

P0167 Dose optimization of micafungin against *Aspergillus fumigatus*

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Background: Micafungin has been used for the treatment of invasive aspergillosis with sub-optimal results. We therefore assessed the pharmacodynamics of micafungin against *A.fumigatus* with a new *in vitro* endpoint that correlated with *in vivo* outcome in mice (Siopi, OS0850-ECCMID2017). The PK/PD relationship was described and the probability of target attainment for different dosing regimens was calculated.

Materials/methods: Different micafungin exposures with fC_{max} 0.1-0.5mg/L q24h for 72h were simulated in a PK/PD model (Meletiadis AAC2012) using a starting inoculum inside a dialysis membrane (DM) of 10^3 cfu/mL. Antifungal activity was determined using the % of DM's height covered by abnormal mycelia (Siopi, OS0850-ECCMID2017). The relationship between $fAUC_{0-24}/MEC$ -% abnormal mycelia was analyzed with the E_{max} model and the $fAUC_{0-24}/MEC$ associated with 50% activity was estimated (EI_{50}). The probability of target attainment (PTA) was calculated for *A.fumigatus* isolates with MECs 0.008-0.032mg/L with Monte Carlo analysis for 5000 hematological patients treated with 100, 150 and 200mg of micafungin q24h attaining steady state mean \pm SD AUC_{0-24} s of 97.11 \pm 28.97, 145.66 \pm 43.46 and 194.22 \pm 57.94mg.h/L (Undre, OJMM2012, Mycamine SPC) taking into account the 99.8% protein binding and the linear pharmacokinetics in humans. The cumulative fractional response (CFR) was calculated for a previously published MEC distribution of clinical *A.fumigatus* isolates (Pfaller, AAC2012) and for micafungin doses of 75 and 150mg previously used for the treatment of invasive aspergillosis (Kohno, Scand J Infect Dis2004).

Results: The *in vitro* PK/PD relationship followed a sigmoid curve ($R^2=0.99$) with an EI_{50} 20 [95%CI:13.92-28.49]. The estimated CFR for 75 and 150mg of micafungin was similar to previously published clinical responses (29% vs 33% and 92% vs 80%, respectively) providing thus a clinical correlation of the *in vitro* model. The PTA was high ($\geq 98\%$) for isolates with MECs ≤ 0.016 mg/L with the 200mg but not with the standard dose of 100mg. In particular, the PTA was 73%,4%,0% for the standard 100mg dose, 100%,47%,0% for the 150mg dose and 100%,98%,0% for the 200mg dose against isolates MEC 0.008, 0.016 and 0.032mg/L, respectively.

Conclusions: The standard 100mg dose was insufficient for treatment of invasive aspergillosis, whereas a 200mg daily dose might be effective against most ($\geq 98\%$) clinical isolates with MECs ≤ 0.016 mg/L (99%) indicating that there is place for dose optimization.