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Paper Poster Session I

News on antifungal prophylaxis and therapy

Impact of dose fractionation on the *in vivo* efficacy of isavuconazole in a murine model of *Aspergillus fumigatus* infection

S. Seyedmousavi[1,2], R.J.M. Brüggemann[2], J.F. Meis[2,3], W.em.J.G. Melchers[2], P.E. Verweij[2], J.W. Mouton[1,2]

[1]*ErasmusMC, Rotterdam, Netherlands*

[2]*RadboudUMC, Nijmegen, Netherlands*

[3]*Canisius Wilhelmina Hospital, Nijmegen, Netherlands*

Objectives

Isavuconazole is an investigational broad-spectrum triazole currently being investigated in the phase III clinical studies for the treatment of severe invasive fungal infections, including invasive aspergillosis (IA). Dose fractionation studies need to explore which pharmacokinetic/ pharmacodynamic (PK/PD) index correlates best with efficacy, and to determine whether the magnitude of the PK/PD index needed for efficacy varies among various dosing intervals.

Methods

The *in vivo* efficacy of q24 (once daily), q12 (fractionated into two doses) and q8 (fractioned into three doses) 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 a clinical *A. fumigatus* isolates isolate (ISA MIC_{EUCAST}, 0.5 mg/L). Mice were treated orally for 14 days. In addition, ISA concentrations in plasma were assayed in a separate pharmacokinetic (PK) study at 10 predefined time points (3 mice per group) post challenge by a validated UPLC method.

Results

The survival curves, dose-response curves, as well as the exposure-response curves were not significantly different with various dosing intervals ($P > 0.05$). 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. The Hill-type model with a variable slope fitted the relationship between the area under the plasma concentration-time curve **(**AUC) and 14-day survival well, with R^2 values of 1 (q24), 1 (q12) and 0.99 (q8), respectively. The 50% effective AUC (ED_{50}) was 12.05 mg·h/liter for the q24, 14.07 mg·h/liter for the q12, and 8.74 mg·h/liter for the q8 treatment. AUC_{0-24}/MIC appeared to be the most reliable pharmacodynamic index correlating with efficacy. For a survival of 50%, the effective AUC_{0-24}/MIC ratio for isavuconazole total drug was 24.73 (95% confidence interval, 22.50 to 27.18).

Conclusions

The efficacy of isavuconazole depended on the total amount of drug (AUC), independently of the dosing interval. There was no significant differences between exposure-response relationships of the groups treated with various dosing intervals. The quantitative relationship between exposure and effect (AUC_{0-24}/MIC) can be used to optimize the treatment of human infections by *A.fumigatus*, including strains with decreased susceptibility.