Background. Itraconazole has become the first choice for treatment of cutaneous sporotrichosis. However, this recommendation is based on case reports and small series. The safety and efficacy of itraconazole were evaluated in 645 patients who received a diagnosis on the basis of isolation of *Sporothrix schenckii* in Rio de Janeiro, Brazil.

Methods. A standard regimen of itraconazole (100 mg/day orally) was used. Clinical and laboratory adverse events were assessed at grades 1–4. A multivariate Cox model was used to analyze the response to treatment.

Results. The median age was 43 years. Lymphocutaneous form occurred in 68.1% and fixed form in 23.1%. Six hundred ten patients (94.6%) were cured with itraconazole (50–400 mg/day): 547 with 100 mg/day, 59 with 200–400 mg/day, and 4 children with 50 mg/day. Three patients switched to potassium iodide, 2 to terbinafine, and 4 to thermotherapy. Twenty-six were lost to follow-up. Clinical adverse events occurred in 18.1% of patients using 100 mg/day and 21.9% of those using 200–400 mg/day. The most frequent clinical adverse events were nausea and epigastric pain. Laboratory adverse events occurred in 24.1%; the most common was hypercholesterolemia, followed by hypertriglyceridemia. Four hundred sixty-two patients (71.6%) completed clinical follow-up, and all remained cured. Only 2 variables were significant in explaining the cure: patients with erythema nodosum healed faster, and lymphocutaneous form took longer to cure.

Conclusions. In the current series, the therapeutic response was excellent with the minimum dose of itraconazole, and there was a low incidence of adverse events and treatment failure.

Sporotrichosis is a fungal infection of worldwide distribution, first described in the late 19th century [1]. Since then, several outbreaks have been reported, mostly related to activities involving manipulation of plants and soil [2]. Zoonotic transmission has been occurring endemically in Rio de Janeiro, Brazil, since 1998 [3–6]. The most affected were women aged 40–50 years who cared for cats with sporotrichosis and lived in a region of low socioeconomic status [4]. By December 2009, >2000 persons and 3200 cats had been treated at Evandro Chagas Clinical Research Institute/Fiocruz with confirmed sporotrichosis [7].

In cats, sporotrichosis frequently presents with disseminated lesions and systemic involvement. Treatment requires long-term administration of itraconazole or ketoconazole and isolation of the animals until the healing of injuries.

Unlike humans, the susceptibility of cats to *Sporothrix schenckii* is high, facilitating the infection among these animals and between cats and humans. To date, there is no evidence of control of disease transmission.

The use of potassium iodide for the treatment of sporotrichosis was proposed by Sabouraud and was first used by De Beurmann and Ramond in 1903 [8]. Despite the adverse effects associated with this compound, it remains a satisfactory therapy. However, since the 1990s, the azoles have been used in developed countries [9].

Currently, itraconazole is the drug of choice for treatment of sporotrichosis [9]. This drug has proven to be effective, with low toxicity and good tolerance, even for long-term treatment. However, this recommendation is based on case reports and small series [10–12].
In the present study, the safety and efficacy of treatment with itraconazole were evaluated in 645 patients who received a diagnosis on the basis of isolation of S. schenckii in culture during 2002–2006, from the current epidemic in Rio de Janeiro.

METHODS

This study was approved by the Research Ethics Committee of Instituto de Pesquisa Clínica Evandro Chagas (IPEC)/Fiocruz and was conducted in accordance with the standards of good clinical practice. After signing the consent form, the patients underwent clinical assessment and collection of material for mycological examination and of blood samples for serum chemical and hematological analysis. The isolation of S. schenckii in culture of secretions or fragments of lesions was used as the criterion for inclusion in the study. A regimen of itraconazole at a dosage of 100 mg/day orally was the first choice of therapy. However, a few patients were started on higher doses, and others had the initial dose increased because the lesions worsened or remained unchanged. Children weighing <20 kg were treated with itraconazole (5 mg/kg/day orally). Laboratory tests were requested before initiation of therapy and after its completion. When required, these tests were repeated at shorter intervals. Symptoms, signs, and laboratory values were assessed by the Severity Grading Toxicity Table, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health [13]. Adverse events in this table are classified as mild (grade 1), moderate (2), severe (3), and life-threatening (4). New events or worsening of previous conditions were captured as adverse events. Complaints were recorded by self-reporting. Prior and concomitant medications were considered to be those used since the beginning of the disease to the end of treatment. Cure was established considering epithelialization, absence of infiltrates, absence of desquamation and erythema of the lesions, and total remission of lymphangitis and subcutaneous nodules. Itraconazole treatment was stopped as soon as lesions were considered to be healed. Medical visits were performed monthly during treatment and 3–6 months after stopping itraconazole. Temporary interruption of treatment was considered to be the absence to 1 visit with temporary discontinuation of the drug. Adherence was calculated on the basis of patient information. Drug accountability was not assessed. Itraconazole was freely supplied by the Department of Clinical Pharmacy at IPEC.

The exclusion criteria of the study were HIV infection, pregnancy, or missing the first assessment after itraconazole prescription.

In the exploratory data analysis, frequencies, intersections, and description of the measures of central tendency (median) were used. To describe the response to treatment (cure, recurrence, or failure), the time to complete regression of lesions was determined using survival models applied to patients who were treated solely with 100 mg/day of itraconazole. Kaplan-Meier survival curves were used to describe the response to treatment, considering each of the potential risk and/or protective factors for the development of sporotrichosis (sex, clinical presentation, transmission, hospitalization, adverse reaction, arthralgia, erythema nodosum, and erythema multiforme). Differences between the survival curves for each risk and/or protection factor were determined using Peto and log-rank tests at the level of 20%. Finally, a multivariate Cox model was used to analyze the response to treatment, considering each of the significant factors in bivariate Kaplan-Meier analyses, at 5% level of significance.

SPSS, version 16.0 (SPSS) was used in data processing and analysis.

RESULTS

Patients

The median age of the 645 patients was 43 years (range, 2–85 years); there was a predominance of women (72.9%). The “domestic activities” (27.8%) category prevailed, followed by “student” (17.1%). With regard to disease transmission, 88.7% reported domestic or professional contact with cats presenting sporotrichosis. Fifty-six percent were scratched or bitten by these animals. The clinical lymphocutaneous form (68.1%) was the most frequent, followed by fixed form (23.1%). Other clinical presentations were disseminated cutaneous (6.7%), mucocutaneous (1.6%), and mucosa (6.6%). The median time from evolution to diagnosis was 4 weeks (range, 1–104 weeks). The lesions were more frequent on the upper limbs (67.9%), occasionally bilateral, followed by lower limbs (11.3%) and face (7.4%).

Signs and Symptoms

Arthralgia was the most common symptom, reported in 127 patients (19.7%). In 69.0% of these patients, the complaint was associated with erythema nodosum or erythema multiforme. Erythema nodosum and erythema multiforme were diagnosed in 53 (8.2%) and 34 (5.3%) patients, respectively. Forty-eight patients (55.2%) with these conditions reported prior use of medications, especially cephalexin. In the remaining 39 patients, no factor frequently associated with these conditions was identified.

Fever was reported by 8.7% of patients. However, blood cultures performed for 8 of these patients showed no fungal growth.

Comorbidities and Prior and/or Concomitant Medication Use

The most frequent comorbidity was high blood pressure (20.5%), followed by dyslipidemia (19.5%) and diabetes mellitus (6.0%). The remaining, because of small frequency, were grouped into gastrointestinal (4.5%), respiratory (4.2%),
neuropsychiatric diseases (3.3%), arthropathy (2.6%), cardiopathy (1.6%), other endocrine diseases (1.4%), nephropathy/uropathy (1.1%), and others (3.6%). Alcoholism was reported by only 6 patients. In these patients, the clinical picture and the response to treatment were similar to those in persons who did not report alcohol use.

Antibiotics were the most frequently used concomitant medications (32.6%), followed by anti-hypertensive and/or anti-diuretic agents (20.6%). Antacid drugs were indicated in 2.4% of patients presenting epigastric pain above grade 1. Other drugs were nonsteroidal anti-inflammatory drugs and/or analgesics (10.1%), hypoglycemic agents (4.1%), and others (9.5%).

Laboratory Tests Before Treatment

Six hundred twenty-one patients underwent laboratory tests before starting therapy. Of these, 45.9% had abnormalities. Cholesterol level increase was the most frequent abnormality (16.3% had an increase from 200 mg/dL to >300 mg/dL), followed by hemoglobin level decrease (15.1% had a decrease from 9.0 g/dL to 10.9 g/dL) and triglyceride level increase (9.3% had an increase from 201 mg/dL to 750 mg/dL). With the exception of triglyceride, cholesterol, and glucose levels, which increased to grade 3, the other basal abnormalities were mild, associated with comorbidities, and monitored during treatment. Twenty-four patients (3.7%) who did not have laboratory tests performed before treatment were excluded from the evaluation of laboratory adverse events.

Treatment

Of the 645 patients included in the study, 26 dropped out of treatment and were lost to follow-up. Six hundred ten patients (94.6%) were cured with itraconazole: 547 with 100 mg/day (Table 1), 59 with 200–400 mg/day, and 4 children with 50 mg/day. Of the remaining 9 patients, 5 switched to other antifungal agents and 4 substituted for thermotherapy.

The median treatment time was 12 weeks (range, 2–64 weeks). The median length of therapy was 10.5 weeks for patients with fixed form and 12 weeks for those with lymphocutaneous and disseminated cutaneous forms. Patients who used antacids presented with a longer median time to healing (14.5 weeks), regardless of clinical form. Table 1 shows the data according to clinical form and length of treatment of patients healed with 100 mg/day of itraconazole.

Outcomes According to Number of Treatment Courses

Five hundred forty-two patients (84.0%) were cured with the first course of therapy (Table 2). Six patients (1.1%) patients treated with 100 mg/day of itraconazole had reactivation of the lesions. These patients used the medication for a median of 19.5 weeks (range, 12–33 weeks), and relapse occurred at a median of 18 weeks (range, 6–36 weeks) after the end of treatment. One

<table>
<thead>
<tr>
<th>Evolution</th>
<th>Initial dose of Itraconazole</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg/day</td>
<td>200 mg/day</td>
</tr>
<tr>
<td>Permanent Cure</td>
<td>523</td>
<td>12</td>
</tr>
<tr>
<td>Recurrence</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Definitively discontinued due to adverse events</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Temporary discontinuation</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Dropout</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Lowering the dose for adverse events</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Increasing the dose</td>
<td>39</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>613</td>
<td>23</td>
</tr>
</tbody>
</table>

Table 1. Treatment Time of Sporotrichosis Healed With 100 g/day of Itraconazole, According to Clinical Form

<table>
<thead>
<tr>
<th>Clinical form</th>
<th>Treatment time, weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 4</td>
</tr>
<tr>
<td>Fixed</td>
<td>12</td>
</tr>
<tr>
<td>Lymphocutaneous</td>
<td>8</td>
</tr>
<tr>
<td>Disseminated cutaneous</td>
<td>1</td>
</tr>
<tr>
<td>Mucosa</td>
<td>0</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
</tr>
</tbody>
</table>

Table 2. Evolution of 645 Cases of Sporotrichosis Initially Treated With Itraconazole, According to the Drug Dosage
patient became pregnant, and another had hypertension. In both cases, itraconazole was discontinued. Twenty-three patients were lost to follow-up.

Eighty patients (12.4%) required additional courses of treatment. Of 6 patients who had experienced relapse, 3 were cured with the same dose of 100 mg/day and 2 after increasing the dose to 200 mg/day. One patient, even with dose escalation to 400 mg/day, only achieved cure after switching to potassium iodide (used for 22 weeks). Other reasons for additional treatment courses were dose reduction, for those who started at higher doses and presented with adverse events (n = 9); dose increase, for those that presented with worsening or insufficient response (n = 42); and drug resumption, because of temporary discontinuation of treatment (n = 21). Temporary discontinuation was attributable to lack of medication at the pharmacy (n = 5), adverse events (n = 10), or temporary abandonment by the patient (n = 6). Of the 80 patients who required additional courses of treatment, 69 were cured with itraconazole. Four patients presented with treatment failure: 2 healed with terbinafine, and the other 2 healed with potassium iodide. The patient who permanently discontinued the first treatment course for hypertension healed with potassium iodide. Two patients with adverse events and the pregnant woman had the lesions healed with thermotherapy. Three patients were lost to follow-up (Table 3). Figure 1 summarizes the treatment.

**Adverse Events**

**Clinical Adverse Events**

Of 613 patients who started treatment with 100 mg/day of itraconazole, 111 (18.1%) had grade 1–3 clinical adverse events, and of 69 patients who received doses of 200–400 mg/day, 16 (23.2%) had grade 1–2 adverse events. The most frequent adverse event was nausea, in 6.5% of the patients in the first group and 14.4% in the second group.

Adverse events that required permanent discontinuation of the drug were pregnancy, nausea, rash, and hypertension. Adverse events that required temporary interruption of the drug were nausea, epigastric pain, dizziness, diarrhea, and headache.

**Laboratory Adverse Events**

Four hundred fifty-three patients underwent laboratory tests at the end of treatment. Of these, 109 (24.1%) presented with adverse events; the most common was hypercholesterolemia (cholesterol level, 200 to >300 mg/dL), followed by hypertriglyceridemia (triglyceride level, 200–750 mg/dL) and hyperglycemia (glucose level, 110–500 mg/dL). Considering the severity grade, the most common event was grade 1 triglyceride level (200–499 mg/dL).

In patients who used 100 mg/day of itraconazole, the frequency of grade 3 adverse events was 2.4% and of grade 2 adverse events was 4.8%. In patients who used 200–400 mg/day of itraconazole, the frequency of grade 3 adverse events was 3.4% and of grade 2 adverse events was 6.8%. Other abnormalities were mild increases in liver enzyme, pancreatic enzyme, blood urea nitrogen and creatinine levels, and anemia.

In patients without previous dyslipidemia, cholesterol and triglyceride levels returned to normal range.

**Other Data**

Seven patients were hospitalized: 2 because of intense arthralgia, 2 elderly with extensive lymphocutaneous form and comorbidities, 1 for cellulitis after a cat bite, 1 because of vascular insufficiency, and 1 for investigation for respiratory disease. All progressed satisfactorily.

Four hundred sixty-two patients (71.6%) completed 3–6 months of follow-up after the end of treatment, and all remained free of disease.

Adherence to treatment was good in 87% of cases.

**Survival Analysis**

The analysis of Kaplan-Meier curves for cure, considering the time of treatment (weeks) for patients receiving 100 mg/day of itraconazole, were stratified by clinical presentation, mode of transmission, erythema nodosum, and erythema multiforme.

### Table 3. Final Outcome of Patients Who Were Not Cured With the First Treatment Course

<table>
<thead>
<tr>
<th>Background</th>
<th>Total of Patients</th>
<th>Cure with Itraconazole 100 mg</th>
<th>Cure with Itraconazole 200 mg</th>
<th>Dropout</th>
<th>Cure with another antifungal</th>
<th>Cure with thermotherapy due to adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Temporary discontinuation</td>
<td>21</td>
<td>21</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Definite discontinuation due to adverse events</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dose decreased</td>
<td>9</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dose increased</td>
<td>42</td>
<td>0</td>
<td>33</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
<td>31</td>
<td>37</td>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

**NOTE.** Excludes 23 patients who dropped out in the first course of treatment.
A multivariate Cox survival model was performed from the 4 risk factors posed by the Kaplan-Meier analysis. Only 2 variables were significant in explaining the cure: clinical form and erythema nodosum (Table 4). The incidence rate of localized forms was significantly higher than that in the lymphocutaneous group (hazard ratio, 1.62), which has the largest course to cure. The group with erythema nodosum tended to provide faster healing than did those who did not have erythema nodosum (hazard ratio, 1.46) (Table 5).

**DISCUSSION**

Since 1998, IPEC has been receiving a continuous demand of patients with sporotrichosis. By the end of 2009, >2000 patients had been treated [7], which explains the prevalence of hypertension, metabolic disorders, and other chronic diseases. Although itraconazole can present numerous drug interactions associated with the inhibition of the cytochrome P-450 3A4 system [14, 15], in the present study, there was no interaction with concomitant medications. Only 2 patients using nifedipine needed to switch this agent. Hypoglycemia related to the use of concomitant sulphonylurea to itraconazole was not observed in 14 patients using this medication. The low dose of itraconazole probably explains the low incidence of drug interaction observed. Drug absorption in capsule form is increased if taken with food and is decreased with the use of antacids. The present study found greater treatment time in patients who used drugs for gastric hyperacidity. The use of antibiotics was reported by most patients before treatment at IPEC. This can be explained by the difficulty in the diagnosis of the mycosis until the beginning of
zoonotic epidemic [3]. Erythema nodosum and erythema multiforme have been previously reported [16, 17]. These manifestations of hypersensitivity were statistically associated with more rapid evolution for healing, compared with patients without these conditions. Considering the use of potassium iodide in the classic treatment of sporotrichosis, a drug also used in treatment of erythema nodosum, it is reasonable to assume that potassium iodide could prevent the onset of this hypersensitivity reaction.

Until 2001, itraconazole was routinely administered in a standard regimen of 100 mg/day orally for at least 12 weeks, even though the lesions could be healed in a shorter period [3]. Since 2002, the length of treatment has been established by the evolution of the lesions. In the current series, the therapeutic response was excellent, because of the 645 patients who received treatment, 94.6% were cured with the use of itraconazole at doses of 100–400 mg/day (81.1% during the first course with the minimum dose of the drug). Patients who temporarily interrupted the treatment responded favorably to the resumption of the drug at the same dose, increasing the cure rate to 84.8%. Although several authors recommend starting sporotrichosis treatment with 200 mg/day [9, 10, 18], the regimen with 100 mg/day is effective and safe, in addition to having a lower cost.

The frequency of severe adverse events and itraconazole discontinuation in this study was similar to that in other treatment series of nonsystemic fungal infections [11, 19–22].

Although many patients stayed in contact with cats with sporotrichosis, the percentage of relapses was low, and there were no re-infections after the initial cure.

Clinical trials to determine the optimal dose of itraconazole for treatment of sporotrichosis has not been found in the literature. Randomized, double-blind, controlled studies may not be feasible in many developing countries. The high efficiency and the lower cost of treatment with 100 mg/day of itraconazole indicate that this regimen can be adopted as a first choice of therapy for fixed and lymphocutaneous forms of sporotrichosis.

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