Delay of Antifungal Therapy Influences the Outcome of Invasive Aspergillosis in Experimental Models of Infections

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Objectives:

The aim of the present study was to evaluate the effects of delay the antifungal therapy in the outcome of invasive aspergillosis (IA) due to *A. fumigatus* in experimental models of infections.

Methods:

A clinical isolate of *A. fumigatus* susceptible to both amphotericin B (AMB, median MIC 0.5 µg/ml) and micafungin (MICA, median MEC 0.03 µg/ml) was used in all experiments.

Two models of infections were investigated in CD1 immunosuppressed female mice: disseminated infection (DI) performed by given the conidia intravenously and pulmonary infection (PI) by given the conidia intranasally. 24 h (early therapy, ET) and 48 h (delayed therapy, DT) postinfection, the mice were given placebo, MICA, liposomal-AMB (L-AMB), and MICA plus L-AMB (Combo). Each drug was utilized at low (3 mg/kg/day) and high (10 mg/kg/day) doses. Therapy was given for three consecutive days.

Drug efficacy was assessed either by survival analysis (15 days) or tissue burden experiments (kidney in DI model). In tissue burden, the mice were euthanized 24 h after the last dose of the drug and the CFUs were determined.

Survivals were plotted as Kaplan-Meier curves and analyzed by log rank (due to multiple comparison, a P < 0.008 was considered statistically significant).

CFUs/organ/mouse were analyzed by one-way Anova followed by the Tukey's test corrected for multiple comparison. A P <0.05 was considered statistically significant.

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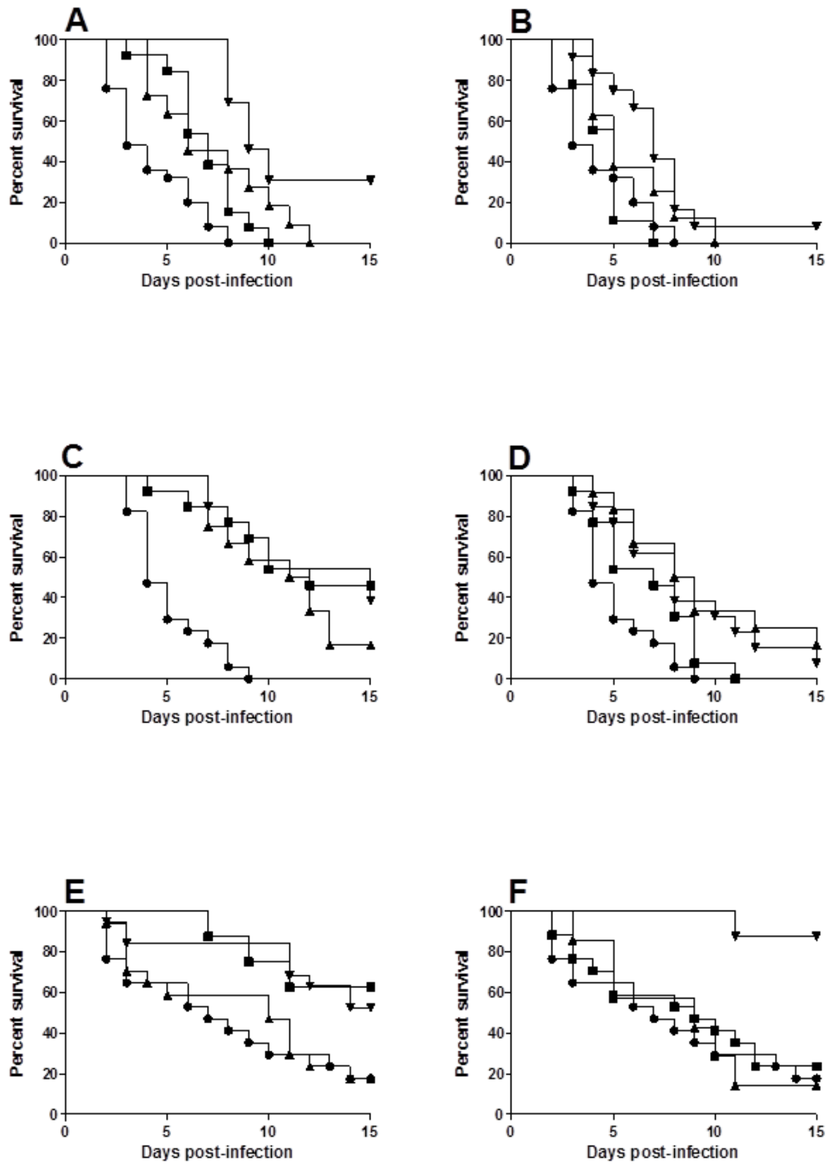

Fig. 1. Survival curves of mice infected intravenously (A,B,C,D) or intranasally (E,F) with of 1x10^5 (A,B,C,D), 1x10^4 (E,F) *A.fumigatus* conidia/mouse and treated with placebo (circle), L-AMB (square), MICA (triangle), and combination of L-AMB plus MICA (upper base triangle). Both drugs, alone or in combination, were given at 3 (A,B,E,F) or 10 (C,D) mg/kg/day for three consecutive days. Therapy was started 24 h (early therapy; A,C,E) or 48 h (delayed therapy; B,D,F) postinfection.

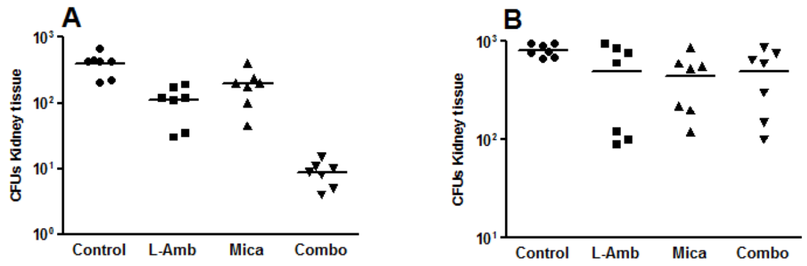

Fig. 2. Tissue burden of mice infected intravenously with approximately 7x10^5 *A.fumigatus* conidia/mouse and treated with placebo (circle), L-AMB, MICA, and combination of L-AMB plus MICA (Combo). Both drugs, alone or in combination, were given at 3 mg/kg/day for three consecutive days. Therapy was started 24 h (early therapy; A) or 48 h (delayed therapy; B) postinfection.

Results:

In ET (Fig. 1A) of DI model either L-AMBI (P = 0.0024) or MICA (P = 0.0031) given at 3 mg were effective against the control. Combo was more effective than control (P <0.0001), more effective than L-AMBI (P = 0.0005) but not more effective than MICA alone (P = 0.02). In DT, the only regimen which prolonged the survival was Combo (P = 0.005, Fig. 1B). When drug doses, singly and in combination, were increased at 10 mg, all regimens were effective at prolonging the survival following ET (Fig. 1C, P <0.0001).

In DT experiments (Fig. 1D), only MICA (P = 0.001) and Combo (P = 0.0026) were effective.

PI was conducted with drugs given at 3 mg. In both ET and DT experiments (Fig. 1E and 1F, respectively) only Combo was more effective than control (P = 0.007 in ET, P = 0.004 in DT).

In ET of tissue burden experiments all regimens given at 3 mg were effective against the controls (Fig. 2A). Conversely, in DT no regimen was effective (Fig. 2B).

Conclusions:

1. Either Mica or L-Ambi are effective in infections due to *A. fumigatus*.

2. No antagonism between drugs has been evidenced; on the contrary a trends toward a potentiation of single drug regimen was seen, mainly when each single drug is used at low dose.

3. The delay onset of therapy is deleterious in experimental model of IA either in terms of survival than in terms of reducing the fungal burden.

4. Combination therapy seems to be a good therapeutic option when therapy is started late.

References:

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