mycoses Study Group (NIAID MSG) coccidioidomycosis point score system before and after treatment and with and without modifications [4].

In these patients, there was a period of combination therapy with itraconazole and amphotericin B or its lipid preparations.

Patient was noncompliant with posaconazole therapy for ~1 month (days 42–72).

After cessation of posaconazole therapy, therapy with voriconazole plus IFN-γ, combination therapy with voriconazole plus caspofungin, and high-dose (1600 mg/day) fluconazole all failed.

She had previously received treatment for tuberculosis and concomitant empirical treatment with itraconazole (200 mg po b.i.d.) for probable coccidioidomycosis for 8 months. Her symptoms persisted, and CT of the chest revealed a large cavitary lesion in the left upper lobe of the lung and a small lesion in the left lower lobe. The Coccidioides IgG titer was 1:2. The patient underwent left upper lobe resection, and histopathologic examination of the resected tissue showed noncaseating granulomas, eosinophilic pneumonitis, and tissue hyphae suggestive of Aspergillus infection. Culture of this tissue subsequently grew C. posadasii. (In retrospect, the hyphae thought to be Aspergillus organisms were probably the tissue hyphae form of Coccidioides organisms [10].) The patient resumed itraconazole treatment, but after 1 month, she returned to the hospital with persistent wheezing, cough, and pleuritic chest pain. A bioassay [11] revealed a serum itraconazole level of 7.4 μg/mL. Because her symptoms had persisted despite having appropriate serum levels of itraconazole, posaconazole therapy was started. During 1 year of posaconazole treatment, her pulmonary symptoms and lower lobe lesion resolved, and results of Coccidioides serologic tests became negative.

A total of 4.5 years after discontinuing posaconazole therapy, the patient presented with a productive cough, pleuritic chest pain, and intermittent hemoptysis. CT of the chest showed a thin-walled cavity measuring 2 cm in diameter, which contained a 1-cm mural nodule suggestive of a mycetoma. A Coccidioides IgG complement fixation antibody titer measured by EIA was 1:8 (a titer ≥ 1:2 is considered to be evidence of active disease).
The patient received 1 week of itraconazole therapy (200 mg po b.i.d.) and then restarted posaconazole treatment. After receiving posaconazole for 16 weeks, cough, hemoptysis, and pleuritic pain resolved, and the Coccidioides titer decreased to 1:4. At the time of writing, she continued to receive posaconazole therapy without adverse effects, 6 months after having restarted treatment.

**Case 3.** A 56-year-old Hispanic man had a history of systemic lupus erythematosus, mixed connective tissue disease, and glomerulonephritis causing renal failure. He had been treated with steroids and cyclophosphamide. During a 1-month period of hospitalization for pneumonia, *C. posadasii* was cultured from a lung biopsy specimen. The patient began therapy with oral fluconazole (100 mg daily; creatinine clearance, 11–14 mL/min). Because no response to therapy was seen, treatment was switched to liposomal amphotericin B (L-AmB) (5 mg/kg daily), but his condition did not improve significantly. Treatment with L-AmB was later discontinued, and posaconazole therapy was started. During the first month of posaconazole therapy, the patient became afebrile. Posaconazole therapy was continued for a total of 11 months, during which time progressive improvement was noted on chest radiography. The patient gained 22.8 kg, and his functional status greatly improved. During a routine visit (on day 191 of posaconazole therapy), electrocardiography demonstrated a prolonged corrected QT (QTC) interval. This prolongation of the QTC interval exceeded the safety guidelines of the protocol, and posaconazole was discontinued for 1 week. Additional examination of the patient’s medical history revealed a history of borderline QTc prolongation, and posaconazole treatment was reinitiated. On day 342 of posaconazole therapy, the patient died of peritonitis, presumably from rupture of an intra-abdominal abscess infected with *C. posadasii*. Before her death, *C. posadasii* was isolated from specimens obtained from respiratory secretions and multiple fistulous cutaneous wounds.

**Case 4.** A 17-year-old African American girl with no significant past medical history sought treatment for fever, pneumonia, a left supraventricular mass, a fluctuant mass on her right eyelid, right leg, and glomerulonephritis causing renal failure. She had been treated with steroids and cyclophosphamide. During a 1-month period of hospitalization for pneumonia, *C. posadasii* was cultured from a lung biopsy specimen. The patient began therapy with oral fluconazole (100 mg daily; creatinine clearance, 11–14 mL/min). Because no response to therapy was seen, treatment was switched to liposomal amphotericin B (L-AmB) (5 mg/kg daily), but his condition did not improve significantly. Treatment with L-AmB was later discontinued, and posaconazole therapy was started. During the first month of posaconazole therapy, the patient became afebrile. Posaconazole therapy was continued for a total of 11 months, during which time progressive improvement was noted on chest radiography. The patient gained 22.8 kg, and his functional status greatly improved. During a routine visit (on day 191 of posaconazole therapy), electrocardiography demonstrated a prolonged corrected QT (QTC) interval. This prolongation of the QTC interval exceeded the safety guidelines of the protocol, and posaconazole was discontinued for 1 week. Additional examination of the patient’s medical history revealed a history of borderline QTc prolongation, and posaconazole treatment was reinitiated. On day 342 of posaconazole therapy, the patient died of peritonitis, presumably from rupture of an intra-abdominal abscess infected with *C. posadasii*. Before her death, *C. posadasii* was isolated from specimens obtained from respiratory secretions and multiple fistulous cutaneous wounds.

**Case 5.** A 24-year-old African American woman at 18 weeks’ gestation developed cough, dyspnea, night sweats, and weight loss. Chest radiography showed diffuse miliary infiltrates (figure 1). Cultures of sputum specimens and bronchoalveolar lavage fluid grew *C. posadasii*. Treatment with amphotericin B was initiated (1 mg/kg daily). Over the course of several weeks, the patient’s clinical condition significantly deteriorated. Her hypoxia rapidly worsened. Antifungal therapy was changed to L-AmB (5 mg/kg daily), but her condition continued to deteriorate, and she had high fevers and decreasing renal function. At 19 weeks’ gestation, the fetus spontaneously aborted. Intra-venous itraconazole (200 mg/day) was added to the treatment regimen. During week 5 of L-AmB therapy, vesicular and bullous lesions appeared on her neck, arm, and leg (figure 2A); analysis of biopsy specimens revealed *C. posadasii*. One month after the spontaneous abortion, the patient continued to require mechanical ventilation (fraction of inspired oxygen [FiO₂], 60%; positive end-expiratory pressure [PEEP], 22 mm Hg) and pressor agents. At that point, antifungal therapy was changed to posaconazole (400 mg b.i.d.) given through the feeding tube. After 1 week of posaconazole therapy, the patient became normotensive and afebrile, and marked improvement was noted in her ventilator status (FiO₂, 40%; PEEP, 14 mm Hg). By day 28 of posaconazole therapy, skin lesions had resolved, and the patient was weaned from mechanical ventilation. Her weight and functional status subsequently returned to previous levels. After 32 months of posaconazole treatment, the titer revealed by immunodiffusion complement fixation testing decreased to 1:32 (compared with a titer of 1:1024 when it was first determined 3 weeks after hospitalization), and results of *Coccidioides* IgG ELISA decreased to 0.932 times the EIA index value (maximum measured value, 11.2 times the EIA index value 10 weeks after the spontaneous abortion).
Figure 1. Chest radiograph of patient 5 at admission to the University Hospital in San Antonio after hospitalization. The patient continued to receive posaconazole maintenance therapy at the time of writing, for a total of >34 months of posaconazole therapy to date.

Case 6. A 28-year-old Hispanic man with untreated AIDS, wasting, and Mycobacterium avium complex infection that was stable because of ongoing treatment presented to the hospital with a dry cough and diffuse reticular nodular infiltrates. C. posadasii was recovered from a lung biopsy specimen. Amphotericin B therapy was initiated at 0.7 mg/kg daily; therapy was then changed to fluconazole (400 mg/day). Three weeks after the patient started antifungal treatment, the CD4+ cell count was 5 cells/mm³, and the HIV load was 451,000 copies/mL. The patient started treatment with lamivudine-zidovudine and nelfinavir. After 6 weeks of sequential amphotericin B and fluconazole therapy, there was no clinical improvement. The Coccidioides IgG serologic titer was 1:32. Antifungal treatment was then changed to posaconazole. The symptoms improved within 3 weeks after initiation of posaconazole. By day 311 of posaconazole therapy, results of Coccidioides serologic tests were negative. By the end of treatment (678 days after starting posaconazole treatment), pulmonary symptoms had totally resolved, and the patient had gained 15 kg. The patient was poorly compliant with antiretroviral therapy and never achieved virologic suppression. Furthermore, the CD4+ cell count never exceeded 50 cells/mm³. The patient, who was an undocumented immigrant, was returned to Mexico, where he ran out of medications. Because he could not return to the United States for additional treatment, his coccidioidomycosis subsequently relapsed, and he died of progressive disease.

DISCUSSION

In 2000, the Infectious Diseases Society of America (IDSA) published guidelines for the treatment of coccidioidomycosis [12]. Amphotericin B is currently recommended as first-line therapy for diffuse pneumonia caused by Coccidioides organisms and for all cases of coccidioidomycosis that occur during pregnancy (because of the presumed teratogenicity of azole antifungals). Long courses of treatment that extend over many months virtually ensure the development of nephrotoxicity due to amphotericin B deoxycholate. The lipid formulations of amphotericin B provide some measure of protection against nephrotoxicity, but they are not completely benign.

In cases of disseminated coccidioidomycosis, fluconazole or itraconazole is commonly initiated as first-line therapy [12]. In a randomized trial of 198 patients with chronic coccidoidal infection, fluconazole and itraconazole were similarly effective treatments, with 50%–60% response rates [3]. However, relapse rates were high at >30%. Amphotericin B serves as an alternative therapy in these cases, with remission rates ranging from 50% to 75% [13]. Therefore, despite in vitro susceptibility of Coccidioides to amphotericin B and all azole antifungals, a substantial number of patients either do not respond to therapy or experience repeated relapses of disease. Therapeutic alternatives are needed for these patients.

Another challenge in treating coccidioidomycosis is that not all patients progress at a rate leisurely enough to permit evaluation on the monthly or quarterly basis that is used for assessing chronic disease. Infection caused by Coccidioides or-
ganisms can be acutely life threatening (as in patients 5 and 6) or it can be slow and inexorably progressive (as in patient 4). Response to treatment is often slow, but when patients are critically ill, one may not have the luxury of 2–3 months of observation before treatment failure must be declared and alternative therapy selected. Patients 4, 5, and 6 were considered to have acutely life-threatening disease. Before the initiation of posaconazole therapy, ≥40 days of therapy with accepted antifungal drugs had failed in each of these patients. All patients had received treatment with fluconazole and/or itraconazole, and 5 of 6 patients had received amphotericin B therapy (table 2). After the initiation of posaconazole therapy, signs and symptoms of coccidioidomycosis improved in all 6 patients, and, in 5 patients, improvements were observed within the first month after initiating treatment.

Clinical evaluation of coccidioidomycosis may be challenging. Resolution of lesions may be incomplete. Radiographic signs may be chronically unchanging, and lesions may resolve at varying speeds. Often, follow-up cultures do not yield growth. To assess the total disease burden, the Mycoses Study Group developed a global scoring system for use in measuring the burden of disease [4]. This system includes symptoms (1 point each); numbers of individual lesions (2 points each); results of culture of samples obtained from respiratory, soft tissue, or osteoarticular sites (4 points each, for a maximum of 12 points); and results of serologic analyses (up to 3 points, depending on the titer determined by IDCF). A successful response was defined as a score that was ≤50% of the pretreatment aggregate score. At the end of treatment, points associated with culture results were "carried over" (i.e., pretreatment points were retained in the posttreatment score), unless results of cultures of specimens obtained from the same site as the samples that underwent pretreatment culture were negative. Similarly, the absence of a follow-up serologic titer led to carrying over the initial point count.

We found this system to have limited value in our patients for 2 reasons. First, 5 of our patients did not have follow-up cultures; thus, culture-related points continued to be added to the Mycoses Study Group score, even when the patients were asymptomatic. Second, our laboratory changed from the traditional IDCF test to the ELISA method halfway through the study. Therefore, we were unable to directly compare ELISA values with titers derived by means of IDCF [14].

Such limitations have been appreciated by others, and the IDSA guidelines for the treatment of coccidioidomycosis do not mention the scoring system [12]. However, the IDSA guidelines provide little assistance with regard to assessing disease severity and response. Thus, we elected to present the initial Mycoses Study Group scores (including points associated with results of cultures and serologic tests) and a modified score by which we excluded culture and serologic data from the scoring system. We believe that the latter method still allowed us to assess the severity of disease and the resolution of symptoms and of external and radiographic lesions, but it did not impose a falsely high score, as does the Mycoses Study Group scoring system. With the use of this modification rather than the original scoring system, patients 2 and 3 were classified as having successful outcomes (and, clearly, these patients improved clinically).

The rapidity of improvement was remarkable and was not typical for the course of disease in patients receiving itraconazole or fluconazole [3]. Overall, successful outcomes were observed in 5 of 6 patients. It is unfortunate that the condition of one of the patients (patient 4) deteriorated after initial improvement, despite continuing posaconazole therapy, and that she ultimately died of coccidioidomycosis. However, it is of note that regimens of voriconazole with INF-γ and high-dose

Figure 2. A, Lesions (ruptured bullae) on the right arm of patient 5 that developed after 5 weeks of amphotericin B therapy. Analysis of biopsy specimens revealed Coccidioides posadasii. B, Appearance of the site of previous lesions after 20 days of posaconazole therapy.

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fluconazole (1600 mg/day) also failed. Apparently, this patient had other host factors that caused the disease to progress, despite the aggressive antifungal and surgical therapies used. Although not all patients achieved successful outcomes, these cases collectively support the use of posaconazole for the treatment of life-threatening infection caused by *Coccidioides* organisms. However, only randomized, controlled trials can definitively demonstrate the utility of this drug versus the utility of other antifungal agents.

Posaconazole therapy was generally well tolerated by all our patients, and no patient reported an adverse effect due to the medication despite up to 24 months of treatment; patient 5 continues to receive long-term maintenance therapy. Recently, additional safety data for posaconazole was reported in which the drug was found to have no effect on the QTc interval in healthy volunteers [15]. Long-term suppressive therapy is often necessary in patients who have had disseminated coccidioidomycosis. This mycosis has a high predisposition to relapse, and thus long-term follow-up is critical. Physicians are well advised to assess patients in terms of remission or disease-free interval rather than cure. Regardless of the patient’s immune function status, disease relapse can occur if maintenance therapy is interrupted [16]. Because noncompliance with such prolonged therapy can have serious consequences, treatment with a well-tolerated and potent drug such as posaconazole may produce significant benefits.

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**References**