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PARACOCCIDIOIDOMYCOSIS TREATMENT

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SUMMARY

Considered to be an emerging endemic mycosis in Latin America, paracoccidioidomycosis is characterized by a chronic course and involvement of multiple organs in immunocompromised hosts. Infection sequelae are mainly related to pulmonary and adrenal insufficiency. The host-parasite interaction results in different expressions of the immune response depending on parasite pathogenicity, fungal load and genetic characteristics of the host. A few controlled and case series reports have shown that azoles and fast-acting sulfa derivatives are useful treatment alternatives in milder forms of the disease. For moderate/severe cases, more prolonged treatments or even parenteral routes are required especially when there is involvement of the digestive tract mucosa, resulting in poor drug absorption. Although comparative studies have reported that shorter treatment regimens with itraconazole are able to induce cure in chronically-infected patients, there are still treatment challenges such as the need for more controlled studies involving acute cases, the search for new drugs and combinations, and the search for compounds capable of modulating the immune response in severe cases as well as the paradoxical reactions.

KEYWORDS: Paracoccidioidomycosis; *Paracoccidioides brasiliensis; Paracoccidioides lutzii;* Fungal infections; Antifungal treatment.

INTRODUCTION

Paracoccidioidomycosis (PCM) was the eighth leading cause of death among systemic chronic mycoses from 1980 to 1995[8]. Hospital morbidity records due to this disease were analyzed from 1998 to 2006 and showed that PCM was registered in 27% of the 5,560 hospital admissions due to systemic mycosis, covering 35% of the country[9].

Recent reports on the *Paracoccidioides brasiliensis* complex in Latin America[31] and the description of *Paracoccidioides lutzii* in central and northwestern regions of Brazil[46] represent new challenges for the knowledge of epidemiological, molecular and serological profile in endemic regions with consequent clinical, laboratory and therapeutic implications for the management of infections caused by both species. In some areas of Rondonia State, Northwestern Brazil, over 2,163 cases from 1997 to 2012 have been described, revealing a very high incidence rate (39.1/100,000)[49].

Parameters to consider for treatment

Clinical forms were classified as proposed at the *Encuentro Internacional de la Paracoccidioidomycosis,* Medellín, 1986[23], in two main clinical presentations, the acute or subacute form (juvenile) and the chronic unifocal or multifocal form.

The juvenile form of PCM affects children, adolescents, and young adults up to 30 years old, of both sexes, presenting a few weeks to several months of duration, mainly involving the mononuclear phagocytic system. In severe or moderate acute cases, the patient has three or more of the following criteria: total body weight loss ≥ 10%; counter immunoelectrophoresis (CIE) titers ≥ 1/64; presence of tumor-like lesions or suppurative lymph nodes; multiple organ involvement (central nervous system, adrenal, bones); and lack of intradermal reaction to paracoccidioidin.

Chronic form of PCM affects adults older than 30 years old; with a male to female ratio of 10-15:1; an insidious symptomatology duration of 4-6 months; affecting lungs, digestive tract, adrenals, skin, oral and respiratory mucosa, and the central nervous system. In severe infections, patients present ≥ 3 of the criteria above mentioned; in the moderate form, total body weight loss ranges between 5 and 10% and the counter immunoelectrophoresis titers are between 1/16-1/32. Severity also depends on other factors such as the hemoglobin level, lymphatic or hematogenous dissemination, number of organs involved, central nervous system commitment, increased levels of specific antibodies, parasite load, and presence of comorbidities causing immunosuppression (HIV infection, drugs, hematological malignancies, organ transplantation). Severe cases are usually related to malnutrition and, in these patients, disseminated lesions, pulmonary

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and adrenal insufficiency, digestive tract malabsorption, and central nervous system impairment can occur[45]. Mild forms present less than 5% of weight loss; counter immunoelectrophoresis titers less than 1/16; and exclusive involvement of the lungs, upper digestive, respiratory tract and skin, associated with a positive intradermic paracoccidioidin.

Recommended treatment for moderate or severe cases of PCM consists in two steps: a) an induction phase to control clinical symptoms until acute phase laboratory parameters return to normal; b) a maintenance phase up to the interruption of treatment based on immunological and other laboratory inflammation markers such as acute phase proteins. The aim of the induction phase is to select more active, although eventually more toxic, drugs. Once the acute phase is under control, the treatment can be changed to oral drugs (once or twice daily), favoring the adherence to longer treatment regimens. A marked decrease of antibody titers (CIE ≤ 1/32) has been used to initiate the maintenance phase. In the case of itraconazole and sulfametoxazole-trimethoprim (SMX-TMT), prescribed at recommended doses, some authors preferred not to use the maintenance treatment.

Considering the drug selection and duration of treatment, the following parameters need to be considered: 1) Lesion site; 2) Disease severity; 3) Contraindication due to previous hypersensitivity reactions; 4) Treatment failure after correctly administered schemes.

Post-treatment evaluation

Although the gold standard to evaluate treatment is the fungal isolation in culture or its identification by direct examination of biological samples, these specimens are not easily available. Moreover, invasive procedures are not recommended for patients presenting improvement of lesions during treatment.

Serological methods are also employed: Ouchterlony double immunodiffusion (DID), CIE, and immunoperoxidase assay[17]. When antibody testing is not available antigen detection in blood or cerebrospinal fluid, and detection of fungal DNA by molecular methods can be used, however they are not performed routinely[5,10,11].

Follow-up

During the follow-up, some clinical parameters should be observed:

- Involution of active lesions and resolution of signs and symptoms should occur within 1-8 weeks of starting therapy.

- Acute phase tests: decreased erythrocyte sedimentation rates and normalization of acute phase proteins should occur in the first 4-12 weeks (C-reactive protein and alpha1 acid glycoproteins).

- Image signs: reduction of alveolar abnormalities on chest X-rays and reduction of edema and small acute nodules in MRI should occur after 3-12 months; fibrosis and pronounced granuloma can persist for many years.

With respect to the serological parameters, antibody titers should decrease 4-6 months after the beginning of treatment, reaching stabilization after 10 months (1/4 of initial titers detected by CIE or negative results in undiluted serum tested by DID). These parameters are very useful to decide if and when to discontinue the treatment depending on the severity and dissemination of the disease and on the patient's adherence to treatment.

***Paracoccidioides* resistance**

The term "sulfa resistance" has been defined in the context of PCM treatment with sulfonamides, when there is no regression of lesions in spite of the patient receiving the course of treatment. To determine resistance to a given drug, three parameters should be considered: 1. *in vitro* resistance to known concentrations of the studied drug; 2. treatment failure according to clinical criteria; 3. appropriate serum levels of the drug.

In our clinic, although therapeutic failure has been documented, fungi were not recovered from patients receiving appropriate posology. Lack of adherence, the most common cause of therapeutic failure, and low serum levels of the drug were associated with the presence of fast sulfonamide acetylators[2].

In vitro studies have shown *Paracoccidioides* resistance to sulfonamides[41,43], amphotericin B and azoles, and a synergistic effect of SMX -TMT on a strain isolated from a patient who received a combination of drugs but presented treatment failure[26].

Drugs for treatment[4]

1. Sulfonamides derivatives

Structural analogues and competitive antagonists of para-aminobenzoic acid (PABA) and sulfonamide derivatives prevent the utilization of PABA in the synthesis of folic acid. Sulfadiazine is the compound most rapidly absorbed in the gastrointestinal tract, and can be detected 30 minutes after ingestion in all tissues and in urine.

Several sulfa compounds have been used to treat PCM since 1940: rapidly excreted compounds (sulfadiazine), slowly excreted (sulfametoxypiridazine) or very slowly excreted ones (sulfadoxine), depending on the disease severity. In our out-patient clinic, sulfadiazine and SMX-TMT have been the choice for non-life threatening PCM, with favorable outcomes. Therapeutic failure has been observed in the majority of cases in which there was poor compliance or poor absorption of these drugs.

Our experience can be compared to the one obtained in response to treatment with sulfonamides, particularly to rapidly excreted sulfa compounds[28,48], revealing a therapeutic failure in 4.3% of cases. Fast acetylation of sulfanilamides, fungal resistance, insufficient daily dosage, non-compliance to treatment, and short treatment regimen were the main causes of relapses happening less than six months after drug discontinuation.

The main advantage of sulfadiazine is that it is highly distributed throughout the body, even in the CNS, and 10-30% of patients with active disease can have asymptomatic CNS lesions detected by MRI. Sulfadiazine is inexpensive for public health care, even for long term

treatment. A disadvantage of sulfadiazine is posology (two or three 500 mg tablets every six hours, or 100 mg/kg/d, maximum 6 g). For maintenance therapy, slowly excreted sulfa (sulfamethoxypyridazin) could be used twice a day or even SMX-TMT 2-3 times a day. For long term treatments, 6-12 months are required for induction and 12-24 months for maintenance. Adverse effects such as hypersensitivity reactions, gastrointestinal symptoms, hemolytic anemia, agranulocytopenia and crystalluria occur in around 5% of patients.

Sulfamethoxazole-trimethoprim (SMX-THT)

It is freely distributed by the Brazilian Ministry of Health. The recommended posology is 480-960 mg every 8-12 hours, and the combination is available for oral or parenteral administration. Cerebrospinal fluid levels are adequate. The main disadvantage is the need for long term treatments (more than 12 months) in moderate and severe cases. Adverse events include hypersensitivity reactions, leucopenia, megaloblastic anemia and trombocytopenia. This association of compounds is known as cotrimoxazole and has been employed in Brazil (400-800 mg, two tablets, each 8-12 hours) in the induction phase or higher intravenous doses in severe cases affecting the CNS. Therapeutic failure was described in 5% of patients with low sulfadiazine serum concentrations due to genetic-related factors altering the liver metabolism (acetylador phenotype)[2]. The main disadvantage is the need for long-term treatments (more than 12 months) in moderate and severe cases. Adverse effects include hypersensitivity reactions, leucopenia, megaloblastic anemia and trombocytopenia.

Azoles

Azoles inhibit the sterol-14α demethylase, a cytochrome P450-dependent enzyme that inhibits ergosterol biosynthesis[4]. Accumulation of 14α demethylase impairs the function of membrane-bound enzymes such as the ATPases and the electron transport system enzymes leading to the inhibition of the fungus growth.

1. Ketoconazole

Ketoconazole's penetration in the CNS is poor and the drug interacts with rifamycin, lowering its serum levels, so these two drugs should not be prescribed in patients with tuberculosis and PCM. Although ketoconazole has been successfully used in the treatment of mild to moderate PCM[42] (200-400 mg/day), it has been replaced by itraconazole due to its poor absorption and adverse events (increased aminotransferase levels, gynecomastia, skin hypersensitivity reaction, pruritus, vomiting, nausea and anorexia).

2. Itraconazole

Considered 10-100 times more active than ketoconazole on fungal cells, its activity has been also demonstrated *in vivo* and *in vitro* in mice and human cells[36]. Unfortunately, its oral form, which is better absorbed than capsules, is not available in Brazil. Itraconazole's half-life is 17-21 days, allowing its prescription once a day; 99.9% of the drug binds to plasma proteins, and it does not cross the blood-brain barrier. Therefore, low levels are found in the cerebrospinal fluid, but it has been effective in CNS mycoses due to its affinity to brain tissue. Absorption is impaired by antacids or inhibited by gastric acid secretion. A risk of its employment in severe cases is its erratic absorption so that in cases with gastrointestinal tract or mesenteric lymph nodes involvement, patients must be carefully monitored. Doses from 100-400 mg a day were effective when administered for 6-24 months[36], and associated with 91% of clinical improvement. Itraconazole can be administered at high doses of 400 mg daily or twice daily, adverse effects are easily controlled and endocrine adverse effects are infrequent at the recommended doses and duration. Some drug interactions with cisapride, quinidine and astemizole can occur resulting in cardiac arrhythmias. Itraconazole can increase the concentration of several drugs: cyclosporine, delavirdine, diazepan, digoxin, indinavir, oral midazolam, phenytoin, saquinavir, simvastatin, ritonavir, sulfonylurea, tacrolimus, triazolam, verapamil, vinca alkaloids and warfarin. Decreased itraconazole concentration can occur with the simultaneous use of receptor blockers, pump blockers, carbamazepine, isoniazid, rifabutin, nevirapine, fenobarbital, phenytoin and rifamycin. Due to itraconazole's adverse effects, monitoring of liver function is recommended and whenever enzyme levels are more than three times the basal values, drug replacement is required. Other adverse effects include nausea, vomiting, increased serum aminotransferases, skin rash, hypokalemia, hypotriglyceridemia and hyperuricemia.

3. Fluconazole

Almost completely absorbed in the gastrointestinal tract, fluconazole reaches maximum levels in serum after two hours. Its bioavailability is 80% and the drug is diffused into sputum, saliva and cerebrospinal fluid reaching 60-90% of plasma values. Fluconazole is recommended when hepatic enzymes are increased, there is hypersensitivity to sulfas or to amphotericin B, and in neuro-PCM cases. Administered at doses of 300-400 mg/day to 37 patients in a multicenter study, clinical improvement was shown in 91.8%. Over 40% received the drug over six months and 2.9% died during the induction phase[38]. Fluconazole advantages are its CNS levels, posology, and the possibility of oral and intravenous administration. The main disadvantage is its lower efficacy in disseminated cases. Increased fluconazole plasma concentrations can occur when there is simultaneous administration of cisapride, cyclosporin, rifamycin, rifabutin, sulfonylurea, theophylline, tacrolimus, and warfarin. Decreased fluconazole concentrations can occur when the drug is administered in combination with rifamycin, resulting in a 25% decrement of the fluconazole concentration. The adverse effects are nausea, skin rash, vomiting, abdominal pain and diarrhea.

4. Voriconazole

Voriconazole exhibits an *in vitro* activity similar to itraconazole's against fungal isolates, is available in oral and intravenous formulations and has an extended spectrum against other fungi. A randomized, open-labeled, study compared voriconazole and intraconazole showing complete or partial global response in 88.6% of the voriconazole group against 94.4% of the itraconazole[40]. Adverse events in the voriconazole group included abnormal vision, chromatopsia, skin rash, and headache; in the itraconazole group were observed bradycardia, diarrhea, and headache. Liver function tests showed slightly higher levels in patients receiving voriconazole (two were withdrawn). In treatment-evaluable patients, the response rate was 100% for both groups and no relapses were observed after eight weeks of follow-up.

Terbinafine

Terbinafine is a synthetic allylamine active against *P. brasiliensis in vitro*. Metabolized by the liver, its bioavailability is about 40%. The drug is contraindicated in patients with hepatic failure or azotemia. *In vitro* sensitivity to terbinafine suggests that it may be included in the treatment of PCM[25]. In fact, it was administered in a patient unsuccessfully treated with SMX-TMT, and the patient evolved with clinical improvement and mycological cure[26].

Amphotericin B

Amphotericin B (AmB) has a half-life of a few days, it can be administered on alternate days, reaching higher serum levels than the minimum inhibitory concentration to inhibit *P. brasiliensis*. It is excreted in bile after hepatic metabolization, and it is not removed by dialysis. As low levels are found in CNS, some authors prescribe AmB intrathecally (0.1-.10 mg) in patients unresponsive to intravenous therapy when the fungus is susceptible to AmB. In this case, hydrocortisone 25-30 mg, or the equivalent dose of dexamethasone, can be administered to avoid arachnoiditis, and could be prescribed to pregnant women as it is not teratogenic. Considered as a highly active fungistatic and fungicidal compound, AmB has been recommended since 1958 for the treatment of the most severe PCM cases. The starting dose varies from 5-10 mg but in severe cases, the total dose should be rapidly increased to 1 mg/kg/day. In a series of 47 patients presenting enlarged liver and spleen, lymph nodes, lung and cutaneous involvement, after a total dose of 2.0-3.0 g/day (30 mg/kg), 57% of clinical and serological cure was observed[12]. Immediate adverse effects such as fever, chills, tachycardia, tachypnea, hyperpnea, arterial hypertension (prostaglandin E2-related) or hypotension, could be controlled by pretreatment with acetaminophen, dipyrone or hydrocortisone 0.7 mg/kg/day at the beginning of the infusion. Other common adverse effects are hypokalemia, renal tubular acidosis, decreased glomerular filtration and normocytic hypochromic anemia. Management of potassium levels and sometimes prophylactic oral potassium supplementation are required. Less frequent adverse effects are ventricular repolarization abnormalities, hepatic dysfunction and hypomagnesemia. Monitoring of urea and creatinine levels is mandatory. A randomized-controlled study comparing the effects of AmB infused during 4-24 hours showed that low infusion rates reduced nephrotoxicity and side effects without changing the mortality in neutropenic patients with fever and invasive fungal infection[20]. As malnutrition and immunosuppression are commonly seen in severe PCM cases receiving AmB, particularly those presenting gastrointestinal malabsorption and hypoalbuminemia, parenteral nutrition has been recommended.

Combination of AmB and rifabutin was successfully used in three patients treated with 1.0, 3.5 and 5.0 g of amphotericin B without success. Rifabutin, 600 mg/day for 3- 56 months, controlled the disease[50].

Liposomal amphotericin

The incorporation of AmB into a lipid preparation led to an improved tissue distribution and therapeutic success index, with a simultaneous decreased toxicity. A total of four patients with the acute form of PCM received liposomal AmB 3 mg/kg/day for 28 days and three of the four patients presented an initial clinical improvement, but relapsed within six months. Thereafter, treatment with cotrimoxazole was prescribed followed by clinical improvement within 6-12 months[18].

Treatment of CNS paracoccidioidomycosis

Parenchymal involvement occurs in 12.5% of patients evaluated by CT-scan in any phase of disease and in 38% of patients with active systemic disease evaluated by MRI[13]. The selection of the treatment should include drugs that reach higher concentrations in cerebrospinal fluid and parenchyma, such as sulfadiazine, SMX-TMT, AmB and voriconazole. Although itraconazole has been used in the treatment of other CNS mycosis because of its good penetration in the parenchyma, it is not recommended for neuro-PCM. Despite its lower efficacy in this mycosis, fluconazole has been successfully used as it presents a good CNS penetration. Our experience is similar comparing the results of intravenous AmB (in rare cases, intrathecal) or sulfadiazine 100 mg/kg/d (maximum 4 g/day) with respect to treatment failure that was found in 23-25% of cases[27]. For post-therapy maintenance, SMX-TMT has been used because of its better posology and patients' adherence. Imaging techniques including spectroscopy were used to describe inflammation and neuronal damage, but they do not have sufficient specificity to indicate treatment discontinuation. Serology has been the most efficient method to monitor patients. Antigen levels in blood or cerebrospinal fluid have been described as a diagnostic marker[10,11] and could be useful during the follow-up, but this is not available in clinical practice. The association of SMX-TMT and fluconazole was prescribed to 14 patients with neuro-PCM. The initial dose was SMX 2,400 mg-TMT 480 mg during two months, followed by SMX 1,600mg-TMT 320 mg until the end of treatment. Fluconazole was administered (200 mg/day) until the end of treatment; i.e. for 24-80 months and the follow-up period was 12 to 196 months. No deaths were observed and, in five patients, no sequelae or disabilities were observed. In three patients there were seizures and in the remaining six patients, hemiparesis, paraparesis, ataxia, and cognitive impairment were observed[22].

Randomized and comparative studies

A few randomized and comparative studies have been published so far. The first randomized study involved patients with moderate PCM[33,44]. Patients were randomly assigned to receive a 4-6 months induction therapy with a low dose of itraconazole (50-100 mg/day), ketoconazole (200-400 mg/day) or sulfadiazine (150 mg/kg/day up to 6 g/day, followed by slow-release sulfamethoxypyridazin) until negative serological results were obtained. In the ketoconazole group, all patients but one presented a positive clinical response to chemotherapy. For treatment periods ≤ 10 months, all of the drugs produced an antibody titer fall ($p < 0.01$). None of the drugs were superior to the others in terms of clinical and serological response.

The second randomized study was that one previously described comparing itraconazole and voriconazole[40]. Considering the cost-benefit and the importance of voriconazole to treat very severe mold infections, and the risk of resistance to azoles, itraconazole should be the recommended azole, except for central nervous system infections.

The first comparative study involved two groups of patients: 32 treated with AmB plus sulfonamides from 1972 to 1981[30]; and 22 treated with ketoconazole from 1981 to 1982. Ketoconazole was administered in a single dose of 400 mg/day for 30-60 days, followed by 200 mg/day

for 18 months; AmB was administered at doses of 1.5-1.75 mg/kg/day for 30-60 days, followed by sulfadoxine (1.0 g/day once-weekly) or sulfadimethoxin (2.0-3.0g/day) for up to 18 months. No statistical difference was found between the groups when clinical, radiological and serological evolution was analyzed.

The second comparative study involved two groups: one composed of 69 patients treated with AmB alone, analyzed from 1958 to 1963, and the other group was treated with AmB followed by maintenance with sulfonamides from 1968 to 1982[19]. No difference was observed between the two groups in phase I (≤ 1 year) or phase V (9-14 years). However, the group that received the maintenance therapy with sulfonamides presented a more favorable outcome.

In a retrospective study involving 200 patients with proven PCM[6] evaluated from 1993 to 2009, the treatment protocol was SMX- TMT 480-1,600 mg for 12 months in mild cases, and for 24 months in moderate/ severe cases. Information on the severity of disease was reported in 131 cases (22 mild, 83 moderate, 26 severe). Severe cases received SMX-TMT intravenously, including those with CNS involvement. The cure rate for itraconazole (86.4%) was higher than that observed for SMX-TMT (51.3%), but the latter increased to 71.4% when only patients that received regular treatments were analyzed. The duration of therapy was shorter for itraconazole (12 months) than for SMX-TMT (23 months). The authors concluded that itraconazole was a better option, but they argued that double-blind randomized studies are necessary to confirm these findings.

A *quasi* experimental study conducted from 1988 to 2012 included 177 proven and probable PCM cases to compare the efficacy and effectiveness of treatment with itraconazole and SMX-TMT[7]. Itraconazole and SMX-TMT efficacy were 95% and 70%, respectively. Treatment was performed in two phases: 1. Induction - until normalization of the erythrocyte sedimentation rate; 2. Complementary - until serological cure was achieved. In this study[7], efficacy and effectiveness was similar in both groups for the initial treatment. However, concerning itraconazole, clinical cure was achieved in a shorter period of time (105 days versus 159 days with SMX-TMT) but this difference was found among the patients with the chronic form, but not among those with the acute form. There is no information about digestive tract involvement or mesenteric lymphadenomegaly in the latter patients that could contribute to low itraconazole absorption. Additionally, the time for the erythrocyte sedimentation rate to return to normal did not differ between the groups. The frequency of side effects was lower for itraconazole than for SMX-TMH, except for increased direct bilirubin.

Another comparative study[21] evaluated three treatment schedules in 45 patients with PCM: cotrimoxazole {1600 + 800mg/day} (SMX-TMT), AmB-AMPH {1 mg/kg/day} followed by cotrimoxazole for maintenance {1600 + 800 mg/day} and itraconazole {200 mg/day} (ITZ). The mean time to clinical improvement and the overall treatment time (varying from 13 to 18 months) showed no difference between the three tested treatments. No difference was found among the groups with respect to signs of clinical improvement, symptoms, and the time required for serology to become negative.

Treatment of immunocompromised patients

Consistent data available on the post-therapy follow-up of onco-hematological cancer patients with PCM in whom a 40% therapeutic failure has been described is scarce. A controlled study involving 53 HIV-positive and 106 HIV-negative PCM patients showed that improvement rates were found six to 24 months in 73.5 to 63% of HIV coinfected patients, and 87.0 to 93.0% of non-coinfected ones. Death due to PCM occurred in 12.2% and 6.6% of patients, respectively, but these differences were not statistically significant. The only significant difference was the rate of relapses at 24 months: 18.5% in coinfected patients and 3.3%[35] in non-coinfected ones suggesting that coinfected patients need to be monitored and receive a maintenance therapy until CD4 levels recover.

Treatment of sequelae

As PCM is a common cause of adrenal insufficiency varying from overt insufficiency to abnormalities detectable only by laboratory tests, all patients have to be evaluated. Glucocorticosteroids and mineralocorticosteroids should be prescribed because stress or infection episodes can induce life-threatening conditions in these patients[15]. As for pulmonary fibrosis, considered one of the most important sequelae of this mycosis, sometimes leading to respiratory failure, the combined therapy of pentoxifylline and itraconazole induced a more rapid reduction of granulomatous inflammation and pulmonary fibrosis in mice in comparison with the itraconazole therapy alone[37].

Paradoxical reactions and adjuvant therapy

Paradoxical reactions were described in two HIV-negative patients with acute PCM who evolved with lymph nodes enlargement during a conventional antifungal treatment, therefore requiring the use of corticosteroids. Although this reaction had not been reported in HIV-negative PCM patients before, it is in accordance with the inflammatory reactions induced by *Paracoccidioides brasiliensis* and/or its antigens or secreted products[14,24,39].

In four cases that received corticosteroids as an adjuvant therapy to control inflammation and the development of destructive lesions, the authors raised some important questions regarding the control of inflammatory lesions in the presence of fungal multiplication[3] that might help the management of these cases.

Experimental models and the use of immune stimulants

Therapeutic studies conducted in isogenic mice have demonstrated that early treatment can modify the animal immune response from a susceptible to a resistant pattern. Since the initial report of the successful use of glucan as an immune stimulant in PCM patients[32], several alternatives have been described in the mouse model. The protective effect of the 43 kDA glycoprotein of *P. brasiliensis* (P10)[47] in the immunosuppressed mice, and other derivatives of *Paracoccidioides* able to stimulate T helper responses have also been reported in mice models[1,29,34].

RESUMO

Tratamento da paracoccidioidomicose

Considerada micose endêmica emergente na América Latina, a paracoccidioidomicose é caracterizada por uma evolução crônica e

envolvimento de múltiplos órgãos em pacientes com comprometimento imunológico. Sequelas da infecção estão relacionadas principalmente à insuficiência pulmonar e adrenal. A interação hospedeiro-parasito resulta em diferentes expressões da resposta imune dependendo da patogenicidade do parasito, carga fúngica e características genéticas do hospedeiro. Alguns estudos controlados e séries de casos têm demonstrado que azóis de ação rápida e derivados de sulfa constituem alternativas terapêuticas úteis nas formas mais leves da doença. Para casos moderados/graves, tratamentos mais prolongados ou mesmo por via parenteral são necessários especialmente quando há envolvimento de mucosa do trato digestivo, resultando em absorção deficiente de drogas. Embora estudos comparativos tenham relatado que esquemas terapêuticos mais curtos com itraconazol sejam capazes de induzir cura em pacientes cronicamente infectados, ainda existem desafios no tratamento, tais como a necessidade de maior número de estudos controlados envolvendo casos agudos, busca por novas drogas e combinações, compostos capazes de modular a resposta imune nos casos graves, e reações paradoxais.

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