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An Open-Label Comparative Pilot Study of Oral Voriconazole and Itraconazole for Long-Term Treatment of Paracoccidioidomycosis

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Background. In previous studies, itraconazole was revealed to be an effective therapy and was considered to be the gold standard treatment for mild-to-moderate acute and chronic clinical forms of paracoccidioidomycosis. A pilot study was conducted to investigate the efficacy, safety, and tolerability of voriconazole for the long-term treatment of acute or chronic paracoccidioidomycosis, with itraconazole as the control treatment.

Methods. A randomized, open-label study was conducted at 3 Brazilian tertiary care hospitals. Patients were randomized (at a 2:1 ratio) to receive oral therapy with voriconazole or itraconazole for 6 months. Patients receiving ⩾1 dose of study drug were evaluated for safety; patients with confirmed paracoccidioidomycosis who completed ⩾6 months of therapy (treatment-evaluable patients) were evaluated for treatment efficacy. Satisfactory global response was assessed at the end of treatment.

Results. Fifty-three patients were evaluated for treatment safety (35 received voriconazole, and 18 received itraconazole). Both drugs were well tolerated. The most common treatment-related adverse events in the voriconazole group included abnormal vision, chromatopsia, rash, and headache; the most common treatment-related adverse events in the itraconazole group included bradycardia, diarrhea, and headache. Liver function test values were slightly higher in patients receiving voriconazole than in those receiving itraconazole; 2 patients in the voriconazole group were withdrawn from treatment because of increased liver function test values. In the intent-to-treat populations, the satisfactory response rate (i.e., complete or partial global response) was 88.6% among the voriconazole group and 94.4% among the itraconazole group. The response rate among treatment-evaluable patients was 100% for both treatment groups; no relapses were observed after 8 weeks of follow-up.

Conclusions. This is, to our knowledge, the first study to demonstrate that voriconazole is as well tolerated and effective as itraconazole for the long-term treatment of paracoccidioidomycosis.

Paracoccidioidomycosis, previously known as South American blastomycosis, is a subacute or chronic systemic mycosis caused by *Paracoccidioides brasiliensis,* a thermally dimorphic fungus [1]. The primary pulmonary infection is subclinical in most cases, and individuals may remain infected throughout life without ever developing clinical signs. A small proportion of patients may first present weeks to months after inhalation of the fungus (acute or subacute form). Most patients develop symptoms of the disease years after the acquisition of the infection because of reactivation of the quiescent foci (chronic form). In both clinical forms, the disease may disseminate, involving many organs, especially the lungs, oropharyngeal mucous membrane, skin, lymph nodes, adrenal glands, and the CNS [2]. Without treatment, the natural evolution of the disease is typically death. In patients with immunosuppression, such as AIDS, the infection can progress to full-blown disseminated disease [3].

Paracoccidioidomycosis is considered to be the most important systemic endemic mycosis affecting South America [2–4]. The prevalence of this infection varies among regions of endemicity, and it is estimated that the incidence of paracoccidioidomycosis ranges from 1 to 3 cases per 100,000 inhabitants in regions where the disease is endemic. However, because the reporting of paracoccidioidomycosis is not compulsory, it is difficult to determine accurately the number of people affected by the disease [3]. Sporadic cases reported in the United States, Europe, and Japan have occurred in individuals who

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had lived in Latin American regions where the disease is endemic. Therefore, paracoccidioidomycosis should also be regarded as a disease of travelers who have spent extended periods of time in areas of endemicity [4].

Itraconazole is considered to be the standard treatment for mild and moderate clinical forms of paracoccidioidomycosis, compared with ketoconazole, fluconazole, and the sulfonamides. The mean duration of itraconazole therapy for paracoccidioidomycosis is 6 months (range, 3–12 months), depending on the assessment criteria [5–7]. Conventional or lipid formulations of amphotericin B are indicated to treat severe disseminated cases in patients who are intolerant of other agents or have refractory infections. Regardless of its toxicity, the rate of relapse associated with amphotericin B is generally higher than that associated with itraconazole (20%–30% of cases) [2]. Voriconazole is an extended-spectrum triazole antifungal agent that is available in both oral and intravenous formulations. According to in vitro susceptibility data, *P. brasiliensis* is highly sensitive to voriconazole, but this triazole has never been evaluated in the clinical treatment of paracoccidioidomycosis [8]. A pilot study was conducted to investigate the efficacy, safety, and tolerability of voriconazole in the long-term treatment of acute or chronic paracoccidioidomycosis, with itraconazole as the control treatment.

METHODS

Study design. Eligible patients were aged ⩾18 years and could be treated as outpatients or inpatients. All patients were required to have received a diagnosis of acute or chronic paracoccidioidomycosis within 4 weeks prior to study entry, documented by either positive histopathologic examination results, with evidence of yeast cells consistent with *P. brasiliensis,* or culture positive for *P. brasiliensis.* The study was conducted in compliance with the 1996 revisions to the Declaration of Helsinki, as well as with national and local regulations. Signed, written informed consent was obtained prior to any study-related procedures.

Patients were ineligible if intravenous therapy was required or if they had received treatment with drug(s) that were active against *P. brasiliensis* (i.e., amphotericin B, sulfonamides, ketoconazole, fluconazole, or itraconazole) for >72 h during the 2 weeks prior to study entry. Patients with active tuberculosis, end-stage liver disease or cirrhosis, or abnormal liver function test (LFT) values (aspartate aminotransferase level or alanine aminotransferase level >2 times the upper limit of normal and alkaline phosphatase level or total bilirubin level >2 times the upper limit of normal), serum creatinine level >2.5 mg/dL, or presence of end-stage renal disease requiring long-term dialysis were also excluded.

Patient populations. Patients were randomized according to a computer-generated pseudorandom code to receive voriconazole or itraconazole in a 2:1 ratio. The intent-to-treat population included all patients who received ⩾1 dose of initial randomized study treatment. The safety population included all patients who received ⩾1 dose of study treatment. The treatment-evaluable population, used for all efficacy assessments, included all patients who had received a confirmed diagnosis of paracoccidioidomycosis during the 4 weeks prior to study entry, received ⩾6 months of study treatment, received no concomitant medication at study entry or during the study that significantly affected efficacy, and did not violate any significant study entry criteria.

Drug administration. Voriconazole tablets were given orally (200 mg twice daily), with a loading dose of 400 mg given twice on the first day of therapy. Doses were received at least 1 h before or 1 h after a meal and were reduced by 50% in patients weighing <40 kg. Itraconazole capsules were given orally (100 mg twice daily) and were taken with a full meal. Patients were expected to receive treatment for 6 months (minimum) to 1 year (maximum)—the actual duration of treatment was determined by the individual investigator. Patients discharged from the hospital while receiving therapy were provided with a minimum of 4-weeks supply of study treatment. Patients were requested to return all bottles or blister packs at the next site visit, so that compliance could be monitored.

Evaluations. Before randomization, each patient was categorized as having acute or chronic paracoccidioidomycosis, and the date of onset of symptoms and details of prior treatment with any drug that was active against *P. brasiliensis* were recorded.

The positive culture result or histopathologic confirmation of diagnosis was reviewed, and isolates were tested for in vitro antifungal susceptibility testing at a central laboratory. Stock inoculum suspensions were prepared according to the Clinical Laboratory Standards Institute M27-A2 document [9], with certain modifications. Yeasts were grown on brain heart infusion agar (Remel) for 7 days, with final test inocula sizes ranging from 1.2×10^3 CFU/mL to 3.8×10^3 CFU/mL. Drug dilutions were prepared 100× the final concentration in dimethyl sulfoxide (for voriconazole, itraconazole, and amphotericin B) or sterile water (for fluconazole) and then diluted in standard RPMI-1640 medium to yield 2-fold drug concentrations of 128–0.25 μg/mL (for fluconazole) and 16–0.03 μg/mL (for other agents). Each microdilution well containing 100 μL of the 2-fold drug concentrations was inoculated with 100 μL of the diluted 2-fold inoculum suspension (the final volume in each well was 200 μL) and was then incubated in ambient air at 35°C. MICs were defined as the lowest concentrations that showed either 50% (for triazoles) or 100% (for amphotericin B) growth inhibition, compared with the control well, and were recorded by visual examination on days 3 and 4. Quality control isolates were tested in the same manner.

A chest radiograph was required of all patients, and CT was also performed if clinically indicated. Blood and urine samples were obtained for laboratory safety tests; these samples were serum tested for paracoccidioidomycosis antibodies by a double-immunodiffusion method [10]. Clinical signs and symptoms of fungal infection, as well as mycological and radiological assessment of response (if clinically appropriate), were recorded at weeks 1, 2, 4, 8, 12, and 24 and at the end of treatment (EOT). The final receiving-treatment evaluation occurred at EOT or at week 52, whichever was first.

Signs or symptoms of paracoccidioidomycosis were categorized as grade 0, 1, 2, 3, or 4 (none, mild, moderate, severe, or life threatening, respectively) [1]. The global response to treatment, which incorporated clinical, radiological, mycological, and serological responses, as applicable, was assessed at weeks 12 and 24 and, for patients who received >6 months of treatment, at weeks 36 and 52. In comparisons with baseline findings, global response was classified as complete, partial, stable disease, or failure, as described elsewhere [5]. In the present study, complete or partial global responses were classified as satisfactory, and stable disease or failure global responses were classified as unsatisfactory.

For patients with a complete or partial global response or stable disease at EOT, follow-up evaluations were performed 8 weeks after EOT. The follow-up response was compared with findings at EOT and categorized as cured (continued resolution), improved (further improvement), stable (no improvement), or relapsed (deterioration).

Removal of patients from treatment or assessment. Severe abnormalities in LFT values or serum creatinine concentrations exceeding predetermined values were grounds for patient withdrawal from treatment. All patients who discontinued initial randomized study treatment prior to week 12 were followed up to week 12, regardless of changes in therapy. EOT assessments were performed at the time of discontinuation of initial randomized study treatment, and the reason for discontinuation was recorded.

Safety assessments. Adverse events (AEs), clinically significant changes in physical examination findings, and abnormal objective test findings (e.g., laboratory abnormalities) that resulted in a change in study treatment dosage or discontinuation were recorded throughout the study. Because of the anticipated long duration of therapy (>6 months), an additional objective of this study was to collect data relating to the long-term tolerability and safety of voriconazole, with particular emphasis on AEs affecting the eyes. The details of the analyses performed and the results of these investigations will be reported separately.

Statistical design. No formal statistical determination of the sample size was performed, because this was a pilot study. A sample size of 42 patients (28 of whom received voriconazole and 14 of whom received itraconazole) was considered to be adequate to allow clinical evaluation and comparison of patients colonized with this rare pathogen. Patients who withdrew from the study prior to completing 6 months of study medication were replaced.

RESULTS

Patients. Fifty-nine patients were screened, and 53 were randomized to treatment (35 received voriconazole, and 18 received itraconazole). In the voriconazole group, there were 34 male patients and 1 female patient, with a mean age of 48.3 years (table 1). In the itraconazole group, there were 17 male patients and 1 female patient, with a mean age of 48.7 years. All but 1 patient had chronic paracoccidioidomycosis; the remaining patient, a 19-year-old man in the itraconazole group, received a diagnosis of acute disease. The median duration from first diagnosis of illness to study drug initiation was 1.33 years for patients in the voriconazole group and 0.98 years for patients in the itraconazole group. The 6 patients who did not receive study drug had demographic characteristics that were similar to those of the treatment groups. Acholoridria was not clinically detected in both groups.

Study populations. All 35 patients randomized to the voriconazole group received ⩾1 dose of initial study drug and were included in the intent-to-treat and safety populations. Five patients who received voriconazole were not included in the treatment-evaluable population; 2 did not receive a confirmed diagnosis of paracoccidioidomycosis at study entry, 1 died after 7 weeks of treatment (with no evidence of disease on autopsy), and 2 were withdrawn from treatment because of increased LFT values. All 18 patients randomized to receive itraconazole were included in the intent-to-treat and safety populations. One patient who received itraconazole was excluded from the treatment-evaluable population; treatment was discontinued after 36 days, when it was discovered that the baseline alkaline phosphatase level was increased.

Clinical symptoms and signs. The most common complaint in patients with documented paracoccidioidomycosis was weight loss, followed by cough and dyspnea. Oropharyngeal lesions were the most common sign on physical examination, followed by lymphadenopathy, dysphonia, and skin lesions. Hepatomegaly was noted in 4% of patients; none were found to have splenomegaly (table 2).

Sites of infection. All patients had lung involvement, with chest radiograph findings consistent with paracoccidioidomycosis. The second most common infection site was the oral mucosa, with oropharyngeal involvement (in 76% of patients) or laryngeal disease (22%). Other sites of infection included the lymph nodes (in 53% of patients) and skin (22%). There was 1 case with both lung and CNS involvement.

Diagnosis. Forty-five patients (85%) had histological evi-

Table 1. Demographic characteristics of patients receiving study drug.

Characteristic	Voriconazole group (n = 35)	Itraconazole group (n = 18)
Ratio of male to female patients	34:1	17:1
Age, mean years (range)	48.3 (30–86)	48.7 (19–70)
Ethnicity		
White	32	12
Black	1	1
Other	2	5
Duration from first diagnosis of illness to study drug initiation, median years	1.33	0.98

NOTE. Data are no. (%) of patients, unless otherwise indicated.

dence of *P. brasiliensis* in a biopsy specimen. In addition, 18 patients (34%) had a result of a wet mount of a sputum, bronchoalveolar lavage, or mucous membrane sample that was positive for *P. brasiliensis*. Nine patients had positive culture results at baseline; 6 isolates from these patients were subcultured for susceptibility tests. Susceptibility test results (MICs) were as follows: voriconazole, ≤0.01 μg/mL to 0.12 μg/mL; itraconazole, ≤0.01 μg/mL to 0.06 μg/mL; fluconazole, 0.25–1.0 μg/mL; and amphotericin B, 0.3–0.5 μg/mL (table 3).

Duration of therapy. The median duration of therapy in the safety-evaluable population was 169 days (range, 5–353 days) for patients treated with voriconazole and 199.5 days (range, 32–363 days) for patients treated with itraconazole. The percentage of patients who received >90 days of treatment was 91.4% in the voriconazole group and 94.4% in the itraconazole group.

Safety and tolerability. The percentage of treatment-related AEs was higher in the voriconazole group than in the itraconazole group (82.9% vs. 55.6%; $P < .05$). The frequency of treatment-emergent AEs is shown in table 4. The most common treatment-related AEs included abnormal vision, chromatopsia, rash, and headache in the voriconazole group and bradycardia and headache in the itraconazole group. There were 10 severe AEs reported among 4 patients in the voriconazole group, and there were 3 severe AEs reported among 2 patients in the itraconazole group. Three of these AEs (pain, visual hallucinations, and increased LFT values) reported in the voriconazole group and 1 (palpitations) reported in the itraconazole group were considered to be related to the study treatment. Two patients receiving voriconazole had treatment temporarily discontinued because of treatment-related AEs (abdominal pain and epigastralgia). Sixteen patients receiving voriconazole reported ≥1 treatment-related visual AE, although none of these necessitated dose reduction or discontinuation of therapy. No visual AEs were considered to be serious or severe, and none led to a dose reduction or discontinuation. Full details of the long-term visual safety data collected during this study will be presented elsewhere.

Six patients who received voriconazole and 1 patient who received itraconazole reported treatment-related skin rashes, but none of these rashes required dose reduction or cessation of therapy, and all resolved satisfactorily. Four patients who received voriconazole also reported mild treatment-related photosensitivity, but these events also resolved without requiring a change in study drug dose.

Two patients who received voriconazole were withdrawn from treatment, as required by the protocol, because of study drug–related increased serum alkaline phosphatase levels and LFT values (alanine aminotransferase, aspartate aminotransferase, and γ–glutamyl transferase levels). The frequency of LFT abnormalities was slightly higher among patients receiving voriconazole than among patients receiving itraconazole, although the median changes from baseline were similar in both groups and were small for most laboratory parameters.

Global response. In the intent-to-treat populations, the rate of satisfactory response (complete or partial global response) was 88.6% in the voriconazole group and 94.4% in the itraconazole group. One patient died after 52 days of treatment with voriconazole because of an aortic aneurysm but had no evidence of paracoccidioidomycosis on autopsy. Forty-seven patients (30 of whom received voriconazole and 17 of whom received itraconazole) who received a confirmed diagnosis of paracoccidioidomycosis received ≥6 months of continuous study treatment and were included in the treatment-evaluable population. The rate of satisfactory response among this population was 100% for both treatment groups. There were no relapses among the patients who had a complete response at EOT in either treatment group after 8 weeks of follow-up.

Table 2. Symptoms and signs in patients with paracoccidioidomycosis who were treated with voriconazole or itraconazole.

Characteristic	No. (%) of patients: Voriconazole group (n = 33)	Itraconazole group (n = 18)
Weight loss	26 (79)	15 (83)
Cough	22 (67)	13 (72)
Dyspnea	20 (61)	32 (63)
Fatigue	20 (61)	11 (61)
Weakness	22 (67)	9 (50)
Chest pain	8 (24)	7 (39)
Mucosal lesions	25 (76)	14 (78)
Lymphadenopathy	16 (48)	11 (61)
Dysphonia	10 (30)	1 (6)
Skin lesions	6 (18)	1 (6)
Hepatomegaly	2 (6)	0 (0)
Neurological signs	1 (3)	0 (0)

Table 3. Results of antifungal susceptibility tests for *Paracoccidioides brasiliensis.*

Patient	Strain source	Incubation time, h	MIC, μg/mL			
			Voriconazole	Fluconazole	Itraconazole	Amphotericin B
11	Lymph node aspirate	72	<0.01	0.25	<0.01	0.5
		96	<0.01	0.25	<0.01	0.5
16	Skin biopsy	72	<0.01	0.25	<0.01	0.5
		96	<0.01	0.25	<0.01	0.5
41	Lymph node biopsy	72	0.06	0.5	0.01	0.2
		96	0.12	1.0	0.03	0.2
65	Oral mucosa biopsy	72	<0.01	1.0	0.01	0.03
		96	<0.01	1.0	0.06	0.06
72	Lymph node biopsy	72	<0.01	0.5	<0.01	0.12
		96	0.03	1.0	<0.01	0.12
74	Lung/Sputum	72	<0.01	0.2	<0.01	0.03
		96	0.01	0.5	<0.01	0.06

One patient, a 37-year-old man from southern Brazil with both pulmonary and CNS paracoccidioidomycosis, responded particularly well to voriconazole treatment. He presented with weakness, weight loss, dyspnea, and a headache associated with vomiting and dizziness. A chest CT showed extensive infiltrates with fibrosis (ground glass appearance); a brain CT revealed 4 intraparenchymal lesions with surrounding edema. The largest lesion (diameter, 4 cm) was in the right frontal lobe; the others were in the right temporal, parietal, and cerebellar lobes. Fibroscopic examination of a bronchoalveolar lavage specimen revealed *P. brasiliensis,* and the patient initiated treatment with voriconazole (400 mg orally twice daily for 1 day, followed by 200 mg orally twice daily). The patient tolerated 12 months of voriconazole treatment, with significant clinical and radiological improvement; a second head CT showed marked improvement, with a decrease in both edema and contrast enhancement (figure 1).

Radiological response. Radiological response was assessed in 39 patients with paracoccidioidomycosis. In 23 patients (76.7%) in the voriconazole group, the radiological response was considered to be completed, and in 1 patient (3.3%), the radiological response was considered to be partial, whereas 15 patients (88.2%) in the itraconazole group presented with complete radiological responses. An example of complete radio-

Table 4. Treatment-emergent adverse events reported by >2 patients in either treatment group.

Adverse event	Voriconazole group (n = 35)		Itraconazole group (n = 18)	
	All events	Treatment related	All events	Treatment related
No. of patients who experienced adverse events (total no. of adverse events)	32 (138)	29 (72)	16 (47)	10 (17)
Abdominal pain	4	4	0	0
Fever	1	0	3	0
Flu syndrome	4	0	4	0
Headache	8	6	4	2
Photosensitivity reaction	4	4	0	0
Bradycardia	2	2	6	5
Cheilitis	3	2	1	0
Dizziness	5	4	2	1
Insomnia	4	2	0	0
Respiratory tract infection	7	0	2	0
Rash	7	6	1	1
Skin disorder	4	2	1	1
Abnormal vision	13	13	0	0
Chromatopsia	7	7	0	0
Increased liver enzyme levels	3	3	0	0

NOTE. Data are no. of adverse events, unless otherwise indicated.

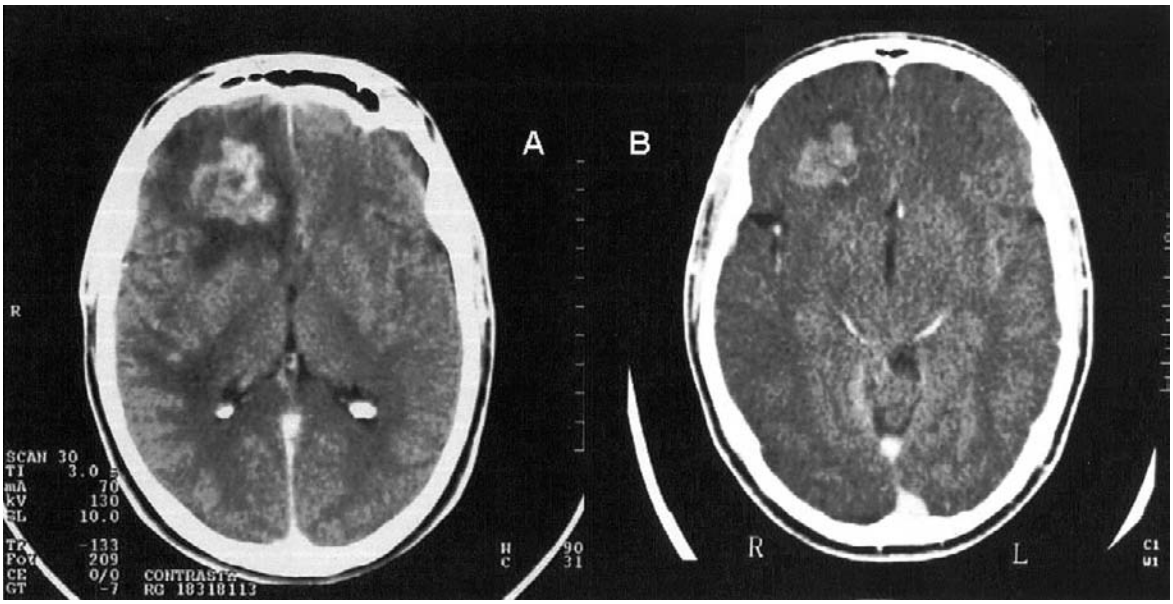

Figure 1. Head CTs for a patient with CNS paracoccidioidomycosis. *A,* Head CT at baseline, showing a heterogeneous and expansive hypodense lesion (diameter, 4 cm), with surrounding edema in the right frontal lobe. Note that the frontal horn of the right lateral ventriculum is deformed by compression. *B,* Head CT for the same patient after 12 months of therapy with voriconazole, with significant improvement of all lesions and disappearance of edema reaction and ventricular compression.

logical response in a voriconazole-treated patient with chronic paracoccidioidomycosis is shown in figure 2.

Immunological response. Anti–*P. brasiliensis* antibody titers at baseline and at EOT were available for 32 patients in the treatment-evaluable population. Twelve patients (63.2%) in the voriconazole group and 5 patients (38.5%) in the itraconazole treatment group had an undetectable titer or a decrease of at least 2 dilutions from baseline to EOT.

DISCUSSION

P. brasiliensis differs from other pathogenic fungi, because it is a very sensitive organism when exposed to antifungal drugs; even sulfonamides can inhibit its growth [11]. A large therapeutic armamentarium is available for patients with paracoccidioidomycosis. Several classes of antimycotic drugs have been used in the treatment of paracoccidioidomycosis, including sulfonamides (sulfadiazine, sulfadoxine, sulfamethoxypyridazine, cotrimazine, and trimethoprim-sulfamethoxazole), amphotericin B, azoles (ketoconazole, itraconazole, and fluconazole), and terbinafine [6, 7, 12, 13].

Itraconazole is considered to be first-line treatment for patients with mild-to-moderate forms of paracoccidioidomycosis [5, 6, 14]. This recommendation is based on the results from a noncomparative study of 47 patients, most of whom had multifocal disease and received itraconazole (100 mg/day) for a mean duration of 6 months. A scoring system indicated a favorable response in 43 patients (89%) [5]. In a randomized study, itraconazole was noninferior to sulfadiazine and ketoconazole for induction-phase therapy for patients with moderate paracoccidioidomycosis, [12]; anti–*P. brasiliensis*-specific antibody levels decreased after 6–10 months of therapy with all 3 drugs. Although published data from controlled studies with clear end points are limited, itraconazole has been suggested as a therapeutic option that would allow the control of mild and moderately severe cases and significantly shorten the duration of treatment for paracoccidioidomycosis, compared with sulfonamide therapy [6, 7]. In nonrandomized studies, itraconazole had been prescribed at the daily dose of 100–200 mg, but controversial results were described concerning recurrence. The rate of recurrence may vary from 0% to 15% after a median time of 12 months, depending on comorbidities, such as alcoholism and AIDS, as well as on the itraconazole dose (100 mg/day vs. 200 mg/day) [5, 6, 12].

The efficacy of voriconazole for the treatment of paracoccidioidomycosis that was demonstrated in this study is consistent with the previously reported high in vitro sensitivity of *P. brasiliensis* to voriconazole [8]. There were no differences with respect to clinical, mycological, and radiological responses between the 2 groups of patients. In addition, the proportion of patients with a favorable serological response to treatment was higher in the voriconazole group than in the itraconazole group.

The involvement of *P. brasiliensis* in the CNS has been described frequently [15]. Patients with CNS paracoccidioidomycosis who receive diagnoses and are treated early have a favorable outcome [16]. Although itraconazole has been used

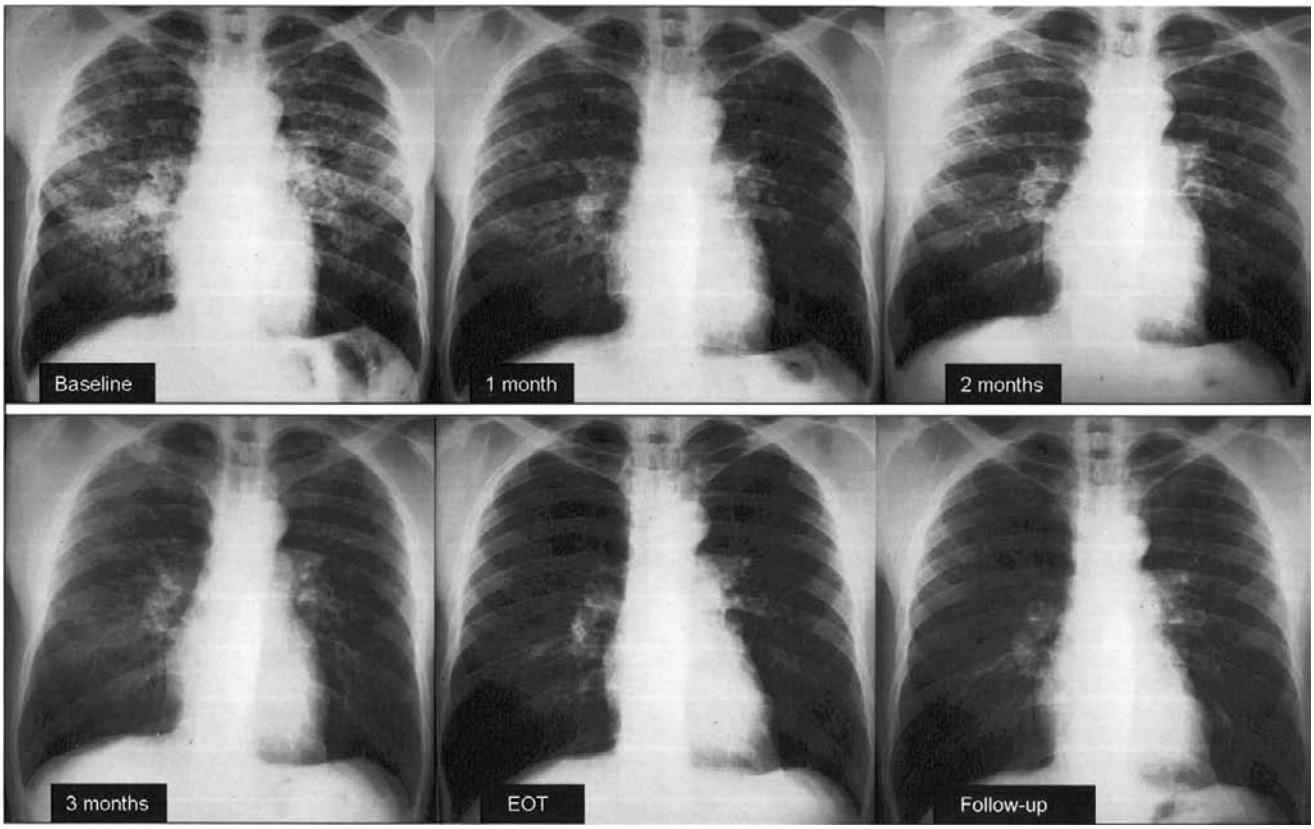

Figure 2. Complete radiological response in a patient with chronic paracoccidioidomycosis who was treated with voriconazole. A progressive improvement of the pulmonary radiological images is clearly observed during treatment, and a follow-up stabilization pattern is achieved. EOT, end of treatment.

successfully to treat neuroparacoccidioidomycosis, the poor penetration of this agent into the CNS may limit its use in such cases [17]. Trimethoprim-sulfamethoxazole has also been reported to be effective for the treatment of CNS paracoccidioidomycosis, but the duration of treatment required may be up to 3 years [18]. Our study included a patient with CNS paracoccidioidomycosis who responded successfully after 1 year of treatment with voriconazole. In fact, voriconazole penetrates the CNS well and has been successful in the treatment of CNS infections caused by other fungi [19, 20].

Although both itraconazole and voriconazole were well tolerated for the relatively long duration of the study, slightly more AEs were reported in patients treated with voriconazole. However, these AEs were mild and included mainly transient visual disturbances and skin reactions. The AE profile of voriconazole was similar to that described previously [21].

Patients with severe paracoccidioidomycosis can require initial intravenous treatment, and amphotericin B is considered to be the drug of choice [4, 14]. On the basis of the results of this study, voriconazole (also available in an intravenous formulation) should be evaluated as an alternative to amphotericin B for the initial treatment of severe paracoccidioidomycosis, especially considering the relapse rate [2] and the toxicity associated with amphotericin B deoxycholate. Although lipid-based formulations have better tolerability than does conventional amphotericin B, they have been associated with treatment failures for paracoccidioidomycosis [22].

In summary, the results of this comparative multicenter study reveal that voriconazole is as effective as itraconazole for the treatment of paracoccidioidomycosis. The availability of oral and intravenous formulations provides new treatment options for mild-to-severe cases of paracoccidioidomycosis. Although itraconazole remains the treatment of choice for paracoccidioidomycosis, voriconazole was generally well tolerated as long-term treatment for paracoccidioidomycosis and is a promising agent. The relative efficacy of voriconazole to itraconazole would appropriately be evaluated in a larger, adequately powered, double-blinded study.

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