Fluconazole Modulates Granulomatous Inflammation and Tissue Remodeling in Experimental Paracoccidioidomycosis

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Introduction: Paracoccidioidomycosis (PCM) is a systemic and endemic mycosis prevalent in Latin America, caused by thermodimorphic fungi of the *Paracoccidioides* spp. complex. This disease is characterized by a chronic granulomatous inflammatory response that can lead to severe anatomical and functional impairment of multiple organs. Currently, therapeutic options remain significantly limited, primarily relying on long-term administration of antifungals such as sulfonamides and amphotericin B. The inherent difficulties of prolonged treatment, including side effects and patient non-compliance, justify the urgent search for alternative antifungal agents with potent anti-*Paracoccidioides* activity. Furthermore, an ideal therapeutic approach should ideally possess immunomodulatory properties, capable of refining the host\'s immune system to achieve greater efficacy and a definitive clinical cure. In this context, Fluconazole (FLZ) a triazole drug widely documented in the literature for treating other systemic fungal infections, such as those caused by *Histoplasma* spp., *Cryptococcus* spp., and *Coccidioides* spp. emerges as a potential candidate for PCM therapy. **Objectives:** This study aimed to evaluate the effects of FLZ on the course of *Paracoccidioides* spp. infection and its impact on host immunity. **Methods:** To achieve this, female Swiss mice were infected with the virulent Pb18 strain of *P. brasiliensis* and subsequently treated daily via gavage. The experimental design included both acute and chronic PCM infection models to mimic different clinical stages of the disease. Following treatment, parameters such as survival rate and body weight gain were rigorously monitored over periods of 15 and 120 days. Upon completion of the experimental period, necropsies were performed, and target organs specifically the spleen, omentum, liver, and lungs were harvested for comprehensive histological analysis. This evaluation focused on tissue architecture, cellularity, and the presence of *P. brasiliensis* yeast cells within granulomatous lesions. Additionally, morphological remodeling was quantified using a stereological method. **Results:** The results demonstrated a high safety profile for FLZ, as no mortality or pathological weight fluctuations were observed in the treated groups. Most notably, a substantial improvement in the histopathological appearance of all collected organs was recorded. The findings revealed a marked reduction in the inflammatory infiltrate, a decrease in the deposition of collagen fibers (fibrosis), and a significantly lower fungal burden compared to untreated controls, with these effects being particularly pronounced during the chronic phase of the disease. Stereological analysis confirmed these observations, showing that the total number of granulomas, as well as the density of vessels and neovessels, was significantly lower in FLZ-treated animals. **Conclusion:** Taken together, these results suggest that Fluconazole effectively improves the histological characteristics of infected organs and modulates the inflammatory environment, potentially offering a robust and viable new therapeutic approach for the treatment of PCM.

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