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ORIGINAL ARTICLE

Terbinafine (250 mg/day): an effective and safe treatment of cutaneous sporotrichosis

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Abstract

Background There are a few studies on the treatment of sporotrichosis. The standard drug used is itraconazole. However, the use of itraconazole is limited by its interaction with other drugs.

Objective To evaluate the effectiveness and safety of 250 mg terbinafine for the treatment of cutaneous sporotrichosis in patients in whom itraconazole use is not possible.

Methods We performed a descriptive study of cutaneous sporotrichosis cases treated with 250 mg terbinafine for which itraconazole was contraindicated or resulted in severe or moderate pharmacological interactions. Sporotrichosis was diagnosed based on the isolation of *S. schenckii*.

Results Fifty patients seen between July 2005 and September 2007 were included. Forty-five (92%) patients reported contact with a sick cat and 47 (94%) presented comorbidities (high blood pressure: 64.0%; diabetes mellitus: 30.0%; dyslipidemia: 16.7%; depression: 10.0%; migraine: 2.1%; Parkinsonís disease: 2.1%; peptic ulcer disease: 2.1%; heart failure: 2.1%, and arrhythmia: 2.1%). All patients used some medication interacting with itraconazole (psycholeptics: 36.0%; antidiabetic agents: 28.0%; hypolipemiant agents: 18.0%; calcium-channel blockers: 16.0%; anticonvulsants: 8.0%; cardiotropic drugs: 6.3%; antacids: 6.3%, and antiparkinsonian agent: 2.1%). Most patients (96%) were cured within a mean period of 14 weeks. The drug was discontinued due to a skin rash in one patient. There were no cases of recurrence of the mycosis within a mean follow-up period of 37 weeks.

Conclusions This study suggests that 250 mg/day terbinafine is an effective and well-tolerated alternative to drug therapy of cutaneous sporotrichosis in a population in which itraconazole use is not possible.

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Keywords

itraconazole, sporotrichosis, terbinafine, treatment

Conflicts of interest

None declared.

Introduction

Sporotrichosis is a subacute or chronic mycosis caused by the dimorphic fungus *Sporothrix schenckii*, which is acquired by traumatic inoculation of contaminated soil, plants and organic matter. The lesions are usually limited to the skin, subcutaneous tissue and surrounding lymph vessels. The disease rarely spreads to other organ systems or is primarily systemic. Sporotrichosis predominates in tropical and temperate zones, and the main endemic areas are found in Japan, India, South Africa, Mexico, Brazil, Uruguay, and Peru.[1,2,3,4]

Itraconazole is currently the treatment of choice for cutaneous sporotrichosis,[5] although its use is complicated by the risk of pharmacological interactions. Itraconazole is metabolized by the liver through the cytochrome P450 isozyme 3A4 pathway, a metabolic pathway shared by many drugs routinely used in primary care.

Potassium iodine treatment is an effective and low-cost option for cutaneous sporotrichosis. However, the administration schedule of the drug is complicated, the frequency of adverse events is high, and its mechanism of action is unknown. Fluconazole is considered to be a second-line drug due to its lower efficacy compared to itraconazole. Amphotericin B is effective but is reserved for the disseminated forms of the disease.

Terbinafine is a fungicidal drug used in dermatology because of its excellent concentration in fat tissue, corneal extract, dermis, epidermis, and nails. Binding of the drug to microsomal cytochrome P450 enzymes is low (approximately 5% of total capacity), thus

not affecting the bioavailability of other drugs metabolized by this enzyme system.[6] Clinical trials and case reports[7–11] investigating the use of terbinafine for sporotrichosis treatment, with doses ranging from 125 mg to 1 g/day, suggested that the drug is safe and effective in the treatment of cutaneous sporotrichosis. However, there is no consensus regarding the optimal regimen and duration of terbinafine treatment in sporotrichosis.

The cat-transmitted sporotrichosis epidemic occurring in Rio de Janeiro since 1998 is characterized by a predominance of patients ≥ 50 years.[12,13] An association with comorbidities and the consequent use of drugs that may interact with itraconazole are commonly observed in this age group.

The objective of the present study was to evaluate the effectiveness and safety of 250 mg/day terbinafine for the treatment of cutaneous sporotrichosis in patients in whom itraconazole use is not possible.

Materials and methods

A descriptive study was conducted involving cutaneous sporotrichosis cases, fixed or lymphocutaneous form, seen between July 2005 and September 2007. The patients were followed up at the mycology outpatient clinic of Instituto de Pesquisa Clínica Evandro Chagas (IPEC), a research institution affiliated to Fundação Oswaldo Cruz (Fiocruz), and a national referral centre for the treatment of subcutaneous and systemic mycoses. The study was approved by the Ethics Committee of IPEC/Fiocruz.

Patients with cutaneous sporotrichosis using other drugs contraindicating the use of itraconazole or implicated in severe or moderate pharmacological interactions were included.[14] These drugs were classified according to the 2nd level of the Anatomical Therapeutic Chemical Classification of the World Health Organization (WHO). Excluded were patients with abnormal liver enzymes, blood urea nitrogen or creatinine upon initial blood collection, pregnant and breastfeeding women, patients previously undergoing sporotrichosis treatment, patients with a history of liver disease, patients taking drugs that interact with terbinafine (cimetidine, cyclosporin, nortriptyline, rifampicin, and warfarin), and patients with a history of hypersensitivity to terbinafine.

In the case of a clinical suspicion of cutaneous sporotrichosis, skin specimens were obtained (exudate, scrapping and skin biopsy) and cultured, and the definitive diagnosis was made by isolation of *S. schenckii* as described previously.[12]

The following laboratory tests were performed at baseline, at 12 weeks, and at the end of the study: complete blood count, blood urea nitrogen, creatinine, electrolytes, glucose, aminotransferases, alkaline phosphatase and gamma-glutamyltransferase. In the case of clinical complications, the patient was submitted to the appropriate exams.

The duration of treatment was conditioned to the clinical cure, defined when healing of the lesions occurred, epithelization, and absence of crusts, infiltrates and erythema. In this case, the terbinafine dose was increased to 500 mg/day. In the case of the lymphocutaneous form, patients were classified as responders to treatment when almost all lesions involuted and only one or two active lesions persisted after 12 weeks. Adjuvant therapy consisted of cryotherapy (2 cycles of 15 s) at intervals of 4 weeks and/or lesion curettage (one episode).

Effectiveness was evaluated based on the proportion of cured patients. Recurrence, defined as the relapse of lesion(s) with isolation of *S. schenckii* after clinical cure, was used as secondary endpoint.

Outpatient visits were scheduled on days 15 and 30 after the beginning of treatment, and then once a month thereafter until 12 months. If the patient did not attend the visit, he/she was contacted by telephone to attend the next scheduled visit.

All clinical and laboratory adverse events were evaluated regarding their severity and relationship with the study drug, through pharmaceutical guide consulting according to the categories of causality of WHO: probable, possible, not probable, conditional/not classified, and not accessible/not classifiable.

Simple frequency measures using means and medians were calculated.

Results

Clinical and epidemiological characteristics of sporotrichosis

Fifty patients were included in this study: 41 (82%) women and 9 (18%) men, with a median age of 57, mean of 56 (95% confidence interval, 52.0–60.0), range: 26–81 years. Forty-nine (98%) patients presented an epidemiological history of sporotrichosis, including contact with a sick cat in 45 patients (92%), traumatic inoculation of contaminated plants in 2 patients (4%), and contact with a rat in 1 patient (2%). Among patients with an epidemiological history of contact with a cat, 30 (61%) reported scratches, 5 (10%) reported bites, 2 (4%) reported scratches and bites, and 8 (16.3%) only had contact without trauma. Thirty-nine patients (78%) had the lymphocutaneous form of sporotrichosis and 11 (22%) had the fixed form.

Associated diseases and drugs used

Comorbidities were observed in 47 (94%), including high blood pressure in 32 (64.0%), diabetes mellitus in 15 (30.0%), dyslipidemia in 8 (16.7%), depression in 5 (10.0%), and migraine, Parkinson's disease, peptic ulcer disease, heart failure, and arrhythmia in 1 patient each (2.1%). The remaining 6% of patients did not present any comorbidity. However, these patients reported sleep disorders and used drugs contraindicating the use of itraconazole.

All patients were taking some medication that interacts with itraconazole: 36 (72.0%) only used one drug, 12 (24.0%) used two drugs, 1 patient (2.1%) used three drugs, and 1 patient (2.1%) used four drugs. The most frequently used groups of drugs were as follows: psycholeptics (36.0%, 18 of 50); antidiabetic drugs (28.0%, 14 of 50); hypolipemiant agents (18.0%, 9 of 50); calcium channel

blockers (16.0%, 8 of 50); anticonvulsants including carbamazepine, phenytoin and phenobarbital (8.0%, 4 of 50); digoxin as cardiotropic agent (6.3%, 3 of 50); antacids (6.3%, 3 of 50); and antiparkinsonian agent (2.1%, 1 of 50).

Clinical response to terbinafine and medication tolerability

In the present study, the incidence of sporotrichosis cure was 86% when considering exclusive treatment with terbinafine and 96% when adjuvant therapy (cryotherapy, curettage or both) within a period of 2 to 42 weeks. Two patients did not conclude the treatment; one was lost to follow-up and one due to adverse effects. Six (12%) presented adverse effects related to terbinafine, including one classified as probably related. In this case, the drug was discontinued due to a skin rash on treatment day 14. The remaining adverse effects were classified as possible (5 patients) and did not require the discontinuation of terbinafine treatment. Gastric pain was observed in 2 patients (4.2%) and nausea in 1 patient (2.1%) within the first 2 weeks of treatment. Two patients (4.2%) presented a 2-fold increase of baseline gamma-glutamyl transferase levels within the first 4 weeks of treatment.

Follow-up

There were no cases of clinical or mycological relapse within a mean post-treatment follow-up period of 37 weeks (range: 20–60 weeks).

Adjuvant therapy

Five patients (10.0%) received adjuvant therapy: 2 patients (4.3%) underwent curettage, 2 patients (4.3%) received cryotherapy, and 1 patient (2.1%) was submitted to both curettage and cryotherapy.

Discussion

The present series corresponded to approximately 16% of the patients followed up at the mycology outpatient clinic of IPEC/Fiocruz within the study period (2005–2007). Most patients were women of advanced mean age treated for high blood pressure or diabetes. In the cat-transmitted zoonotic sporotrichosis epidemic occurring for more than 10 years in Rio de Janeiro, women are more exposed to the disease because transmission occurs near and inside home and women are usually involved in domestic activities and in the care of sick animals.[12,13]

The population studied did not receive itraconazole because the patients were taking drugs contraindicating its use or presented severe to moderate interactions. Terbinafine 250 mg/day was chosen in these cases due to the impossibility of serum monitoring of the drugs.

Administration of terbinafine at a dose of 250 mg was chosen based on *in vitro* studies demonstrating an excellent sensitivity profile of *S. schenckii*, as well as on clinical reports showing successful treatment of cutaneous sporotrichosis with this dose.[8–11] Terbinafine has shown low minimum inhibitory concentrations (0.007–0.5 μg/mL) against the fungus in *in vitro* studies, and some investigators reported terbinafine to be the most active drugs among other antifungal agents tested, including itraconazole and amphotericin B.[15,16] Although differences in sensitivity among *S. schenckii* strains from distinct geographical regions have been reported, terbinafine showed a homogeneous profile among these strains.[16,17]

Open-label studies investigating the treatment of cutaneous sporotrichosis with 50–250 mg/day itraconazole have shown 84–100% efficacy within a mean period until cure of 44 to 130 days.[5,18] In the present study, the incidence of sporotrichosis cure was high when considering exclusive treatment with terbinafine, and even higher when adjuvant therapy (cryotherapy, curettage or both) was administered. These results are excellent considering that the study population presented comorbidities, especially diabetes, which are associated with macro and microangiopathies, delaying the healing process, as well as altered mechanisms of response to infections.[19]

Some patients with lymphocutaneous sporotrichosis, who presented involution of almost all lesions after 12 weeks but persistence of one or two active lesions, were submitted to cryotherapy and curettage. These lesions were considered to be 'encysted', with consequent difficulty of antifungal penetration. In the present study, adjuvant therapy was necessary in five patients who showed a good response. Cryotherapy is often used as single treatment for other types of subcutaneous mycosis such as chromoblastomycosis. We consider it to be an alternative to adjuvant therapy of sporotrichosis.

Chapman *et al.*[7] advocated higher terbinafine doses of 500 to 1000 mg for the treatment of cutaneous sporotrichosis. These authors conducted a multicentre randomized trial in four countries (United States, Brazil, Colombia and Peru) involving 63 patients, most of them males. The frequency of cure was higher in the group treated with 1000 mg (87% vs. 52%, $P = 0.004$). However, the incidence of adverse effects was also higher, with two patients requiring discontinuation of the drug due to gastrointestinal bleeding and progressive abdominal pain. Recurrence was only observed in the group receiving 500 mg/day.

One explanation for the present finding that patients with cutaneous sporotrichosis were successfully treated with a lower dose of terbinafine might be related to the fact that the study was conducted at a single centre involving a homogenous population originating from the same epidemic. According to a previous study,[15] the strains of this epidemic have shown excellent *in vitro* sensitivity to terbinafine.

In the present study, 250 mg terbinafine was well tolerated and, although the overall incidence of adverse events was relevant (12%), most effects were of mild or moderate intensity. It should be emphasized that definitive drug discontinuation was required in only one case because of hypersensitivity, the most frequently reported cutaneous adverse effect in cases treated with terbinafine.[20]

The present results suggest that 250 mg/day terbinafine is an effective and well-tolerated alternative to drug therapy of cutaneous

sporotrichosis in a population in which itraconazole use is not possible. Further controlled and randomized trials are necessary to test the hypothesis related to this daily dose.

References

1 Conti Diaz IA. Epidemiology of sporotrichosis in Latin America. *Mycopathologia* 1989; **108**: 113–116.
2 Kusuhara M, Hachisuka H, Sasai Y. Statistical survey of 150 cases with sporotrichosis. *Mycopathologia* 1988; **102**: 129–133.
3 Kwon-Chung KJ, Benett JE. Sporotrichosis. In Kwon-Chung KJ, Benett JE, eds. *Medical Mycology*. Lea & Febiger, Philadelphia, 1992: 707.
4 Pappas PG, Tellez I, Deep AE *et al*. Sporotrichosis in Peru: description of an area of hyperendemicity. *Clin Infect Dis* 2000; **30**: 65–70.
5 Kauffman CA, Bustamante B, Chapman SW *et al*. Clinical practice guidelines for the management of sporotrichosis: 2007 Update by the Infetious Diseases Society of America. *Clin Infect Dis* 2007; **45**: 1255–1265.
6 Micromedex DrugDex E MARTINDALE Terbinafine – The Complete Drug Reference http://www.thomsonhc.com/hcs/librarian/ND_PR/Main/SBK/2/PFPUI/BpY1SQ1yTn4wf/ND_PG/PRIH/CS/97A06F/ND_T/HCS/ND_P/Main/DUPLICATIONSHIELDSYNC/5B2E6F/ND_B/HCS/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/2679p/ContentSetId/30/SearchTerm/terbinafine/SearchOption/BeginWithReference (last accessed 12 December 2008).
7 Chapman SW, Pappas P, Kauffmann C *et al*. Comparative evaluation of the efficacy and safety of two doses of terbinafine (500 and 1000 mg day) in the treatment of cutaneous or lymphocutaneous sporotrichosis. *Mycoses* 2004; **47**: 62–68.
8 Hay RJ. Therapeutic potential of terbinafine in subcutaneous and systemic mycoses. *Br J Dermatol* 1999; **141**(Suppl. 56): 36–40.
9 Hull PR, Vismer HF. Treatment of cutaneous sporotrichosis with terbinafine. *Br J Dermatol* 1992; **126**(Suppl. 39): 51–55.
10 Tanuma H, Asai T, Abe M. Case Report. Lymphatic vessel-type sporotrichosis immunohistochemical evaluation and cytokine expression pattern. *Mycoses* 2001; **44**: 316–320.
11 Terbinafine Study Group. Clinical evaluation of terbinafine, an orally active antifungal agent for rare types of dermatomycosis with terbinafine. *Nishihon J Dermatol* 1994; **56**: 584–594.
12 Barros MB, Schubach AO, Valle AC *et al*. Cat-transmitted sporotrichosis epidemic in Rio de Janeiro, Brazil: description of a series of cases. *Clin Infect Dis* 2004; **38**: 529–535.
13 Barros MB, Schubach AO, Galhardo MCG *et al*. Sporotrichosis with widespread cutaneous lesions: report of 24 cases related to transmission by domestic cats in Rio de Janeiro, Brazil. *Int J Dermatol* 2003; **42**: 677–681.
14 Micromedex DrugDex. E MARTINDALE Itraconazole-The Complete Drug Reference http://www.thomsonhc.com/hcs/librarian/ND_PR/Main/SBK/2/PFPUI/BpY1SQ1yTn4wf/ND_PG/PRIH/CS/97A06F/ND_T/HCS/ND_P/Main/DUPLICATIONSHIELDSYNC/5B2E6F/ND_B/HCS/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/2679p/ContentSetId/30/SearchTerm/Itraconazole/SearchOption/BeginWithReference (last accessed 12 December 2008).
15 Galhardo MC, De Oliveira RM, Valle ACF *et al*. Molecular epidemiology and antifungal susceptibility patterns of Sporothrix schenckii isolates from a cat-transmitted epidemic of sporotrichosis in Rio de Janeiro, Brazil. *Med Mycol* 2008; **46**: 141–151.
16 Kohler LM, Monteiro PC, Hahn RC *et al*. *In vitro* susceptibilities of isolates of *Sporothrix schenckii* to ITC and terbinafine. *J Clin Microbiol* 2004; **42**: 4319–4320.
17 Coskun B, Saral Y *et al*. Sporotrichosis successfully treated with terbinafine and potassium iodine: Case report and review of literatura. *Mycopathologia* 2004; **158**: 53–56.
18 Bustamante B, Campos PE. Sporotrichosis: a forgotten disease in the drug research agenda. *Expert Rev Anti Infect Ther* 2004; **2**: 85–94.
19 Bub JL, Olerud JE. Diabetes Mellitus. In Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz I. *Fitzpatrick's Dermatology in General Medicine*, 6th edn. McGrawHill, United Sates of America, 2003: 1651.
20 Sandoz Pharmaceuticals Corporation. US product monograph on terbinafine (Lamisil). East Hanover, NJ. Sandoz Pharmaceuticals Corporation, April 1996.