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Antifungal susceptibility

Efficacy of isavuconazole against wild-type and *Cyp*51 mutant isolates of *Aspergillus fumigatus* in a mouse infection model

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Objectives

Azole resistance is an emerging problem in *Aspergillus fumigatus* which translates into treatment failure. Alternative treatments with new azoles may improve therapeutic outcome in invasive aspergillosis (IA) even for strains with decreased susceptibility to current azoles.

Methods

The *in vivo* efficacy of 0.25, 1, 4, 16, 64, 128, 256 and 512 mg/kg/day prodrug isavuconazonium sulfate (BAL8557) (ISA-equivalent doses of 0.12, 0.48, 1.92, 7.68, 30.7, 61.4, 122.9 and 245.8 mg/kg/day, respectively) was assessed in an immunocompetent murine model of IA against four clinical *A. fumigatus* isolates: a wild-type isolate (ISA MIC_{EUCAST}, 0.5 mg/L) and three azole-resistant isolates harboring substitutions in the *cyp51A*-gene: G54W (ISA MIC_{EUCAST}, 0.5 mg/L), M220I (ISA MIC_{EUCAST}, 4 mg/L) and TR_{34}/L98H (ISA MIC_{EUCAST}, 8 mg/L). Mice were treated orally q24 (once daily) for 14 days. Survival and reduction in kidneys fungal burden measured by a real-time quantitative PCR (qPCR) were the primary endpoint in groups of 11 and 3 mice, respectively. Left and right kidney from each animal were homogenized. Targeting the 28S region of *A.fumigatus*, the ratio of copies/ml and total DNA isolated (ng/ml) was calculated to determine the *Aspergillus* load of each organ sample.

Results

The survival curves for all control groups receiving saline by oral gavage, showed a mortality of 100%. The maximum effect (100% survival) was reached at a pro-dose of 64 mg/kg for the wild-type isolate, 128 mg/kg for the G54W and 256 mg/kg for M220I mutant. A maximal response was not achieved with the TR_{34}/L98H isolates with the highest dose of prodrug isavuconazonium sulfate (256 mg/kg). Using qPCR, isavuconazole therapy significantly reduced kidney *Aspergillus* copy numbers at day 3 post infection. The mean number of genome copies detected in untreated animals was $3.69x10^5$ in kidneys (n=3, range= $3.5x10^5$-$3.7x10^5$) at day 3 post infection. Further, there was a mean 3-4 $\log_{10}$ reduction of *A. fumigatus* genome copies in infected animals treated with the highest dosage of isavuconazole. The relationship between reduction in kidneys fungal burden at day 3 post-infection and 14 days survival were similar for all isolates ($p<0.05$).

Conclusions

Our results indicated that for each prodrug dose, survival decreased as the MIC increased. Similarly, when the prodrug dose was increased, an improved response was observed. The results of 14 days survival mirrored the qPCR results at day 3 post challenge, which suggest the real-time qPCR assay as a reliable promising tool for early prediction of dose-response and exposure-response relationships of antifungals in animal model of IA.