Itraconazole vs. trimethoprim–sulfamethoxazole: A comparative cohort study of 200 patients with paracoccidioidomycosis

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Abstract

Paracoccidioidomycosis (PCM) is a systemic mycosis endemic to Latin America. Brazil accounts for approximately 80% of cases, where it represents a major public health issue due to its disabling impact and the number of premature deaths it causes. We present a retrospective cohort study that was conducted in order to better understand factors that relate to cure of the infection in the treatment of 200 patients with PCM. We evaluated the influence of sociodemographic and clinical factors as well as therapeutic regimen (trimethoprim–sulfamethoxazole [TMP–SMX] and itraconazole) on the progress of PCM (cure and noncure). There was a higher incidence of cure (83%) among patients who regularly received treatment for their infections and completed the treatment protocol. Moreover, itraconazole (86.4%) was significantly superior to TMP–SMX (51.3%) in terms of cure rate and had a median treatment period that was significantly shorter (12 months) than that for TMP–SMX (23 months). A Cox proportional hazard regression model showed that use of itraconazole increased the hazard of cure, regardless of sex, age, education, clinical form, completion of treatment, and regularity. Although the results of this study show that itraconazole was the best treatment option for PCM patients, a double-blind, randomized, controlled trial is necessary to confirm this conclusion.

Key words: paracoccidioidomycosis, treatment, trimethoprim-sulfamethoxazole (TMP–SMX), itraconazole.
Introduction

Paracoccidioidomycosis (PCM) is a systemic mycosis caused by the thermomorphogenic fungus *Paracoccidioides brasiliensis* [1], which is endemic to most countries of Latin America, especially Brazil. The latter accounts for at least 80% of all reported cases [2], and 3360 new cases per year are estimated to occur with a 5% mortality rate [3]. In addition, PCM is the eighth leading cause of death from predominantly chronic or recurrent infectious and parasitic diseases [4]. The disease affects primarily rural workers through contact with contaminated soil. Barrozo and colleagues [5] suggested that climatic anomaly, namely, the El Niño event, could influence endemic mycoses incidence, determining clusters of cases of the acute form of PCM. Those most affected are aged 30–50 years and more than 80% of the cases occur in males [6]. More recently, Bellissimo-Rodrigues and colleagues reported that most patients (73.6%) had the chronic form of PCM, with a mean age of 47.1 years, 93.9% were males and 84.4% were white [7]. In most cases, the affected individuals were in their most productive period of life, which causes a big social and economic impact [8]. *P. brasiliensis* differs from other pathogenic fungi in that it is very sensitive to antifungal drugs, even sulfonamides can inhibit growth. Consequently, a large therapeutic armamentarium is available for patients with PCM, including sulfonamide derivatives (sulfadiazine, sulfadoxine, sulfaethoxypyridazine, cotrimazine, and trimethoprim–sulfamethoxazole [TMP–SMX]), amphotericin B, azoles (e.g., ketoconazole, itraconazole, fluconazole, voriconazole, and posaconazole), and terbinafine [9–12].

There are few comparative clinical studies [13–15] of the pharmacotherapy used for PCM. In a comparative study of itraconazole and TMP–SMX, Queiroz-Telles et al. demonstrated that itraconazole was the best option for PCM as it significantly reduced the duration of treatment [16]. Marques et al. [14] evaluated the clinical, serological, and radiological features that developed in 54 PCM patients (37 with the chronic form and 17 with the juvenile form), 32 of whom were treated with amphotericin/sulfonamides and 22 with ketoconazole, and reported that neither of the two therapeutic regimens was superior to the other. Wanke and Aidê reported that TMP–SMX used to treat mild to moderate forms of PCM did cure up to 80% of their patients [8]. Typically, the treatment for PCM is long term (lasting as long as 2 years), and adherence with therapy is important for success [12]. Occasionally, the patient requires subsequent treatments to achieve cure.

Despite the shortage of comparative therapeutic studies [10], the literature suggests that treatment with itraconazole (once a day for 6 to 18 months) leads to control of mild and moderate forms of PCM in a short period of time. In contrast, treatment with TMP–SMX twice a day for 12 to 24 months can be useful for mild and moderate cases [12,17]. The results from this cohort study, despite its limitation, may enhance our understanding of the association between risk factors or treatments and clinical outcome and, in this way, provide information needed for appropriate planning of randomized, controlled trials [18].

Generally, survival analysis involves a collection of statistical procedures as part of data analysis for which the outcome variable of interest is time until an event occurs. An event can be defined as death, incidence, recovery, or cure of a disease or any designated experience of interest that may happen to an individual [19]. Kaplan–Meir survival curves can be used to analyze data from these cohort studies when the target parameter is the time until the occurrence of an event [19,20]. In the present cohort, 22-year study, we investigated the risk factors associated with the events “cure” and “not cure” in the management of patients with PCM treated at Evandro Chagas Clinical Research Institute (Ipec), Oswaldo Cruz Foundation, Rio de Janeiro, Brazil (Fiocruz).

Patients and methods

This retrospective, cohort study of 316 patients with PCM took place from 1993 to 2009. All patients had mycologically proven infection, confirmed by the observation of *P. brasiliensis* in biological material. Excluded were patients (*n* = 7) who had received amphotericin B as the initial treatment for PCM and patients (*n* = 109) who were not treated in accordance with the Brazilian Consensus on PCM (Fig. 1) [12]. Thus, 200 patients were included in the investigation, which was approved by the institutional review board of Ipec-Fiocruz (prot. no 0039.0.009.000–09, 8 October 2009).

Data were collected from medical records using a standardized form that allowed for the recording of sociodemographic data (sex, age, schooling, and domicile), comorbidity, tobacco smoking, cure, relapse, clinical resistance, drug prescription, intolerance, treatment regularity, severity of PCM, complete/Incomplete treatment, abandonment of treatment, and death. Treatment regularity was defined as a patient not missing any doses, either in the initial intensive phase or in the suppressive continuation phase of therapy.

The treatment protocol for chronic forms of PCM (adult type) was oral TMP–SMX 480/2400 mg/d for 12 months in mild cases and for 24 months in moderate cases. Oral
316 patients were treated for PCM

7 patients were treated with amphotericin B

109 patients were not treated according to Brazilian Consensus

200 patients were included

119 patients were treated with TMP–SMX

81 patients were treated with itraconazole

7 patients were treated with amphotericin B

109 patients were not treated according to Brazilian Consensus

Patients excluded

16% relapse

2.5% clinical resistance

18.5% abandonment

119 patients were treated with TMP–SMX

86.4% cure

6.2% relapse

1.2% clinical resistance

6.2% abandonment

81 patients were treated with itraconazole

51.3% cure

16% relapse

2.5% clinical resistance

9.2% intolerance

2.5% death

Figure 1. General overview of the cohort study. Organogram of the number of patients with paracoccidioidomycosis (PCM) for each type of treatment and corresponding percentage for outcome at the end of treatment. TMP–SMX, trimethoprim–sulfamethoxazole.

Itraconazole, 200 mg/d for 6 to 9 months, was used for mild disease and 200 mg/d for 12 to 18 months for moderate disease. The treatment protocol for neuroparacoccidioidomycosis was TMP–SMX 480/2400 mg/day for 24 months.

Patients with severe forms of PCM who required hospitalization were treated with intravenous TMP–SMX at a dose of two ampoules (each vial contained 80 mg of TMP and 400 mg SMX) every 8 h until clinical improvement allowed the introduction of oral antifungal therapy [12]. Prolonged treatment (24 months) with oral TMP–SMX was provided after intravenous administration of TMP–SMX had been stopped. TMP–SMX or itraconazole therapy was chosen based on Ipec stock availability, drug–drug interactions, allergy, clinical resistance, intolerance to sulfonamides, and contraindications.

The favorable outcome was cure or apparent cure. Cure was defined as the simultaneous occurrence of three favorable outcomes (clinical, radiological, and immunological) that contributed to the decision to interrupt drug treatment. The clinical criterion for cure included disappearance of signs and symptoms of the disease, for example, healing of the skin and mucosal lesions, regression of lymphadenopathy, and recovery of normal body weight. The radiological criterion for cure was stabilization of pulmonary scar images for at least 3 months, with progressive improvement of the pulmonary radiological images [12,15]. Immunological cure was associated with long-lasting (1 or more years) negative or low titers (1:1 or 1:2) of the double-immunodiffusion test for PCM without clinical manifestations of the infection [21,22]. All patients who were considered to have been cured or appeared cured remained healthy for at least 4 years after ending treatment.

The most important unfavorable outcomes were defined as relapse (reappearance of signs and symptoms after a period of clinical remission) or clinical resistance (persistent lesions after at least 2 months of regular and continual therapy). Other unfavorable outcomes were intolerance (defined as the inability or refusal to continue the medication because of adverse drug reactions), abandonment of treatment (defined as the patient who never returned to the service), and death.

The clinical follow-up included complete blood count, platelet count, medical anamnesis, and physical examination biweekly in the first month, then once every 1 to 3 months until the end of treatment (scheme of treatment with TMP–SMX or itraconazole). In both schemes of postantifungal treatment, the follow-up lasted at least 4 years.
Data analysis

In the descriptive analysis, we associated variables to outcome (cure at the end of treatment). Regarding the different times of patient entrance in this open cohort, the survival analysis considered the initial and final dates of treatment. For exploratory survival analysis [23], the Kaplan-Meier method was used to estimate the probability of survival until the occurrence of cure. Kaplan-Meier curves were stratified according to each variable (sociodemographic, clinical, and treatment) and were compared by log-rank test and Breslow test. The simple Cox proportional hazards regression model was used to estimate the probability until the occurrence of cure according to each variable, referred to as the crude hazard ratio. Afterward, the significant variables from previous analyses were inserted into the multiple Cox proportional hazard regression models, in which the hazards of cure (or incidence of cure) were interpreted as hazard ratios (HRs), controlled by sex, age group, education, clinical form, treatment completion, and regularity. Last, crude and adjusted HRs, which were obtained in the simple Cox model and the multiple Cox model, were compared in order to detect possible confounding or modifying effects. The 5% significance level was used in all statistical tests.

Survival analysis was performed using package survival in statistical software R 2.14 [24].

Results

Exploratory analysis

Samples were obtained from 178 men (89.0%) and 22 women (11.0%). PCM most commonly affected patients aged 40–59 years (127 patients; 63.5%), followed by individuals aged 20–39 years (39 patients; 19.5%), those aged ≥60 years (30 patients; 15.0%), and two patients aged ≤19 years (1.0%). One hundred and thirty-eight patients (69.0%) had not completed elementary education or were illiterate and 56 (28.0%) presented with at least a complete elementary education. Regarding the severity of PCM, 60 (30.0%) had severe forms of the disease, 111 patients (55.5%) had moderate involvement, and 29 (14.5%) had mild PCM manifestations. Comorbidities were observed in 161 patients (80.5%), and tobacco smoking was reported for 174 patients (87%; Table 1).

TMP–SMX was used to treat 119 patients (59.5%) and itraconazole was used for the remaining 81 patients (40.5%). One hundred and thirty-six patients (68%) had completed treatment and 20 (12%) did not.

Table 1. Distribution of variables according to cure outcome in the treatment of patients with PCM at Ipec-Fiocruz.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Cure</th>
<th>Crude hazard ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes, n (%)</td>
<td>No, n (%)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>15 (68.2)</td>
<td>7 (31.8)</td>
</tr>
<tr>
<td></td>
<td>Male*</td>
<td>116 (65.2)</td>
<td>62 (34.8)</td>
</tr>
<tr>
<td>Age, y</td>
<td>40–59</td>
<td>87 (68.5)</td>
<td>40 (31.5)</td>
</tr>
<tr>
<td></td>
<td>≥60</td>
<td>20 (66.7)</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td></td>
<td>≤39*</td>
<td>23 (56.1)</td>
<td>18 (43.9)</td>
</tr>
<tr>
<td>Education</td>
<td>Completed elementary school</td>
<td>43 (76.8)</td>
<td>13 (23.2)</td>
</tr>
<tr>
<td></td>
<td>Did not complete elementary school/illiterate*</td>
<td>85 (61.6)</td>
<td>53 (38.4)</td>
</tr>
<tr>
<td>Severity of PCM</td>
<td>Moderate</td>
<td>83 (74.8)</td>
<td>28 (25.2)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>26 (43.3)</td>
<td>34 (56.7)</td>
</tr>
<tr>
<td></td>
<td>Mild*</td>
<td>22 (75.9)</td>
<td>7 (24.1)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>No</td>
<td>27 (69.2)</td>
<td>12 (30.8)</td>
</tr>
<tr>
<td></td>
<td>Yes*</td>
<td>104 (64.6)</td>
<td>57 (35.4)</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td>No</td>
<td>14 (66.7)</td>
<td>7 (33.3)</td>
</tr>
<tr>
<td></td>
<td>Yes*</td>
<td>113 (64.9)</td>
<td>61 (35.1)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Itraconazole</td>
<td>70 (86.4)</td>
<td>11 (13.6)</td>
</tr>
<tr>
<td></td>
<td>TMP–SMX*</td>
<td>61 (51.3)</td>
<td>58 (48.7)</td>
</tr>
<tr>
<td>Complete treatment</td>
<td>Yes</td>
<td>113 (83.1)</td>
<td>23 (16.9)</td>
</tr>
<tr>
<td></td>
<td>No*</td>
<td>18 (28.1)</td>
<td>46 (71.9)</td>
</tr>
<tr>
<td>Treatment regularity</td>
<td>No</td>
<td>19 (29.2)</td>
<td>46 (70.8)</td>
</tr>
<tr>
<td></td>
<td>Yes*</td>
<td>112 (83.0)</td>
<td>23 (17.0)</td>
</tr>
</tbody>
</table>

Asterisk indicates reference category.

PCM, paracoccidioidomycosis; TMP–SMX, trimethoprim–sulfamethoxazole.
completed their treatment, and 64 patients (32%) abandoned treatment (never returned to our service). With respect to regularity of therapy, 135 patients (67.5%) completed the treatment according to Ipec protocol; the remaining patients (32.5%) were treated in an irregular manner (Table 1).

With respect to the organs involved in the present PCM cases, 168 patients had lung involvement, oropharyngeal mucous membranes were affected by the infection in 142 patients, adrenal glands in 5 patients, the central nervous system in 3 patients, and the intestines in 1 patient. As is obvious from the total number of patients and numbers of involved organs, 110 patients had multifocal disease. Considering treatment of patients with lung involvement, 85.9% were cured after itraconazole treatment, while only 52.9% achieved cure after TMP–SMX treatment. A similar result was observed in cases involving oropharyngeal mucous membranes. Cure was noted for 85.2% patients treated with itraconazole, but only 47.7% were cured with TMP–SMX treatment. Two examples of apparent clinical cure after itraconazole or TMP–SMX treatment in chronic PCM patients are shown in Figure 2.

Cure was achieved in 131 patients (65.5%) who were treated according to the Brazilian Consensus on PCM [12]. Negative outcomes ("not cure" after the treatment) were recorded in 69 (34.5%) patients, whereas some patients were classified as having a relapse (n = 24), clinical resistance (n = 4), were intolerant (n = 11), abandoned treatment (n = 27), or died (n = 3; Fig. 1).

Survival analysis

The log-rank test and Breslow test showed statistical significance in the survival curves of patients treated with TMP–SMX and itraconazole. Regarding treatment, the comparison between the curves indicated that the cure was achieved faster with itraconazole (median survival time was 12 months) when compared with those who used TMP–SMX (median survival time was 23 months).

According to the simple Cox model, treatment was the only variable that could explain the cure at the 5% significance level. Patients who used itraconazole achieved cure with higher hazard (crude HR = 2.13) than those managed with TMP–SMX (Table 2).

The multiple Cox model also showed that the type of treatment explained the occurrence of cure, even when these effects were controlled for sex, age group, education, severity of PCM, treatment completion, and...
Table 2. Predictor variables of the cure outcome in patients with PCM treated at Ipec-Fiocruz from 1987 to 2009, according to Cox regression.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference</th>
<th>Crude HR</th>
<th>Adjusted HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>1.14</td>
<td>1.19</td>
<td>0.496</td>
</tr>
<tr>
<td></td>
<td>Male*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>40–59</td>
<td>1.06</td>
<td>1.06</td>
<td>0.867</td>
</tr>
<tr>
<td></td>
<td>≥60</td>
<td>1.08</td>
<td>1.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤39**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>Completed elementary school</td>
<td>1.17</td>
<td>1.18</td>
<td>0.314</td>
</tr>
<tr>
<td></td>
<td>Did not completed elementary school*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of PCM</td>
<td>Moderate</td>
<td>0.91</td>
<td>0.89</td>
<td>0.790</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0.72</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regularity</td>
<td>Absence</td>
<td>0.63</td>
<td>0.77</td>
<td>0.067</td>
</tr>
<tr>
<td></td>
<td>Presence*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete treatment</td>
<td>Presence</td>
<td>1.62</td>
<td>1.11</td>
<td>0.450</td>
</tr>
<tr>
<td></td>
<td>Absence**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Use of Itraconazole</td>
<td>2.13</td>
<td>1.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>TMP–SMX*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Asterisk indicates reference category.
HR, hazard ratio; PCM, paracoccidioidomycosis; TMP–SMX, trimethoprim–sulfamethoxazole.

regularity. The use of itraconazole increased up to 1.99 times the occurrence (or hazard) of cure compared with the use of TMP–SMX (Table 2). We highlight that there were no interactions between controlling variables and type of treatment.

**Discussion**

We collected information from a cohort of 316 patients diagnosed with PCM and treated with TMP–SMX, itraconazole, or amphotericin B. A total of 116 patients were excluded from the study because their treatment did not conform with the Brazilian Consensus (n = 109) or treatment involved the use of amphotericin B (n = 7), which resulted in only 200 patients fulfilling the inclusion criteria for the study [12]. The studied population was composed primarily of men aged 40–59 years with the adult chronic form of the disease and profiles similar to those described in the literature [7,25,26]. Most patients had low levels of formal education, which is in agreement with information in the literature [7,15,27,28].

One important limitation of this study was its retrospective nature, as the data were collected from a nonrandomized study population. Because of this, the results should be interpreted with caution despite the fact that all patients in this study had a prolonged follow-up of at least 4 years after ending antifungal treatment. However, there are few reports in the medical literature concerning randomized, double-blind, controlled clinical trials that compare the efficacy of itraconazole with that of TMP–SMX in the treatment and cure of patients with PCM. The cohort study can provide important information concerning multiple exposure variables that influence outcomes in a study population. Regarding therapy, such studies may generate hypotheses and provide indication for the effect size, which is necessary for sample size calculations in randomized, controlled trials [29]. In this context, the present study shows a higher incidence of cure among patients treated with itraconazole (86.4%) than among those treated with TMP–SMX (51.3%). Our results support the general belief that itraconazole is the best treatment option for mild and moderate forms of PCM [12,27,30]. There were fewer negative outcomes for patients treated with itraconazole when compared with those treated with TMP–SMX. The relapse rate for itraconazole in the present study was 6.2%, which is similar to the 3%–5% found in other studies [30]. On the other hand, the relapse rate for sulfonamides was about 20%–30% [27,31], which was similar to the rate we report here (16%).

According to Brummer and colleagues, severe forms of PCM could result in poor prognosis [27]. Of the 69 patients who were not cured in the present study, 34 had severe forms of the disease, which could contribute to clinical resistance.
Marques reported that therapy for PCM could be influenced by severity, comorbidity, nutritional status of patients, and alcohol and tobacco consumption [17]. In this setting, we evaluated eight variables (sex, age, education, clinical form, comorbidities, tobacco smoking, complete or incomplete treatment, and treatment regularity) that could influence cure in patients with PCM. In our study, the Cox regression model demonstrated that patients who completed itraconazole treatment proved to have the best outcome.

Brummer and colleagues reported that disease progression was more frequent in males than in females, possibly due to hormonal differences [27]. The present study also indicated a lower cure frequency in male patients, but without statistically significant differences.

Usually, the acute/subacute form of the disease affects younger subjects, typically those aged <30 years, while the chronic form is characteristic of older patients (>30 years) [7,32]. After a variable interval, which can be up to 60 years, the clinical picture may change from a quiescent focus to open disease [17]. By considering the context, we observed a lower cure rate in patients aged <39 years and >59 years.

As noted previously, comorbidities and tobacco consumption could influence clinical treatment of PCM patients [17]. In our cohort study, although not statistically significant, a higher cure rate was observed in patients who did not present comorbidities. The same was observed for tobacco smoking by patients; this group had lower cure rates when compared with nonsmoking patients.

Only antifungal treatment was found in the present study to be a statistically significant factor affecting cure in PCM patients. Since therapy for PCM may require a prolonged period of time, we used a survival analysis that considers time until the occurrence of cure. The survival analysis showed that treatment can directly influence cure in PCM patients. In fact, the profiles of patients treated with itraconazole showed shorter periods until cure compared with those treated with TMP–SMX, that is, a median period of 23 months for TMP–SMX compared with 12 months for patients treated with itraconazole. Indeed, itraconazole significantly affected the cure rates of our patients: 86.4% with itraconazole and 51.3% with TMP–SMX. We believe that this difference is due to the regularity at which patients administered TMP–SMX; this is indicated by the fact that if regularity or adherence problems were removed from the analysis, the incidence of cure increased to 71.4%. The same was observed in the overall population of patients; when we excluded from analysis patients treated without regularity and adherence, the total cure percentage rose to 83%.

Based on our results, itraconazole was superior to TMP–SMX in terms of cure rate. This is consistent with the Guidelines in Paracoccidioidomycosis [12], which recommend itraconazole as a therapeutic option that allows the control of mild and moderate forms in the shortest period of time. However, a randomized, double-blind trial is needed to confirm the superiority of itraconazole over TMP–SMX in the treatment of PCM.

When analyzing only treatment with itraconazole for regularity and adherence, the cure rate increased to 95.4%. Despite the fact that itraconazole provides more convenient dosage schedules that require a shorter treatment period, our results suggest that treatment can be influenced by other factors that should be analyzed in a multidisciplinary context. In order to control for other factors (e.g., sex, age, education, clinical form, treatment completion, and regularity) related to cure, we performed a Cox proportional hazard regression model. From model results, we observed that patients who were treated with itraconazole had an increased hazard of cure. However, these results need to be interpreted with caution due limitation of the retrospective nature of our study, even considering the long follow-up of at least 4 years after treatment.

Itraconazole was superior to TMP–SMX in terms of cure rate. From survival analysis it was possible to observe that itraconazole had a median treatment period that was significantly shorter when compared with the period of TMP–SMX. In addition, it is possible to note that itraconazole has a fungicidal effect on *P. brasiliensis*, while sulfonamide derivatives are only fungistatic. The Cox proportional hazard regression model showed that use of itraconazole increased the hazard of cure compared with the use of the TMP–SMX, even when this effect was controlled by sex, age, education, severity of PCM, completion of treatment, and regularity. Although the results of this study show that itraconazole was the best treatment option for PCM patients, a double-blind, randomized, controlled trial is necessary to confirm this effect.

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**Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

**Author Contributions**

Conceived and designed the experiments: SRCB, GMSS, ACFV. Performed the experiments: SRCB, MCC, RLBC. Analyzed the data: SRCB, RVCO, GMSS, ACFV. Contributed reagents/materials/analysis tools: SRCB GMSS. Wrote the manuscript: SRCB, RVCO, GMSS, BW, ACFV.
References