Case Report

Alternate week and combination itraconazole and terbinafine therapy for chromoblastomycosis caused by Fonsecaea pedrosoi in Brazil

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Patients with long-standing chromoblastomycosis may respond poorly to standard treatments such as amphotericin B, oral antifungals, surgical measures or thermotherapy. The objective of this study was to determine the potential of alternate week and combination therapy with itraconazole and terbinafine in the treatment of poorly responsive, or non-responsive, chromoblastomycosis. Four patients with long-standing chromoblastomycosis (8–23 years) caused by Fonsecaea pedrosoi had responded poorly to standard therapies including monotherapy with the oral antifungal agents. In order to try and improve the response to oral itraconazole and terbinafine, alternate week or combination therapy with itraconazole and terbinafine was initiated. Bloodwork including complete blood count and liver function tests were performed every 3–8 weeks to ensure patient safety. Reduction or resolution of lesions of chromoblastomycosis was noted with alternate week or combination treatment using oral itraconazole and terbinafine. Three of four patients experienced no clinical side-effects; the third reported mild, transient gastric discomfort which responded to antacids. Bloodwork generally remained within normal limits throughout the entire course of treatment with no clinically significant changes. The combination therapy was considered effective in treating the poorly responsive chromoblastomycosis of all four patients. Some success with alternative week therapy was also noted in one patient. The favorable response and lack of significant adverse effects suggests that these regimens may be an option for some patients with chromoblastomycosis.

Keywords chromoblastomycosis, combination therapy, Fonsecaea pedrosoi, itraconazole, terbinafine, therapy

Introduction

Chromoblastomycosis is a chronic, often debilitating, deep fungal infection that affects skin and subcutaneous tissues. It can be a difficult disease to treat successfully with persistent recrudescence of the fungus in ≈ 43% of cases [1]. Many treatment regimens have been reported, for example, intravenous antymycotics (amphotericin B), oral antifungals (5-flucytosine, itraconazole, terbinafine, fluconazole), surgical measures (cryotherapy, excision), and others (thermotherapy) [2–10]. In this case report we present four patients with long-standing chromoblastomycosis who had been poorly responsive, or not responsive to several treatment regimens. Some of the patients had responded only partially to monotherapy with oral itraconazole or oral terbinafine.

We report the use of alternate week and combination therapy incorporating oral itraconazole and terbinafine to treat chromoblastomycosis. Each of the four patients experienced marked improvement when administered
these regimens, with minimal to no clinical adverse effects and no clinically significant laboratory abnormalities. To our knowledge, these treatment regimens have not been reported previously for chromoblastomycosis. Although the results are preliminary in nature, it is important to be aware that these strategies may be of benefit in chromoblastomycosis, a disease with limited therapeutic options, when monotherapy with itraconazole or terbinafine has not been effective or has demonstrated a poor response.

Case reports

Four patients with chromoblastomycosis due to Fonsecaea pedrosoi were treated with alternate week or combination therapy using oral itraconazole and terbinafine.

In the alternate week regimen, itraconazole was administered for one week and terbinafine the next week. The starting dose of itraconazole was 200 mg day\(^{-1}\) or 400 mg day\(^{-1}\) and terbinafine was generally commenced at the dose of 250–500 mg day\(^{-1}\).

In the combination regimen both itraconazole and terbinafine were administered together with the starting dosages being itraconazole 200–400 mg day\(^{-1}\) and terbinafine 250–750 mg day\(^{-1}\). If the clinical response was not deemed effective, and the patient was tolerating therapy, the dosage of itraconazole was increased, to a maximum of 400 mg day\(^{-1}\) and terbinafine was increased, to a maximum of 1000 mg day\(^{-1}\).

Patient 1

A 61-year-old Brazilian male, weight 57 kg, presented in November 1998 with a 23-year history of chromoblastomycosis. During the previous year the lesions had continued to worsen with pruritus and localized pain following minimal trauma. The crural lymph nodes had become enlarged and painful. A lymph node biopsy from the crural region demonstrated miliary bodies and culture revealed F. pedrosoi.

The patient had been treated previously with a variety of therapies, including oral ketoconazole, oral terbinafine, cryotherapy, electrosurgery and thermotherapy, all leading to minimal or no improvement. In November 1998, the patient was commenced on alternate weeks of itraconazole 200 mg day\(^{-1}\) and terbinafine 500 mg day\(^{-1}\) for 6 weeks, until January 1999 (Fig. 1). There was

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Fig. 1 Therapeutic regimen used to treat Patient 1 initially with alternate week therapy using itraconazole and terbinafine, and subsequently with combined therapy using itraconazole and terbinafine.
initially some improvement in the lesions but the response appeared to plateau. We therefore increased the dose of the two systemic antifungal agents gradually to itraconazole 300 mg day$^{-1}$ and terbinafine 500 mg day$^{-1}$ (Fig. 1). By May 1999 there was clear improvement in the lesions with diminution of pain and pruritus. The older and more chronic lesions were slower to respond and the tarbinafine dosage was increased to 750 mg day$^{-1}$. There were no adverse effects from therapy.

In June 1999, the patient decided to discontinue therapy for personal reasons, however, he returned two months later with two new lesions. Given the lack of adverse events attributable to the antifungal agents and normal laboratory parameters, the patient was placed on combined therapy with intracranazole and terbinafine. The initial regimen was itraconazole 300 mg day$^{-1}$ and terbinafine 250 mg day$^{-1}$. Because treatment was well tolerated and there was some response the dosage regimen was stepped up, eventually to itraconazole 400 mg day$^{-1}$ and terbinafine 1000 mg day$^{-1}$. The patient reported improvement in all lesions with complete resolution of some of the lesions. There were no adverse effects. Bloodwork (complete blood count [CBC], liver function tests, urea and creatinine) was performed every 3 weeks and remained within normal limits. Clinical resolution of the lesions has been accompanied by mycologic confirmation of healing (negative microscopy and culture).

**Patient 2**

A 50-year-old white Brazilian male, weight 92 kg, presented to us in September 1999, with an 8-year history of chromoblastomycosis. There was no lymphadenopathy. A skin biopsy from a lesion on the left leg confirmed the diagnosis of chromoblastomycosis. Light microscopic examination of a lesion revealed muriform bodies and on culture *F. pedrosoi* was grown.

The patient was being treated with continuous itraconazole therapy 400 mg day$^{-1}$ without improvement (Fig. 2). In September 1999, the patient was placed on combined therapy with itraconazole 400 mg day$^{-1}$ and terbinafine 500 mg day$^{-1}$. Within 3 weeks the patient observed clinical improvement of the chromoblastomycosis with a decrease in the size of the verrucous lesions and an absence of pruritus. Because the patient was not experiencing any adverse effects, the daily dosage of terbinafine was increased to 750 mg day$^{-1}$. The patient experienced mild gastric pain, which responded to antacids. There was response to therapy with regression in size of the violaceous patches. Over the next two months the patient noted improvement of leg and thigh lesions with residual scars in place of the once-active lesions. The patient ceased to experience any symptoms related to the chromoblastomycosis and new lesions stopped developing. Mycologic evaluation of skin from the resolved lesions demonstrated negative mycology (negative light microscopic examination and culture). Bloodwork including CBC, liver function tests, urea and creatinine were performed every 3 weeks and remained within normal limits.

**Patient 3**

A 55-year-old Brazilian female farmer, weight 47 kg, disclosed a 17-year history of chromoblastomycosis. Cryotherapy was unsuccessful. In 1990, the patient was treated with intravenous amphotericin B (total dosage 1725 mg) and 5-flucytosine. There was initial healing with the resulting scar revealing a negative culture. The chromoblastomycosis relapsed and was retreated with oral 5-flucytosine with partial improvement. In 1997, the patient was administered itraconazole 200 mg day$^{-1}$ for 16 months with poor response. In May 1998, the patient was placed on terbinafine 250 mg day$^{-1}$ for two months and the dose was then increased to 500 mg day$^{-1}$. The patient again demonstrated poor response to this regimen, which was continued until May 2000.

Combination therapy with itraconazole 400 mg day$^{-1}$ and terbinafine 500 mg day$^{-1}$ was started in May 2000. After being on this regimen for four months the patient reported a marked improvement in the lesions with

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70% healing. The patient indicated that the lesions were no longer verrucous or painful, and that no new lesion developed while on this regimen of oral itraconazole and terbinafine.

During the course of antifungal therapy with itraconazole and terbinafine the patient did not report any clinical side-effects. Bloodwork including CBC, liver function tests, urea and creatinine were performed every 3 weeks and remained within normal limits.

Patient 4

A 39-year-old white male, weight 60 kg, presented with a 15-year history of a small violaceous papule on the dorsum of the left foot (Fig. 3a). When he first presented in January 2000, the lesion was a 5 cm diameter pruritic, verrucous plaque with black dots within it; the plaque was located on the lateral aspect of the left foot. There was no associated lymphadenopathy. In October 1999, a skin biopsy of the lesion confirmed chromoblastomycosis. Light microscopic examination demonstrated miform bodies and on culture *F. pedrosoi* was recovered. Baseline CBC and liver function tests were within normal limits.

The patient had been previously treated with itraconazole 100 mg day⁻¹ for eight months with minimal improvement. In January 2000, the patient was placed on combined therapy with itraconazole 200 mg day⁻¹ and terbinafine 250 mg day⁻¹. After two months of combination therapy, the lesion was no longer pruritic and there was remarkable reduction in the size of the lesion, which had decreased by ≈ 70%. In April 2000, light microscopy examination of material obtained from the lesion were negative. Following six months of combined therapy there was complete healing of the lesion (Fig. 3b) and the regimen was discontinued. The patient has remained free of symptoms and the disease has not recurred during a six-month follow-up period. No adverse effects were experienced at any point and laboratory parameters, CBC and liver function tests, obtained every 4–8 weeks while on therapy, remained within normal limits.

Discussion

Chromoblastomycosis can be difficult to treat with a limited number of oral antimycotics being available in the therapeutic armamentarium. Traditional therapy includes continuous dosing with itraconazole or terbinafine. In some cases, monotherapy with these antimycotics is ineffective or is associated with a less than acceptable response. In the cases reported here, we show that chromoblastomycosis may respond to either alternate week or combination therapy with itraconazole and terbinafine.

The rationale for alternate week therapy with itraconazole and terbinafine was based on the pharmacokinetics of these agents. The half-life of elimination of itraconazole from the plasma is $21 \pm 5$ h [11]. For oral terbinafine the corresponding elimination is biphasic with elimination half-lives following a single 250 mg dose of $\approx 22$ and 90 h [12]. When either drug is given for one week it does not reach steady state, and the drug remains in the plasma for only a short time after stopping active treatment. Therefore, when an alternate week regimen using itraconazole and terbinafine is followed, the drug will continue to reach the site of interest, that is the cutaneous lesions of chromoblastomycosis, in this ‘off’ week. The alternate week regimen may enable a reduction in drug usage and have the potential for a

![Fig. 3 A, Patient 4: Lesion of chromoblastomycosis on dorsum of left foot prior to combination therapy with itraconazole and terbinafine. B, Complete healing of chromoblastomycosis following therapy.](image-url)
safer adverse effects profile compared to dosing with both itraconazole and terbinafine simultaneously on a long-term basis.

Combination therapy may be effective because of a synergistic effect. Following a thorough literature search we could not identify any report in which chromoblastomycosis had been treated with a combination of itraconazole and terbinafine, nor did we find in vitro studies examining such a synergistic effect in *F. pedrosoi*. However, several in vitro studies have shown the possible synergistic effect of terbinafine and itraconazole in *Candida albicans* [13,14]. Fothergill *et al.* [14] noted synergy (defined as a four-fold decrease in the minimum inhibitory concentration for both agents being used) in 90% of the strains tested. Similarly, Ryder *et al.* [15] demonstrated synergy in vitro between terbinafine and itraconazole in *Aspergillus fumigatus*. Terbinafine and itraconazole have also been shown to be synergistic against 95% of isolates of *Scedosporium prolificans* [16]. Urbina *et al.* [17] showed that both terbinafine and ketoconazole are potent antiproliferative agents against both forms of the parasite *Trypanosoma (Schizotrypanum) cruzi*, and that each agent potentiates the action of the other, especially against the clinically relevant form, the amastigote.

Clinical evidence is less common, though a combination of terbinafine and itraconazole has been used successfully to treat pythiosis [18]. Chromoblastomycosis has previously been treated with a combination of azoles with some clinical success [19]. However, in one report there was a failure of terbinafine and itraconazole in the treatment of post kala-azar dermal leishmaniasis [20].

Several publications report the successful treatment of some chromoblastomycosis patients with itraconazole monotherapy. Restrepo *et al.* [21] described 10 patients with mild to severe chromoblastomycosis who responded to treatment with either 100 or 200 mg of itraconazole daily. The treatment period lasted 12–24 months, and only one patient, with severe chromoblastomycosis, failed to improve during that time. In another study [22], 19 patients were treated with 200–400 mg of itraconazole per day until clinically and biologically (negative mycology and histological improvement) cured. Eight patients met this criterion and the other 11 were continuing to improve at the time of publication. More recently, one case report [2] described the successful treatment of a 68-year-old woman with chromoblastomycosis using an itraconazole pulse regimen (7 pulses of: 200 mg b.i.d. of itraconazole for one week, followed by 3 weeks with no drug treatment). Three of our four patients, however, had previously failed to respond to itraconazole monotherapy.

There are some guidelines in the literature about the highest possible daily dosage of itraconazole and terbinafine. High dose itraconazole (600 mg day$^{-1}$) in eight patients with severe or life-threatening systemic mycoses was found to produce significantly reduced serum potassium, as well as adrenal suppression, which has not been noted with lower doses of itraconazole [23]. Thus, the dosage of itraconazole was not increased beyond 400 mg daily (200 mg twice a day) in order to reduce the possibility of adverse effects. This daily dosage is consistent with that used to treat superficial fungal infections including onychomycosis with the ‘pulse’ regimen of 200 mg twice daily for one week [24,25].

The maximum daily dosage of terbinafine was increased from 250 to 1000 mg (250 mg four times a day) in some of our patients. Similar dosages of terbinafine have been used in the treatment of other systemic mycoses and have been well tolerated [26–28]. There is a report of fungal mycetoma (Madura foot or eumycetoma) in eight patients being treated safely with terbinafine 1000 mg day$^{-1}$ for up to 48 weeks [29]. In another study, high-dose terbinafine (up to 2000 mg day$^{-1}$) was used to treat fluconazole-resistant oral mucosal candidosis in HIV patients [30]. Esterre *et al.* [31] treated 37 patients with chromoblastomycosis using terbinafine 500 mg day$^{-1}$ for 6–12 months and found it to be well accepted by the patients. In many of these patients, significant improvement was noted after two to four months of treatment. Despite these reports of successful therapy for chromoblastomycosis with itraconazole and terbinafine, all of the patients presented in this report had previously been treated with itraconazole and/or terbinafine as monotherapy, with little or no improvement.

In our four patients alternate week and combination therapy with itraconazole and terbinafine was well tolerated and laboratory work performed every 3–8 weeks demonstrated that the CBC and liver function tests generally remained within normal limits. Owing to the possibility of adverse effects, we started these four patients at a low dose of each drug, increasing the dosage only when it had been shown that the patient tolerated the medication well.

In our experience, then, alternate week and combination therapy with itraconazole and terbinafine have been effective for some cases of chromoblastomycosis in which those patients demonstrated minimal to poor response to monotherapy with oral itraconazole or terbinafine. The regimens have been well tolerated. Further experience will help provide more insight into the utility of itraconazole/terbinafine alternate week and combination therapy in chromoblastomycosis, and perhaps other systemic mycoses.
References


