

CAVALCANTE RS¹, MAZA L¹, LEÃO PS², BATAH SS², FABRO AT², MENDES RP¹.

¹Universidade Estadual Paulista (UNESP), Faculdade de Medicina de Botucatu, Botucatu, São Paulo – Brazil; ²Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Ribeirão Preto, São Paulo – Brazil.
E-mail: mip.ricardo@gmail.com

I. INTRODUCTION

Paracoccidioidomycosis (PCM) is systemic mycosis caused by thermodynamically fungi of the genus *Paracoccidioides*. Trimethoprim-sulfamethoxazole, also called cotrimoxazole (CMX), is one of the main therapeutic options. In the current treatment of PCM, CMX is used in the dose of 2,400 mg of sulfamethoxazole, which corresponds to six tablets divided into two daily doses, a fact that has led to the patient's lower adherence to antifungal therapy. Experimental studies have observed that the single daily dose may be sufficient to treat PCM.

II. OBJECTIVES

This study aimed to evaluate the efficacy of murine PCM treatment with CMX administered in one and two daily doses.

III. PATIENTS AND METHODS

Study groups: isogenic mice of the Balb / c line were randomly assigned
G1: healthy, uninfected control (n = 23)
G2: infected control (n = 27)
G3: CMX once daily after 28 days of infection (n = 25)
G4: CMX twice a day after 28 days of infection (n = 25)

Moments of sacrifice: 8th, 12th, 16th and 20th week after infection

Recovery of fungi in tissues
Antibody Dosage (double immunodiffusion reaction – DID)
Lung histopathological analysis
Cumulative survival analysis at 140 days

The Kruskal-Wallis and Mann-Whitney tests were used for comparison of medians, linear regression to analyze the parameters in the successive moments of sacrifice and Kaplan-Meier for the evaluation of survival. P values less than 0.05 were considered significant.

IV. RESULTS

There was no difference in cumulative mortality between G3 and G4 (0.0% vs 4.0%, p>0.05).

Table 1. Recovery of fungi from the lungs of isogenic BALB/c mice infected with *Paracoccidioides brasiliensis*, according to therapeutic regimen and duration of treatment. Quantification of fungi in colony forming units per gram of tissue.

Week	G2	G3	G4
8 ^a	12.223,0 [10.400,0 – 20.000,0] ^{A, a}	4.861,0 [0,0 – 15.000,0] ^{A, ab}	1.875,0 [0,0 – 5.000,0] ^{A, b}
12 ^a	10.416,5 [6.000,0 – 12.400,0] ^{A, a}	2.933,5 [0,0 – 11.500,0] ^{A, ab}	124,0 [0,0 – 3.703,0] ^{A, b}
16 ^a	20.000,0 [5.557,0 – 24.443,0] ^{A, a}	3.000,0 [0,0 – 11.250,0] ^{A, a}	6075,0 [0,0 – 15.242,0] ^{A, a}
20 ^a	23.750,0 [5.557,0 – 40.000,0] ^{A, a}	0,0 [0,0 – 6.750,0] ^{A, b}	1.605,0 [0,0 – 12.785,0] ^{A, b}

Capital letters compare different weeks within a group while lower case letters compare the same weeks between groups. Different letters indicate statistically significant differences (p<0.05), where a or A > b or B and ab or AB does not differ from a or A nor from b or B

Table 2. Serum levels of specific antibodies determined by the reaction of double immunodiffusion in agar gel in isogenic BALB/c mice infected with *Paracoccidioides brasiliensis* according to the therapeutic schedule and treatment time.

weeks	G2	G3	G4
8 ^a	1:2 [ND – 1:2] ^{B, b}	1:16 [1:2 – 1:16] ^{A, a}	1:4 [ND – 1:4] ^{A, ab}
12 ^a	1:4 [1:2 – 1:4] ^{AB, a}	1:2 [ND – 1:4] ^{AB, a}	1:2 [NR – 1:8] ^{AB, a}
16 ^a	1:4 [1:2 – 1:4] ^{AB, a}	NR [NR – 1:8] ^{AB, a}	ND [NR – ND] ^{AB, a}
20 ^a	1:8 [1:4 – 1:8] ^{A, a}	ND [NR – ND] ^{B, b}	NR [NR – ND] ^{B, b}

Capital letters compare different weeks within a group while lower case letters compare the same weeks between groups. Different letters indicate statistically significant differences (p<0.05), where a or A > b or B and ab or AB does not differ from a or A nor from b or B

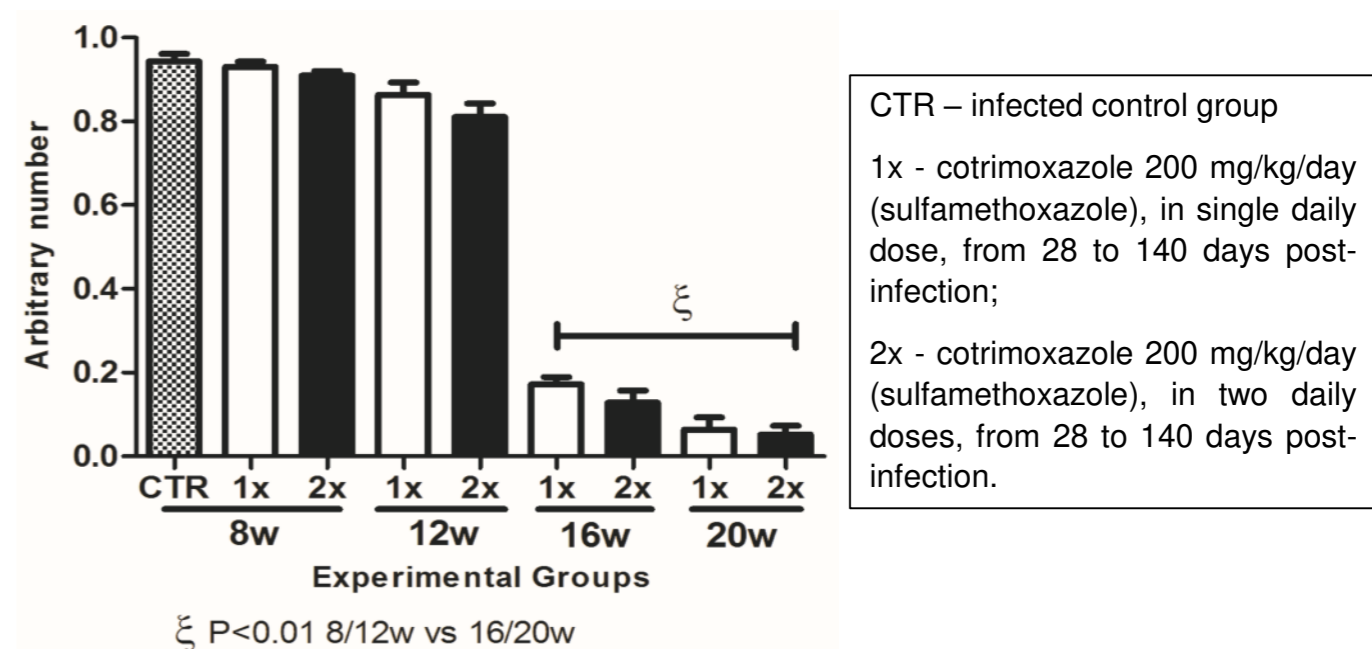


Figure 1. Determination of the fungal load by histopathological examination of the lung by the periodic acid staining of Schiff (PAS) in male, isogenic, Balb/c mice, infected by *Paracoccidioides brasiliensis*, according to the therapeutic scheme used.

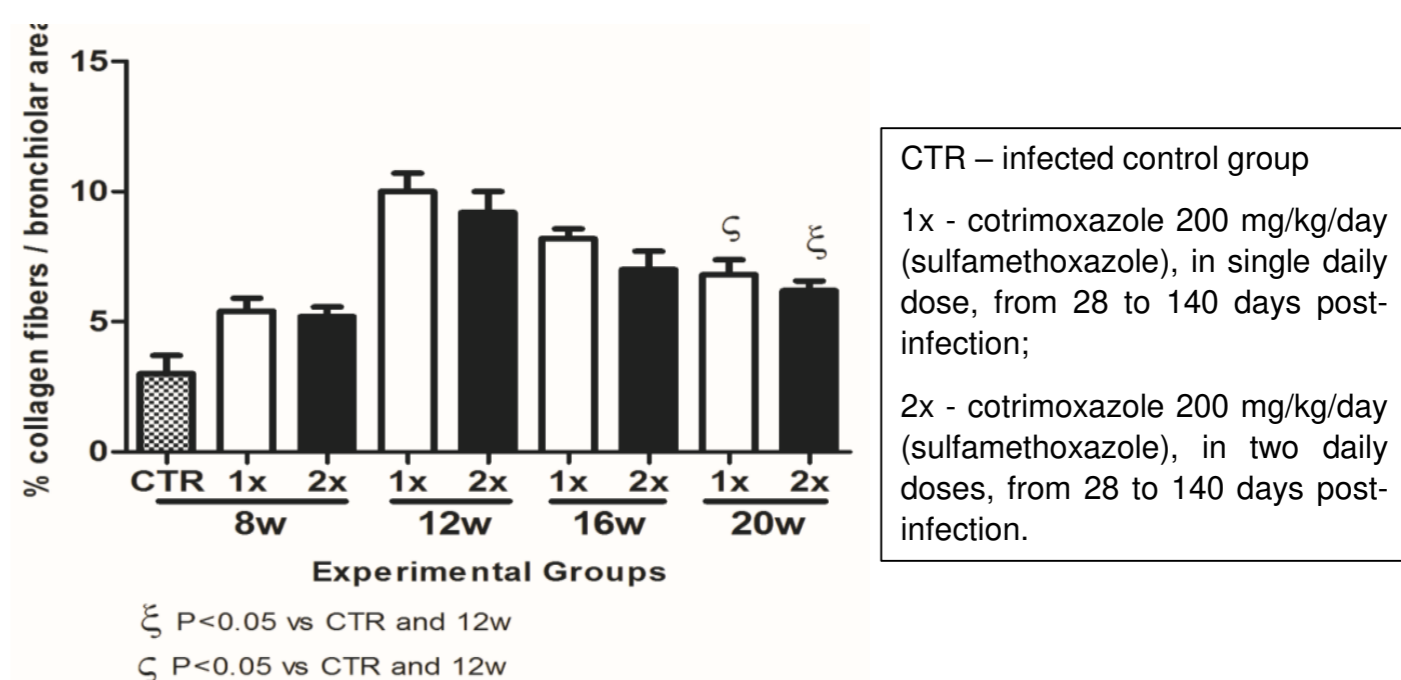


Figure 2. Percentage of collagen fibers, measured by Picrosirius staining, of lungs of male, isogenic, Balb/c mice, infected by *Paracoccidioides brasiliensis*, according to the therapeutic regimen used.

V. CONCLUSION

These findings demonstrate efficacy of the two murine PCM treatment regimens with CMX. Although there were no direct differences between the two CMX treatment regimens, the group receiving two doses per day presented a higher response when compared to the infected control, a fact that did not occur with the single daily dose group. This suggests that differences may exist between the two schemes and that future studies are needed to better understand the efficacy of these therapeutic regimens.