
COMBINATION ANTIFUNGAL THERAPY WITH MICAFUNGIN (MICA) AND AMPHOTERICIN B DESOXYCHOLATE (AMB-D) PROLONGS SURVIVAL IN THE P47PHOX-DEFICIENT MOUSE MODEL OF CHRONIC GRANULOMATOUS DISEASE (CGD) WITH EXPERIMENTAL PULMONARY ASPERGILLOSIS

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Background: CGD is an inherited disorder of the NADPH oxidase characterized by recurrent life threatening bacterial and fungal infections and excessive inflammatory responses. We evaluated combination antifungal therapy in CGD mice with experimental aspergillosis.

Methods:

Survival: CGD mice were challenged with intratracheal *A. fumigatus* conidia (1.25 x 10E4 CFU/mouse). Mice (n=10-12 per treatment group pooled from 2 experiments) received one of the following regimens daily from day 0 to 4 after challenge: 1) IV vehicle + IP vehicle; 2) IV Mica (10 mg/kg) + IP vehicle; 3) IV vehicle + IP Amb-d (1 mg/kg); or 4) IV Mica (10 mg/kg) + IP Amb-d B (1 mg/kg).

Histopathology: In separate experiments, CGD mice received a sub-lethal challenge of *A. fumigatus* (1.25 x 10E3 CFU/mouse), and antifungal therapy was administered (n=3-4 mice per treatment group) daily on days 7-11 after challenge. Mice were sacrificed and lungs harvested for pathology on day 14.

Results:

Survival: Mice receiving combination Mica + Amb-d had significantly longer survival than any other group (log rank, p <0.005). Mice receiving Amb-d alone had improved survival compared with Mica alone or vehicle (p<0.01). Mica alone produced no significant survival benefit over vehicle. No morbidity or invasive disease occurred in wildtype control mice challenged with *A. fumigatus* conidia.

Histopathology: There was a striking swelling of invasive hyphae particularly at the tips in mice treated with Mica alone. This morphology was not observed with combination Mica and Amb-d or Amb-d alone.

Conclusions: CGD mice are highly susceptible to *A. fumigatus* challenge and are an excellent model to evaluate antifungal regimens. As no exogenous immunosuppression is required and spontaneous infections are rare, long-term responses to antifungal agents can be effectively modeled. Mica alone but not in combination with Amb-d produced distinctive hyphal swelling in vivo. This may be an adaptive response to loss of cell wall integrity resulting from B-glucan depletion in which hyphal tips swell and rupture while the proximal hyphal elements remain viable. This response to the echinocandin may be abrogated in the presence of Amb-d. Combination Mica and Amb-d was more effective than either agent alone in prolonging survival.

Candida albicans, *Candida dubliniensis*, growth at 42°Celsius, CHROMagar *Candida*