Evaluation of Efficacy and Safety of Itraconazole Oral Solution for the Treatment of Oropharyngeal Candidiasis in AIDS Patients

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This study was a non-comparative multicenter clinical trial to evaluate the efficacy and tolerability of itraconazole oral solution 200 mg/day (100 mg twice a day in the fasting state) for the treatment of oropharyngeal candidiasis in AIDS patients. We included 50 patients who were treated and followed for up to 3 weeks after ending therapy in the analysis. Mycological cures at the end of therapy occurred in 20/50 patients (40%), but colonization by *Candida* sp. was recorded in 42/50 (84%) by the end of follow-up. A high rate of clinical response was observed in 46/50 (92%), and the response was sustained for up to 21 days after stopping therapy in 24/46 patients (52%). Clinical relapses were documented among 22 patients, but all causative fungal organisms associated with a relapse were susceptible to itraconazole. There were many patients with persistence or recurrence of *Candida*, but without mucositis. Relapse of *Candida* mucositis was significantly related to low levels of CD_4 lymphocytes exhibited by symptomatic patients. The drug was well tolerated by all but 1 patient.

We conclude that itraconazole oral solution (100 mg bid for 7-14 days) is a well tolerated and effective treatment for suppressing the symptoms of oropharyngeal candidiasis in AIDS patients. Patients with severe immunosuppression may relapse and require frequent cycles of treatment or longterm suppressive therapy.

Key Words: AIDS, candidiasis, itraconazole.

The prognosis of individuals infected with HIV has changed considerably since the introduction of antiretroviral drug combinations, including protease inhibitors and non-nucleoside analogue reverse transcriptase inhibitors. Several authors have reported reductions in morbidity and mortality among AIDS patients under antiretroviral therapy. However, continued increases in HIV infection have been documented in under developed countries, mainly from sub-Saharan Africa, Southeast Asia and some Latin American countries. The public health systems in these region are not able to provide antiretroviral drugs to HIV-infected patients. As a consequence, it is expected that opportunistic infections associated with AIDS patients will remain a major problem in these parts of the world [1].

Oropharyngeal candidiasis (thrush) is the most common opportunistic infection in AIDS patients and its occurrence increases as CD_4 counts decrease [2]. Topical antifungal therapy may be used to treat mild episodes of thrush [3,4] but systemic antifungal therapy is needed for the treatment of extensive and recurrent episodes of thrush [5-7]. Itraconazole has demonstrated a broad spectrum of antifungal activity *in vitro*, including a wide range of *Candida* spp [8-

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10]. However, the benefit of itraconazole treatment of *Candida* mucosal infections in AIDS patients may be limited by the low bioavailability of the capsule formulation [11].

To overcome some of the limitations associated with capsule formulation, a soluble formulation of itraconazole in hydroxypropyl-b-cyclodextrin was developed [12]. This has a better systemic absorption as well as topical action [13,14]. Itraconazole oral solution (IOS) has been successfully used to treat thrush and *Candida* esophagitis in AIDS patients [15-21]. We present the clinical and mycological results of the first non-comparative clinical trial performed in Brazil to evaluate the efficacy and tolerability of itraconazole oral solution for treatment of adult AIDS patients with thrush.

Materials and Methods

Male and female HIV-infected patients over 18 years of age were eligible for the study if they met the following criteria: a clinical picture of pseudomembranous oropharyngeal candidiasis and findings on direct microscopic examination (KOH smear) consistent with *Candida* spp, further confirmed by a positive fungal culture.

Patients were excluded from study participation for any of the following reasons: a history of topical or systemic antifungal therapy within 7 or 14 days, respectively, of entering the study; presence of symptoms suggestive of esophageal candidiasis; a history of hepatic failure; life expectancy of less than 1 month; pregnancy or women of child-bearing potential not practicing adequate birth control, and lactating females; patients requiring concomitant therapy with drugs that could interact with itraconazole (H2-receptor blockers, antiacids, rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine, terfenadine and astemizole). All volunteers signed an informed consent prior to inclusion in the study.

This study was a non-comparative multicenter clinical trial performed to evaluate the efficacy and tolerability of itraconazole oral solution (IOS) 200 mg/day (100 mg twice a day) for 7 or 14 consecutive days. IOS was given in the fasting state. Patients were instructed to swish the oral cavity with 10 mL aliquots of solution (100 mg/10 mL) for several seconds and then swallow.

Following the initial visit on entering the study, visits were scheduled on days 7, 14, and 28. Clinical and epidemiological data for all patients, as well as the laboratory results (complete blood count, CD_4 count and biochemical tests) were recorded. At the first visit, the severity of lesions was evaluated as localized (single lesion) or extensive (multiple or confluent lesions). The efficacy of the antifungal therapy was assessed based on resolution of signs and symptoms noted at the first visit and by mycological investigation. The clinical response was rated as cured (clearance of all signs and symptoms), improved (minimal signs and symptoms compared with the first visit) or failed (persistence or worsening of signs and symptoms). For mycological investigation, oral samples were obtained by swabbing the oral cavities of all patients during all scheduled visits, and the biologic material was cultured.

The primary efficacy parameter was the initial clinical response. Patients rate as cured or improved after 7 or 14 days of therapy were considered to have a successful outcome and were eligible for the follow-up phase. Recurrence was defined as a return of signs and symptoms in a patient with a previously successful clinical response.

A mycological cure was defined as a negative culture of the oral sample obtained at the end of therapy, and re-colonization as a positive culture obtained following a negative culture, regardless of the presence or absence of signs and symptoms.

All cultures were performed on plates of Sabouraud-dextrose agar with chloramphenicol and incubated at 30°C for 7 days. Positive cultures were sent to the Special Micology Laboratory of the Division of Infectious Diseases and Parasitology at the Federal University of São Paulo, for further analysis and determination of the antifungal susceptibility profile. The identification of the yeast isolates was based on micromorphology characters of the colonies and the biochemical profile evaluated with the aid of API galleries [22]. The fungal isolates obtained at the first visit, at the end of therapy, and at any recurrent episodes

were submitted to antifungal susceptibility tests performed according to the NCCLS standard procedures [23].

For safety evaluation, a medical history, physical examination and laboratory tests of blood samples (hemogram, hepatic and renal functions) were collected before therapy and at the end of therapy.

Results

Patients

Fifty patients from 5 centers were included in the present study. Baseline and demographic characteristics of all patients are presented on Table 1. The low mean CD_4 count and the high incidence of concomitant diseases exhibited by most of the patients confirmed the advanced status of AIDS among this population. *Candida albicans* accounted for 100% of the yeasts obtained at the baseline cultures and all isolates were susceptible to the azoles tested (see data in Table 1).

Efficacy analysis

The clinical and mycological assessments were performed for up to 3 weeks following treatment withdrawal. Forty six of the 50 treated patients (92%) were considered clinically cured 14 days after beginning treatment. Forty-three of these patients were free of lesions after 7 days of treatment. There were 4 failures.

During the follow-up period, we identified 22 clinical recurrences (48%). Of note, 16 of the 22 patients had a previous positive culture before the clinical evidence of thrush at the third week visit. Twenty four patients (52%) remained lesion-free at the end of the follow-up period.

The mycological cure rate was 20/50 (40%). The colonization rate among the initial responders was 91% (42/46 patients) at the third visit, but only 22 patients developed oral thrush at that time.

At the end of the follow-up period, the species distribution of the 42 colonized patients was: *C. albicans* (39), *C. krusei* (1), *C. tropicalis* (1) and *C. inconspicua* (1). All those clinical isolates were still susceptible to itraconazole (MIC range 0.015 mg/mL to 0.25 mg/mL), but 1 isolate was resistant to fluconazole (*C. krusei*). There were significantly more recurrences in the group of patients with CD_4 counts < 50 mm^3, than in those with CD_4 counts > 50 mm^3 (Figure 1). There was no relationship between recurrences and high values of itraconazole or fluconazole MICs of the isolated yeasts.

Safety analysis

Safety evaluations in all 50 patients revealed only 1 patient with significant adverse events related to the study drug (epigastric pain and flatulence) but the treatment was continued. No significant changes were observed in clinical or laboratory evaluations of the enrolled patients.

Discussion

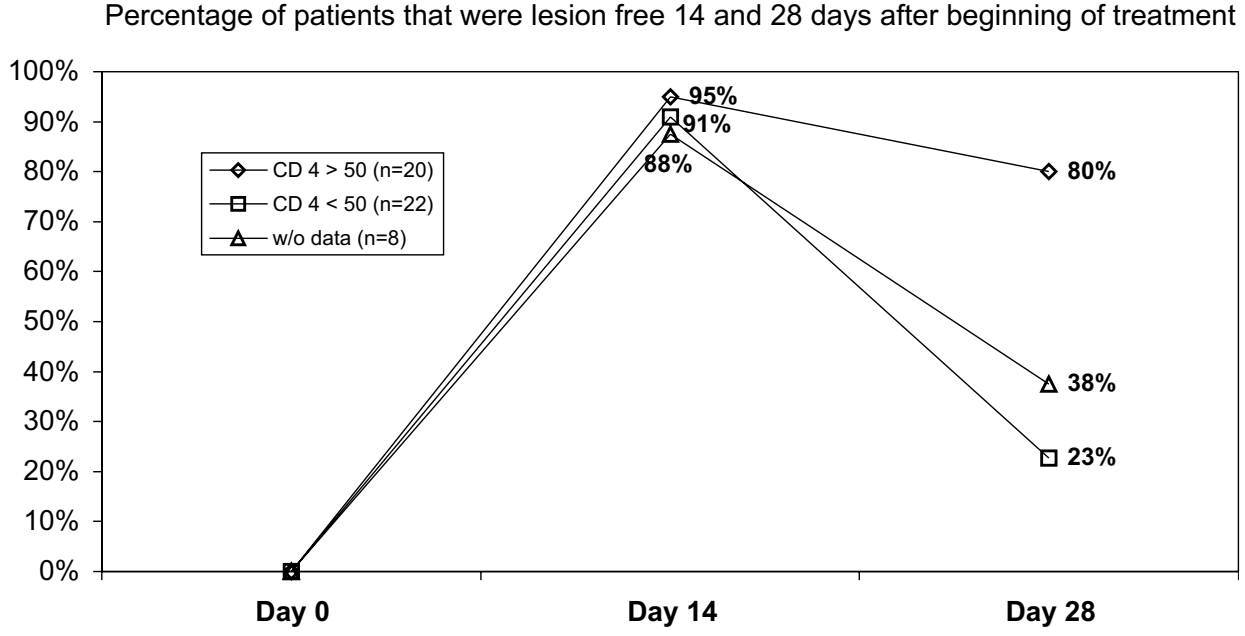
Fluconazole is a predictably absorbed, well-tolerated, safe and very useful drug for the treatment of mucosal candidiasis [24]. However, fluconazole refractory oropharyngeal candidiasis has emerged as an important illness among advanced AIDS patients. Morbidity related to this condition may cause significant difficulty for adequate nutritional intake as well as for swallowing oral medications. Incidence of fluconazole refractory mucosal candidiasis is reported from 4% to 7% of such patients [25]. The rates of *Candida* spp ketoconazole and itraconazole resistance have been reported less frequently, but the clinical use of both azoles is less frequent for treatment of candidiasis due to their limited bioavailability.

The occurrence of mucosal candidiasis refractory to azoles may be a result of several causes including poor compliance with the prescribed antifungal drug treatment protocol, drug interactions causing low azole plasma levels, poor absorption of the drug, significantly impaired immune response, or selection of isolates with primary or secondary resistance to azoles [26]. Consequently, the development of a new formulation of IOS exhibiting greater

Table 1. Demographic, clinical and laboratory baseline data of 50 patients with AIDS and oral candidiasis

Characteristics		
Gender (Female / Male)	18/32	
Age (years) (median - range)	34.5 (21 - 49)	
Weight (median - range - kg)	53.5 (30 - 92)	
CD_4 count/mm^3		
mean ± SD	37.9 ± 44.3	
median (range)	26 (3 - 210)	
Concomitant diseases n %)	36 (72%)	
Extension of oral thrush		
Localized n (%)	16 (32%)	
Extended n (%)	34 (68%)	
Baseline oropharyngeal culture		
C. albicans n (%)	50 (100%)	
Pretreatment MIC (mg/mL)	Itraconazole	Fluconazole
MIC 50% (median)	0.06	0.25
MIC (range)	0.015-0.07	0.125-2.0

Figure 1. Correlation between CD_4 cells count and clinical outcome of patients with thrush treated with itraconazole oral solution ($p < 0.0004$, Fischer)



bioavailability than itraconazole capsules may have beneficial effects in the clinical management of azole refractory mucosal candidiasis.

In the present study, IOS was successfully used to treat extensive oral candidiasis lesions among AIDS patients in advanced stages of disease. We obtained a high rate of clinical response (92%) that was sustained for up to 21 days after ending therapy for 24 patients. All cases of thrush were caused by *C. albicans* isolates susceptible to fluconazole and itraconazole. The drug was well tolerated by all but 1 patient who developed epigastric pain and flatulence.

Clinical relapses were documented among 22 patients, but all causative fungal organisms were susceptible to itraconazole. Patient compliance with the treatment protocol was unremarkable according to the information collected during the clinical visits. Unfortunately, we were not able to measure the serum levels of itraconazole among the treated patients. Considering the data we collected, relapse of *Candida* mucositis was clearly related to the depletion in the levels of CD_4 lymphocytes. These results are in accordance with data published by other investigators who have also reported a higher incidence of recurrent disease among patients with low CD_4 levels.

The itraconazole solution formulation is prepared with a hydroxypropyl-b-cyclodextrin vehicle and absorption is optimal in the fasting state [27]. The bioavailability of the solution has been shown to be 24% to 60% greater than that of the capsules [28]. Better absorption may, in part, account for the improved efficacy of the solution in refractory OPC patients [17]. However, clinical responses were observed in several patients despite steady state itraconazole levels being well below the MIC for the *Candida* spp. isolates [18]. This suggests an important topical effect of the solution. Further support for this observation is provided by the finding of high salivary levels of itraconazole that were sustained up to 4 h after dosing during treatment [14].

Reynes studied the pharmacokinetics of IOS showing that its bioavailability is not modified by the stage of HIV infection. Effective concentrations in plasma (> 250 ng/ml) are achieved at day 4. Concentrations > 250 ng/ml are present in saliva 4 hours after intake and probably contribute to the rapid clinical response [14].

The clinical efficacy and safety of the new formulation of itraconazole has been studied in several controlled, randomized, open label trials in HIV/AIDS patients with oral trush and esophagitis. Preliminary clinical studies in AIDS patients with severe oral candidiasis have shown that IOS (100 mg bid) produced a 100% clinical cure rate [15] and is more effective than topical therapy with clotrimazole [16].

Graybill and colleagues compared the efficacy and tolerability of the IOS (100 mg bid) for 7 or 14 days, with 14 days of fluconazole tablet for the treatment of oral candidiasis in HIV/AIDS patients. Both 7 days and 14 days of IOS were equivalent to 14 days of fluconazole. The clinical response was 97% and 87% for the 14 day regimen of itraconazole and fluconazole, respectively, and 86% in the itraconazole 7 day group. In this study, mycological cure was 88% for itraconazole (14 days), and 77% for fluconazole. Nearly half of all patients relapsed within 30 days of terminating of treatment [19].

Phillips and colleagues evaluated the efficacy of IOS in 36 cases of fluconazole refractory oropharyngeal candidiasis. Clinical response was observed in 65% of evaluated cases. The median MIC of fluconazole was 64 mg/mL, compared to 0.5 mg/mL for control cases. The median itraconazole MIC was 1.25 mg/mL compared to 0.078 mg/mL for controls [18].

Wilcox showed a clinical response rate of 94% in patients with esophageal candidiasis treated with IOS [20]. Moskovitz showed that clinical and endoscopic efficacy between IOS and fluconazole for the treatment of esophageal candidiasis were equivalent [21].

In conclusion, itraconazole oral solution (100 mg bid for 7 or 14 days) is a well tolerated and effective treatment in suppressing the symptoms of oropharyngeal candidiasis in AIDS patients. Patients with severe immunosuppression may develop relapses

and require frequent cycles of treatment or ongoing suppressive therapy. Itraconazole offers an important alternative to other azoles currently in clinical use, with superior efficacy of IOS over capsules due to enhanced bioavailability and additional topical activity.

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