

EFFICACY OF MICAFUNGIN (FK) ALONE OR IN COMBINATION AGAINST EXPERIMENTAL PULMONARY ASPERGILLOSIS

Clemons KV, and Stevens DA*.

Santa Clara Valley. Med. Ctr., Calif. Inst. for Med. Res., San Jose, CA and Stanford Univ., Stanford, CA, United States

Mortality from invasive pulmonary aspergillosis approaches 80% with few useful therapeutic options available. We previously reported FK to have comparable efficacy to amphotericin B (AmB) and itraconazole (ITZ) versus systemic aspergillosis in immunocompetent animals, and FK + nikkomycin Z (Nik Z) were additive. We now examined the efficacy of FK, an echinocandin, alone or in combination in a murine model of pulmonary aspergillosis. Eight-week-old DBA/2 mice were immunosuppressed with 1 mg of triamcinolone s.c. one day prior to infection. In the initial study, animals were infected intranasally with 2.95×10^4 conidia of *Aspergillus fumigatus* 10AF. Beginning day 1, groups of 10 mice were given 10 days of saline, or 1, 3 or 10 mg/kg of FK b.i.d., s.c. The model was extremely lethal, with all saline controls and 90% of untreated mice succumbing to infection by day 8. The efficacy of FK was difficult to assess because of an apparent toxicity, with mice given FK at 10 mg/kg/dose dying sooner than those given a lower dose of FK. Antagonistic toxicity with steroids was confirmed in studies with uninfected animals. FK given at 1 mg/kg significantly prolonged survival over the saline controls ($P = 0.008$). FK at 3 mg/kg versus the saline controls approached significance ($P = 0.072$) as did FK at 10 mg/kg/dose ($P = 0.09$). No treatment regimen was different in efficacy. The efficacy of combination therapy was assessed. Immunosuppressed mice were infected intranasally with 3.9×10^4 conidia. Mice received either no treatment, FK at 1 mg/kg/dose, 0.8 mg/kg of AmB in D5W given QD i.v., 100 mg/kg of ITZ in hydroxypropyl- β -cyclodextrin given QD PO, or 100 mg/kg/dose of Nik Z given in 5% DMSO-PEG200. FK and Nik Z were given b.i.d., s.c. Through the 12 days of the experiment AmB alone and FK + AmB or FK + Nik Z significantly prolonged survival ($P < 0.05-0.02$) over that of the untreated controls. Neither ITZ alone nor ITZ + FK or Nik Z alone provided significant prolongation of survival. Analysis further indicated that 1 mg/kg of FK alone approached significance in prolonging survival, but was not different from untreated controls. The combination of FK and ITZ appeared to be potentially antagonistic, with the mice receiving the combination therapy dying slightly earlier than those treated with FK alone. Although AmB + FK was efficacious, no synergistic activity was noted for any of the regimens; studies using a less rigorous infection might demonstrate synergistic activity. Overall, these results indicate that FK has moderate activity against pulmonary aspergillosis and might be useful in combination with conventional AmB. Additional studies are warranted.