P0010
Poster Session I
News from the fungal frontier

IN VIVO EFFICACY OF A JAK1/2 INHIBITOR IN A MURINE MODEL OF HEMATOGENOUSLY DISSEMINATED CANDIDIASIS

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Objectives. *Candida* infection is a common cause of nosocomial bloodstream infection associated with 30-50% mortality despite antifungal therapy. Given the low prevalence of antifungal resistance among *Candida* strains, the high mortality of these infections may attribute and other factors like underlying conditions, severity of infection, immune response etc. *Candida* cause severe sepsis which is characterized by a massive production of pro-inflammatory cytokines at an early phase of infection and anti-inflammatory cytokines at a late phase of the infection. Controlling sepsis may enhance the outcome of systemic candidiasis. The production of cytokines is a result of activation of JAK-STAT pathway which consists of four kinases JAK1, 2, 3 and Tyk2. We therefore investigated the in vivo efficacy of ruxolitinib, a potent Jak1/2 inhibitor used to treat myelofibrosis, in an experimental model of hematogenously disseminated candidiasis by *Candida albicans.*

Methods. 4-6 week CD1 20-25gr mice were infected intravenously via the tail vein with $5x10^6$ CFU of *Candida albicans.* This inoculum results in 100% mortality in 7 days. The model simulates bloodstream infections and septic sock conditions by *Candida albicans* as previously described (Sellberg JID 2005). Ruxolitinib was dissolved in 0.5% methylcellulose. Mice were treated with 50 mg/kg of ruxolitinib and placebo intraperitoneally once daily starting one day before (d-1) and after (d+1) the day of infection and continue for 10 days. A lower dose of 6.25 mg/kg starting one day after infection was also tested. All infected mice were monitored twice daily and survival and body weight were recorded daily for 15 days. After death, kidneys were excised and cultured to ensure *Candida* infection. Survival data were analyzed with log-rank test whereas body weight data were analyzed with analysis of variance between control and different treatment groups.

ReusIts. The % survival and median survival time of control, 50 mg/kg (d-1), 50 mg/kg (d+1) and 6.25 mg/kg (d+1) groups was 0%, 0%, 0% and 17% and 5, 2, 7 and 10.5 days. The log-rank test showed statistically significant differences (Chi square=12, p=0.0074) with a significant trend among the different treatment groups (p=0.031). Fungal burden were lower in mice treated with the lowest dose of ruxolitinib compared to control.
Conclusions: Inhibition of Jak1/2 improved the survival of mice with *Candida* bloodstream infection opening a new field of investigation for treating fungal sepsis. Further studies are required to elucidate the protective mechanism of action of Jak1/2 inhibitors.