Combination treatment of liposomal amphotericin B and isavuconazonium sulfate is synergistic in treating experimental mucormycosis

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BACKGROUND

Mucormycosis is a life-threatening infection that predominantly occurs in immunocompromised hosts.[1] Liposomal amphotericin B (L-AMB) and isavuconazole (ISAV) are commonly used antifungal drugs to treat mucormycosis.[2] However, the efficacy of combination therapy of L-AMB + ISAV compared to monotherapy is unknown. We used an immunosuppressed mouse model of pulmonary mucormycosis to compare the efficacy of L-AMB + isavuconazonium sulfate (prodrug of ISAV) vs. either drug alone.

METHODS

ICR mice were immunosuppressed with cyclophosphamide (200 mg/kg) and cortisone acetate (500 mg/kg) on Days -2, +3, and +8 relative to intratracheal infection with 2.5 x 10^5 cells of *Rhizopus delemar* 99-880, or 2.5 x 10^6 cells of *Mucor circinelloides*.[3] Treatment with L-AMB (10 mg/kg, given intravenously qd), isavuconazonium sulfate (equivalent to 56 mg/kg of ISAV, by oral gavage TID), or a combination of both started 8 h post infection and continued through day +4. Placebo mice received vehicle control. Survival studies through day +21 and tissue fungal burden (by conidial equivalent [CE] using qPCR) on Day +4, served as primary and secondary endpoints.

RESULTS

For mice (n=20) infected with *R. delemar*, L-AMB and ISAV equally prolonged median survival time and enhanced survival vs. placebo (19 and 16 days for L-AMB and ISAV, respectively, and an overall survival of 50% to either drug alone, vs. 8 days and 5% overall survival for placebo, P<0.002 for either drug vs. placebo by Log Rank test). Importantly, combination treatment enhanced median survival time (>21 days) and resulted in an overall survival of 80% (P<0.05 vs. all treatments). Both antifungal drugs reduced tissue fungal burden of mice (n=10) lungs and brain by ~1.0-2.0 log vs. placebo-treated mice (P<0.02 by Wilcoxon Rank Sum). Consistent with the survival data, treatment with combination therapy resulted in 2.0-3.5 log reduction in fungal burden of either organ vs. placebo and 1.0 log reduction vs. either drug alone (P<0.005). Similar results were obtained using mice infected with *M. circinelloides*.

CONCLUSIONS

L-AMB + ISAV demonstrates greater activity vs. monotherapy treatment in immunosuppressed mice infected with either of two common causes of mucormycosis. These studies warrant further investigation of LAmB + ISAV combination therapy as an optimal therapy of human mucormycosis.

REFERENCES

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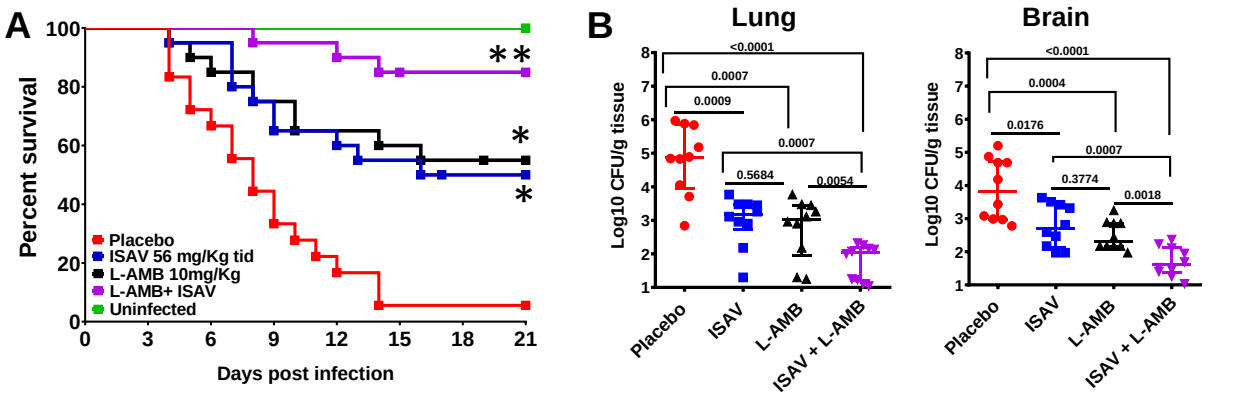
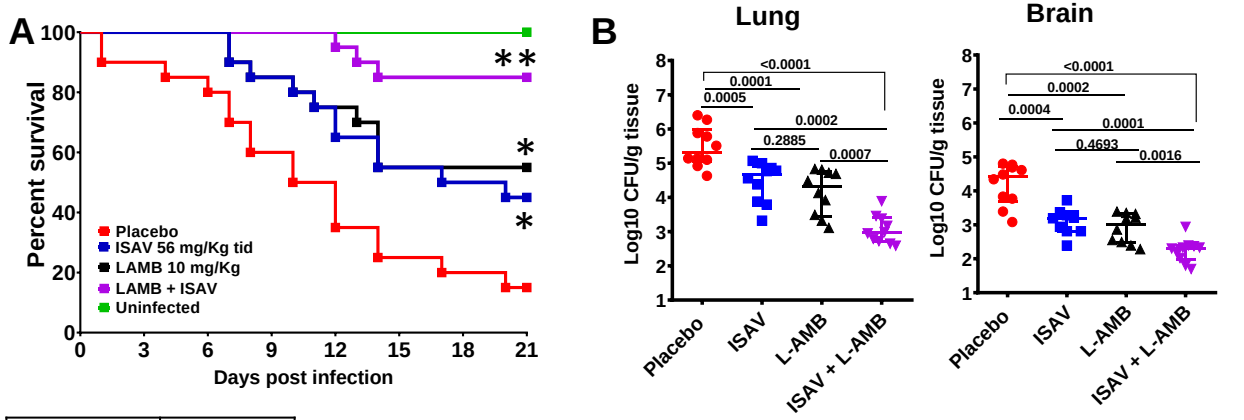


Treatments	Median survival (day)
Placebo	8
ISAV	16
L-AMB	19
ISAV + L-AMB	>21

Figure 1. Combination therapy of ISAV and L-AMB synergistically protect mice from *R. delemar* infection. (A) Mice survival (n= 20/group from 2 experiments) were infected intratracheally (average inhaled inoculum of 2.9 x 10^3 spores). **P*<0.002 vs. placebo and ***P*<0.0001 vs. placebo and P<0.05 vs. either drug alone. (**B**) Tissue fungal burden of lungs or brain of mice (n=10) euthanized on Day +4 post infection. *P* values are shown on each graph and conducted by Wilcoxon Rank Sum test.



Treatments	Median survival (day)
Placebo	11
ISAV	17
L-AMB	>21
ISAV + L-AMB	>21

Figure 2. Combination therapy of ISAV and L-AMB synergistically protect mice from *M. circinelloides* infection. (A) Mice survival (n= 20/group from 2 experiments) were infected intratracheally (average inhaled inoculum of 4.6 x 10^4 spores). **P*<0.05 vs. placebo and ***P*<0.0001 vs. placebo and P<0.05 vs. either drug alone. (**B**) Tissue fungal burden of Lungs or brain of mice (n=10) euthanized on Day +4 post infection. *P* values are shown on each graph and conducted by Wilcoxon Rank Sum test.