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P2220 Determination of EUCAST PK/PD breakpoints for posaconazole and *Candida albicans* using an *in vitro* PK/PD dilution model

Maria-Ioanna Beredaki*[1], Panagiota-Christina Georgiou[1], Johan W. Mouton[2], Maiken C. Arendrup[3,4,5], Spyros Pournaras[1], Joseph Meletiadis[1,2]

[1] Medical School, National and Kapodistrian University of Athens, Clinical Microbiology Laboratory, Attikon University General Hospital , Athens, Greece, [2] Erasmus MC, Dept Medical Microbiology and Infectious Diseases, Rotterdam, Netherlands, [3] Unit of Mycology, Statens Serum Institut, Copenhagen, Denmark, [4] Department of Clinical Microbiology, Rigshospitalet, Copenhagen, Denmark, [5] Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Background: Posaconazole has potent activity against *Candida albicans* with a EUCAST ECOFF and susceptibility breakpoint of 0.06 mg/l. Clinical efficacy (~90%) has been shown against oropharyngeal candidiasis. We therefore determined PK/PD breakpoints for the oral and i.v. formulation of posaconazole using a one-compartment dilution *in vitro* PK/PD model.

Materials/methods: Three clinical *C. albicans* isolates with EUCAST MICs 0.015, 0.03 and 0.12 mg/L identical to the isolates previously tested in an animal model of disseminated candidiasis (Andes et al, *AAC*2004) were tested with a 10^4CFU/ml starting inoculum. The in *vivo* posaconazole exposures after dosages of 20, 80 and 320 mg/kg/od were simulated in a one-compartment dilution PK/PD model for 48h with fC_{max} 0.15, 0.25 and 0.5mg/L, respectively, and an average $t_{1/2}$=15h. The 48h$\log_{10}$CFU/mL-AUC_{0-24}/MIC relationship was analyzed with the Emax model and the exposure index associated with 50% of maximal activity (EI_{50}) was determined. The probability of attaining the EI_{50} was calculated with Monte Carlo analysis for patients treated with 400 mg bid oral suspension and 300 mg qd iv of posaconazole attaining a $tAUC_{0-24}$ of 17.24±14.83 and 34.3±14.4mg.h/l, respectively (Ullmann et al, AAC2006, Maertens et al, AAC2014) taking into account the 99% protein binding.

Results: Fungal burden increased by 2.5±0.3$\log_{10}$CFU/mL in drug-free control whereas posaconazole progressively decreased it at high exposure reaching a fungistatic effect against the isolate with the lowest MIC in agreement with *in vivo* findings. The *in vitro* PK/PD relationship followed a sigmoid curve (R^2=0.79) with an EI_{50} (~2$\log_{10}$CFU/ml reduction compared to drug free control) of 68(34-134) *f*AUC/MIC. This PK/PD target was achieved in ≥93%, 71%, 34% and ≤9% of patients treated with the oral formulations for isolates with MICs of ≤0.06, 0.125, 0.25 and ≥0.5 mg/L and in ≥93%, 40% and ≤3% of patients treated with the iv formulation isolates with MICs of ≤0.25, 0.5, ≥1, respectively.

Conclusions: High probability of target attainment was found for *C. albicans* isolates with MIC ≤0.06/≤0.25 mg/L for the oral/iv formulation of posaconazole. This would translate into PK/PD breakpoints of S≤0.06 mg/L, I=0.125-0.25 mg/L and R >0.25 mg/L as increased exposure is necessary for isolates with MICs 0.125-0.25 mg/L.