

Title: REPOSITIONING OF DRUGS FOR CRIPOTOCOLOSE TREATMENT CAUSED BY *Cryptococcus gattii*

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Abstract:

The cryptococcosis caused by *Cryptococcus gattii* pathogen is a systemic infection responsible for high rate mortality. In Brazil it is the second more cause of death from a systemic mycosis that affects even healthy individuals. There are numerous difficulties in standard antifungal therapy, due to strict therapeutic option currently available, increased resistance of these yeasts front of the drugs and the high toxicity of these drugs the health human. Therefore, the development of new antifungal drugs is of very importance for the treatment of cryptococcosis. In this context, repositioning of drugs emerges as an interesting option in the treatment of *C. gattii*. This approach is to use already established drugs which may be administered as single or in combination with drugs commonly prescribed, not necessary to make a new record, as the pharmacology and toxicology of these drugs are already known. Based on this context, this study was conducted to evaluate the effect of atorvastatin (ATO) in the treatment of cryptococcosis in an experimental model in vitro and in vivo. This drug was tested by the minimum inhibitory concentration test (MIC) and fractional inhibitory (FIC) (in combination with Fluconazole (FLC)) against 13 strains of *C. gattii*. The ATO was tested at concentrations between 256 mg/mL to 0.5 mg/mL. For evaluation of activity of the drugs in combination was used checkerboard method. For the in vivo experiment was done intratracheal infection model in male mice, which were inoculated 30µL of a solution containing 1×10^4 cell/animal of *C. gattii*. The animals were divided in groups: 1) ATO 30 mg/kg; 2) FLC 20 mg/kg; 3) ATO 30 mg/kg + FLC 20 mg/kg; 4) NT (untreated). The treatments were started 24 hours after infection and carried out daily. The MIC values for the ATO were equal to or greater than 256 mg/mL. In FIC test, the result was indifferent, witch mean between strains of 1.76. In vivo, after 55 days of treatments, the survival of animals treated with the combination ATO + FLC was statistically higher ($P < 0.05$) compared to other groups (increase of six days after to the FLC alone, and 18 days compared with the group not treated). At the end of the experiments, we proved that the association ATO + FLC, consisted of an excellent therapy to be used to combat and control of cryptococcosis.

Keywords: Cryptococcosis, repositioning of drugs, atorvastatin

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