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O0840 Pharmacokinetic/pharmacodynamic modelling of posaconazole against *Candida glabrata* isolates: determination of EUCAST PK/PD breakpoints

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Background: *C. glabrata* is associated with clinically significant azole-resistance across different azoles although very few data are available on the efficacy of posaconazole against infections due to *C. glabrata*. We therefore assessed the pharmacodynamics of posaconazole in an *in vivo* validated one compartment *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) dilution model. The PK/PD relationship was described and the probability of target attainment for the available posaconazole formulations was calculated.

Materials/methods: One fluconazole-susceptible and three fluconazole-resistant clinical *C. glabrata* isolates with EUCAST posaconazole MICs 0.06, 0.5, 1 and 4 mg/L, were included. Steady state posaconazole serum concentration-time profile previously reported in patients receiving 400 mg b.i.d. was simulated for 48h in a one compartment *in vitro* PK/PD dilution model with fC_{max} 0.15, 0.85 and 2.25 mg/L and with $t_{1/2}$=36h. The 48h log_{10}CFU/mL-AUC_{0-24}/MIC relationship was analysed with the Emax model and the exposure index associated with 50% of maximal activity (EI_{50}) was determined. Monte Carlo simulation analysis was performed to calculate EI_{50} target attainment rates (PTA) for isolates with EUCAST MICs 0.015-8 mg/L in patients treated with 400 mg oral posaconazole b.i.d (Ullmann et al, *AAC* 2006) or with 300 mg tablet/i.v posaconazole od (Duarte et al, *AAC* 2014, Maertens et al, *AAC* 2014) taking into account the 99% protein binding.

Results: No antifungal activity (4log_{10}CFU/mL increase) was found against the isolates with MIC 1 and 4 mg/L, whereas a fungicidal effect (2log_{10}CFU/mL reduction) was found with fC_{max} 2.25 mg/L against the isolate with MIC 0.06 mg/l. The *in vitro* PK/PD relationship followed a sigmoid curve (R^2 =0.85) with a mean (95% CI) EI_{50} of 19(10-38). Monte Carlo showed that PTA for *C. glabrata* isolates with EUCAST MICs ≤0.25, 0.5 and ≥1mg/L was 67%, 31% and <9% for the oral formulation whereas for the tablet/i.v formulation the PTA was 95%, 36% and <2% for *C. glabrata* isolates with EUCAST MICs ≤0.5, 1 and ≥ 2mg/L respectively.

Conclusions: The determined PK/PD breakpoints of 0.25/0.5 mg/l for oral and tablet/i.v. formulations of posaconazole are 1-2 two-fold dilutions lower than the corresponding EUCAST epidemiological cutoff value (1 mg/L) questioning the use of posaconazole against *C. glabrata* infections.