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Comparative Study of 250 mg/day Terbinafine and 100 mg/day Itraconazole for the Treatment of Cutaneous Sporotrichosis

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Abstract Itraconazole is currently used for the treatment of cutaneous sporotrichosis. Terbinafine at a daily dose of 250 mg has been successfully applied to the treatment of cutaneous sporotrichosis.
Objective To compare the efficacy of 250 mg/day terbinafine and 100 mg/day itraconazole for the treatment of cutaneous sporotrichosis.
Materials and methods A bidirectional cohort study was conducted on 55 patients receiving 250 mg/day terbinafine and 249 patients receiving 100 mg/day itraconazole. The latter patients were matched for age and clinical form to the terbinafine group at a ratio of 5:1. *Sporothrix schenckii* was isolated by culture from all patients (age range: 18–70 years), who were submitted to the standard care protocol consisting of clinical and laboratory evaluation and periodic visits.
Results Cure was observed in 51 (92.7%) patients of the terbinafine group and 229 (92%) of the itraconazole group within a similar mean period of time (11.5 and 11.8 weeks, respectively). An increase in the terbinafine dose to 500 mg was necessary in two patients due to the lack of a response, and one patient presented recurrence. In the itraconazole group, two patients required a dose increase and three presented recurrence. Adverse events were equally frequent among patients receiving terbinafine ($n = 4$, 7.3%) and itraconazole ($n = 19$, 7.6%) and were generally mild without the need for drug

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discontinuation, except for two patients of the itraconazole group.

Conclusion Terbinafine administered at a daily dose of 250 mg is an effective and well-tolerated option for the treatment of cutaneous sporotrichosis.

Keywords Sporotrichosis · Itraconazole · Terbinafine · Treatment

Introduction

Sporotrichosis is a subacute or chronic infection caused by the dimorphic fungus *Sporothrix schenckii* and is especially frequent in Latin American countries. Classical infection is associated with the subcutaneous traumatic inoculation of organic matter and plants contaminated with the fungus [1, 2]. Recent molecular studies have demonstrated that this species constitutes a complex of numerous phylogenetic species, and the creation of three new species as *Sporothrix brasiliensis*, *Sporothrix globosa*, and *Sporothrix mexicana* was proposed [3].

Sporotrichosis is a benign disease, which is restricted to the skin in most cases. The lymphocutaneous and fixed forms are the most common. The disease rarely disseminates to other organs, but if dissemination occurs there is generally an underlying immunodepression. Recently, HIV infection has been associated with severe and fatal forms of sporotrichosis [4, 5].

Few controlled studies regarding the treatment of sporotrichosis exist and current recommendations are based on the results of open studies involving a small number of patients [6]. Recently, a randomized study comparing itraconazole pulse regimen × continuous itraconazole (200 mg/day) demonstrated the latter to be an effective and safe alternative treatment of cutaneous sporotrichosis [7].

Itraconazole is effective and well tolerated and currently the treatment of choice for cutaneous sporotrichosis [4]. However, since itraconazole is metabolized by cytochrome P450 isoenzyme 3A4 in the liver, it interacts with various drugs, a fact limiting its use [8]. Since the 1990s, some studies, most of them case reports, have described the good response of patients to terbinafine used for the treatment of cutaneous sporotrichosis [7, 9–11]. Similarly, in vitro sensitivity studies have emphasized the potent antifungal activity of terbinafine against *S. schenckii* [12–14]. The interaction with other drugs is nonsignificant, since terbinafine is mainly metabolized by non-cytochrome P450 enzymes in the liver (the latter accounts for only 5%) [3, 15]. This fact is important since mycoses can arise as complications in patients with co-morbidities, especially immunosuppressed patients.

Within the context of the sporotrichosis epidemic that has been occurring in the form of a zoonosis in Rio de Janeiro, Brazil, since 1998, we recently conducted an uncontrolled open study in which terbinafine at a dose of 250 mg per day was administered to 50 patients with cutaneous sporotrichosis. The use of itraconazole was not possible in these patients, because they were taking drugs whose concomitant administration with itraconazole is contraindicated or because of the presence of a moderate to severe interaction with itraconazole. Terbinafine was found to be effective and well tolerated, presenting a cure rate of 96% [16]. Thus, the objective of the present study was to compare the efficacy of 250 mg/day terbinafine and 100 mg/day itraconazole for the treatment of cutaneous sporotrichosis.

Materials and Methods

This study was carried out between January 2005 and December 2008 at the Mycology outpatient clinic of the Evandro Chagas Clinical Research Institute (IPEC), which is a research center affiliated to the Oswaldo Cruz Foundation (Fiocruz) and a national referral center for the treatment of subcutaneous and deep mycoses. The study was approved by the Ethics Committee of IPEC/Fiocruz.

A bidirectional cohort study was conducted on patients with cutaneous sporotrichosis (fixed and lymphocutaneous form) divided into two treatment groups: patients receiving 250 mg/day terbinafine and patients receiving 100 mg/day itraconazole. Patients of the terbinafine group were selected randomly among individuals consecutively admitted to the Mycology outpatient clinic, who agreed to participate in the study and who signed an informed consent form. The group receiving itraconazole was randomly selected among a set of patients from the database of the Mycology outpatient clinic, who were matched for

age and clinical form to the terbinafine group at a ratio of 5:1. Both groups presented the same epidemiological characteristics, were seen by the same team, and underwent the same protocol for the diagnosis and treatment follow-up of sporotrichosis.

Criteria for exclusion from the study were the presence of any co-morbidity and elevated liver enzyme levels on initial assessment, previous treatment of sporotrichosis, and a history of medication used and hypersensitivity to the drugs tested. Pregnant women and puerperae who were breast feeding were also excluded.

The definitive diagnosis of sporotrichosis was established by isolation of the fungus from skin specimens (exudate, scales, and skin biopsy), which were sent to the Laboratory of Mycology. The definitive diagnosis was made by isolation of *S. schenckii* as previously described [2].

A complete blood count and biochemical tests (urea, creatinine, glycemia, transaminases, alkaline phosphatase, and gamma-glutamyltransferase) were performed on the initial visit, after 12 weeks and at the end of treatment. In the case of clinical complications, appropriate tests were carried out. The terbinafine group was submitted to funduscopy of the eye at the beginning and at the end of treatment.

The duration of treatment was determined according to clinical cure, which was defined as complete healing of the lesions (epithelization and absence of crusts, infiltration, and erythema). Persistence or an increase in the initial size of the lesion after 12 weeks of treatment was classified as treatment failure. In this case, the dose of itraconazole or terbinafine was adjusted to 200 or 500 mg/day, respectively. Treatment efficacy was determined by the proportion of cured patients, and secondary efficacy was based on the frequency of recurrence that is defined as the reappearance of lesions and isolation of *S. schenckii* after clinical cure.

Outpatient visits were scheduled at 2-week intervals during the first month and then monthly until completing 12 months. Patients who did not appear for the scheduled visits were contacted by telephone and asked to attend the next visits. Dropout was defined in the case of patients who did not return for the scheduled visit after 30 days.

All clinical or laboratory adverse events were evaluated regarding their severity. The causal relationship of the adverse events to the drug tested was evaluated using the causality categories of the World Health Organization: probable, possible, unlikely, conditional/unclassifiable, and non-assessable/unclassifiable.

The clinical and laboratory data were entered into the Statistical Package for the Social Sciences (SPSS) V 15.0. Independent categorical variables and nominal sociodemographic and clinical parameters are reported as relative frequencies and their respective 95% confidence interval. Continuous variables (age, time until cure) are reported as mean, median, and standard deviation (SD). Time until cure was compared by the Student t-test. The chi-square test was used to compare proportions of primary (cure) and secondary (adverse events) outcomes, with the calculation of the relative risk (RR) and 95% confidence interval.

Results

Clinical and Epidemiological Characteristics

The clinical and epidemiological characteristics of the patients are shown in Table 1. There was a predominance of women in both groups (terbinafine group: $n = 41$, 74.5%; itraconazole group: $n = 169$, 67.9%). The mean age of the patients was also similar (terbinafine: 39 years; itraconazole: 41 years). Most patients were from the municipality of Rio de Janeiro (neighborhoods in the western and central region) and municipalities of Baixada Fluminense, and presented an epidemiological history of sporotrichosis (terbinafine group: $n = 51$, 92.8%; itraconazole group: $n = 240$, 96.4%). Forty-eight (87%) patients of the terbinafine group and 225 (90.4%) of the itraconazole group reported contact with a sick cat (bite and/or scratch or contact without trauma). Infection after plant injury was reported by two (4%) patients of the terbinafine group and seven (2.8%) of the itraconazole group. The lymphocutaneous form was the most frequent in both groups (terbinafine group: $n = 41$, 74.5%; itraconazole group: $n = 176$, 70.7%). The fixed form was observed in about one-fourth of patients of each group (terbinafine: $n = 14$, 25.5%; itraconazole: $n = 73$, 29.3%). The two groups were also similar in terms of the body distribution of the lesions. In the terbinafine group, 43 (78%) patients had lesions on the upper limbs, nine (16%) on the

Table 1 Clinical and epidemiological characteristics of patients with cutaneous sporotrichosis, duration of treatment, and response to treatment

	Itraconazole ($n = 249$)	Terbinafine ($n = 55$)
Gender		
Female	169 (67.9%)	41 (74.5%)
Male	80 (32.1%)	14 (25.5%)
Mean age (years)	41	39
Epidemiological history		
Cat with sporotrichosis	225 (90.4%)	48 (87%)
Clinical form		
Lymphocutaneous	176 (70.7%)	41 (74.5%)
Fixed	73 (29.3%)	73 (29.3%)
Location		
Upper limbs	211 (84.7%)	43 (78%)
Lower limbs	33 (13%)	9 (16%)
Face	5 (2%)	3 (5.5%)
Cure	229 (92%)	51 (92.7%)
Mean duration of treatment (weeks)	11.8 (2–44)	11.5 (2–24)
Dose increase	2 (0.8%)	2 (3.6%)
Recurrence	3 (1.2%)	1 (1.8%)
Dropout	19 (7.6%)	3 (5.5%)

lower limbs, and three (5.5%) on the face. In the itraconazole group, 211 (84.7%) patients had lesions on the upper limbs, 33 (13%) on the lower limbs, and five (2%) on the face.

Evaluation of Treatment Efficacy

The cure rate was similar in the two groups (terbinafine: 51/55, 92.7%; itraconazole: 229/249, 92.0%), with an RR of 1.01 (0.93–1.09). The mean (±SD) time until achieving clinical cure did not differ between the two groups (terbinafine: 11.5 ± 4.7 weeks; itraconazole: 11.8 ± 6.1 weeks).

In the terbinafine group, the duration of treatment until cure ranged from 2 to 24 months. Three (5.5%) patients abandoned treatment. In two (3.6%) cases, the terbinafine dose was increased to 500 mg/day. One (1.8%) patient presented recurrence 3 months after the end of treatment. Terbinafine was reintroduced using the same dose regimen, and the duration of retreatment until cure was 4 weeks.

In the itraconazole group, 229 (92.0%) patients were cured within a period of time of 2–44 months. Nineteen (7.6%) patients did not complete treatment due to dropout. Two (0.8%) patients required an increase in the itraconazole dose to 200 mg/day. Three (1.2%) patients presented recurrence. In these cases, itraconazole was reintroduced using the same dose regimen and the patients were cured.

In four of the eight patients, who received a dose increase or presented recurrence, the lesions were located on the hands, probably as a result of their professional activities which required constant hand washing (a cook and an animal caregiver in the terbinafine group and a waiter in the itraconazole group).

Safety (Adverse Events)

The adverse events frequencies are shown in Table 2.

No difference in the frequency of adverse events was observed between the two groups (terbinafine group: 4/55, 7.3%; itraconazole group: 19/249, 7.6%) (RR = 0.91, 0.39–2.07).

In the terbinafine group, all clinical adverse events were mild and were classified as possible according to the WHO, thus not requiring discontinuation of the drug. Four (7.3%) patients presented adverse events that occurred during the first 2 weeks of treatment, including epigastralgia in two (3.6%), and nausea and tachycardia in one patient each (1.8%). The patient with tachycardia presented this symptom when drinking coffee, and improvement was observed after the patient stopped drinking coffee. None of the patients presented laboratory alterations.

Adverse reactions to itraconazole were observed in 19 (7.6%) patients, which were classified as probable in two. Drug treatment was discontinued in these two cases due to urticaria (skin hypersensitivity) in

Table 2 Adverse events observed in the two groups treated for sporotrichosis

Adverse effect	Itraconazole	Terbinafine
Epigastralgia	7 (2.8%)	2 (3.6%)
Nausea	10 (4%)	1 (1.8%)
Tachycardia	–	1 (1.8%)
Urticaria[a]	1 (0.4%)	–
Laboratory alterations[a]	1 (0.4%)	–
Total	19 (7.6%)	4 (7.3%)

[a] Treatment discontinued due to elevated liver enzymes

one (0.4%) and liver toxicity in the other (threefold increase in baseline transaminases and twofold increase in baseline gamma-glutamyltransferase), which occurred in the third month of treatment. The remaining adverse events were classified as possible in 17 (6.8%) patients and did not require the discontinuation of drug treatment. Seven (2.8%) patients presented epigastralgia and 10 (4.0%) nausea, which occurred during the first 2 weeks of treatment. The severity of clinical adverse events was mild to moderate, and laboratory adverse events were classified as grade 2.

Discussion

The present study evaluated the efficacy of terbinafine compared to itraconazole for the treatment of cutaneous sporotrichosis in a total of 304 patients, the largest series studied so far. In this bidirectional cohort, the groups studied were highly homogenous in terms of demographic and epidemiological characteristics and clinical aspects of sporotrichosis (Table 1). As reported in previous studies and also observed here, women of adult age and transmission of sporotrichosis by cats are characteristics of this epidemic, since these patients are more exposed to this type of contact due to their domestic activities [1, 2]. The lymphocutaneous form and location of the lesions on the upper limbs were the predominant findings in the two groups, confirming that this form is the most common clinical presentation of sporotrichosis. The predominant location of lesions on the upper limbs is probably due to the handling of sick animals [1, 2].

The cure rate obtained for treatment with terbinafine at a daily dose of 250 mg was high (92.7%), with this drug being as effective as 100 mg/day itraconazole (92%). Terbinafine at daily doses ranging from 125 to 1,000 mg has been used by some investigators with excellent responses [9–11, 15]. Open studies administering itraconazole at a dose of 100 mg have reported a cure rate of 90–100% over a period of 2–9 months [17, 18]. The minimum standard doses of ITC and TRB for the treatment of mycoses are 100 and 250 mg, respectively, and this dose regimen has been used by our institute since the beginning of the epidemic with high cure rates [2]. The duration of treatment was similar in the two groups.

The successful treatment of the present patients with cutaneous sporotrichosis using a dose lower than that recommended by other investigators [4, 9, 19], irrespective of the antifungal agent employed, might be related to the fact that the study was conducted at a single center and involved a homogenous population originating from the same epidemic. Previous studies have shown that the strains involved in this epidemic exhibited excellent in vitro sensitivity to the antifungal agents used, especially terbinafine and itraconazole [12, 14].

Generally, in the treatment of cutaneous sporotrichosis, only a small number of patients require a dose increase in the antifungal agent [2, 6]. The frequency of recurrence of the mycosis was similar in the two groups. Both drugs are lipophilic and reach an excellent concentration in skin tissue even after suspension. However, in view of its fungicidal action, terbinafine was not superior to itraconazole, which is a fungistatic drug [20].

With respect to tolerance, terbinafine was found to be safe and the adverse events reported did not require its discontinuation. Gastrointestinal complaints were the predominant adverse effects in the two groups, which are observed in less than 5% of patients [8, 21].

We conclude that terbinafine administered at a daily dose of 250 mg was as effective and well tolerated as itraconazole in the treatment of patients with cutaneous sporotrichosis and might be an alternative for the treatment of this mycosis.

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