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

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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 10⁴ CFU/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 fCmax 0.15, 0.25 and 0.5 mg/L, respectively, and an average t1/2 = 15h. The 48hlog₁₀CFU/mL-AUC₀-2₄/MIC relationship was analyzed with the Emax model and the exposure index associated with 50% of maximal activity (EJoe50) was determined. The probability of attaining the EJoe50 was calculated with Monte Carlo analysis for patients treated with 400 mg bid oral suspension and 300 mg qd iv of posaconazole attaining a tAUC₀-2₄ of 17.24 ± 14.83 and 34.3 ± 14.4 mg.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 log₁₀ 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 ($R²=0.79$) with an EJoe50 (~2 log₁₀ CFU/ml reduction compared to drug free control) of 68(34-134) fAUC/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.