
THE COMBINATION OF LOW DOSE AMPHOTERICIN B AND MICA FUNGIN IS COMPARABLE IN ACTIVITY TO HIGH DOSE AMPHOTERICIN B ALONE IN TREATMENT OF EXPERIMENTAL INVASIVE PULMONARY ASPERGILLOSIS

Petraitis V, Petraitiene R, Sarafandi A, Kelaher A, Leguit RJ, Irwin RG, Peter J, Bacher J, Walsh TJ, National Institute of Health, National Cancer Institute, POB, Bethesda, United States

Background: Micafungin is a new echinocandin with broad-spectrum fungicidal activity against *Candida spp.* and fungistatic activity against *Aspergillus spp.* In order to increase the efficacy of micafungin against invasive aspergillosis, we investigated the in vitro and in vivo interaction and antifungal activity of micafungin in combination with deoxycholate amphotericin B (AMB). **Methods:** The combination of micafungin and AMB was studied over a range of concentrations (micafungin (0 to 0.25 µg/ml) and AMB (0 to 0.25 µg/ml)), using checkerboard MTT assays. We then proceeded to investigate the in vivo antifungal activity of micafungin and AMB in experimental invasive pulmonary aspergillosis in persistently neutropenic rabbits. Antifungal therapy was started 24h after endotracheal inoculation of 1.25x10⁸ *Aspergillus fumigatus* conidia and continued for 12 days in surviving animals. Treatment groups consisted of untreated controls (UC), micafungin at 1 (MICA1), low-dose AMB at 0.25-0.5 (AMB0.5), MICA1+AMB0.5 (MICA+AMB), or high-dose AMB at 1 mg/kg (AMB1). **Results:** MTT checkerboard assays demonstrated an additive interaction between micafungin and AMB. A total of 77 rabbits were studied. Rabbits treated with the combination of micafungin plus AMB demonstrated significant decrease of pulmonary CFU/g in comparison to that of MICA1 (p<0.001), AMB0.5 (p<0.05), and UC (p<0.001). In addition, rabbits treated with MICA+AMB showed a significant reduction in organism-mediated pulmonary injury as measured by infarct scores and lung weights in comparison to MICA1 (p<0.01), AMB0.5 (p<0.05) or UC (p<0.01) rabbits. Survival through the entire study was achieved in 15 (87.5%) of 17 micafungin plus AMB-treated rabbits versus 10 (62.5%) of 16 AMB0.5 (p=0.08), 5 (0.01%) of 16 MICA1 (p<0.001), and 0 of 16 UC (p<0.001) rabbits. **Conclusions:** In summary, the combination of micafungin and AMB was more effective than single agent treatment and comparable to treatment of AMB at 1 mg/kg in treatment of experimental pulmonary aspergillosis.