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ePoster Viewing
Antifungal drug susceptibility and resistance

In vitro evaluation of the efficacy of voriconazole-anidulafungin combination against azole-susceptible and -resistant Aspergillus fumigatus strains with a novel pharmacokinetic-pharmacodynamic (PK-PD) model

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Objectives: Voriconazole has been adopted as the gold standard for the treatment of invasive aspergillosis. Nevertheless, the alarming increase in the frequency of azole-resistant *A. fumigatus* clinical isolates challenger current monotherapeutic strategies. Azoles are often combined with echinocandins since the two classes of antifungal compounds possess different mechanisms of action. We therefore investigated the *in vitro* pharmacodynamics of the combination of voriconazole and anidulafungin against azole-susceptible and -resistant *A. fumigatus* isolates in a new *in vitro* PK-PD model.

Methods: Two clinical *A. fumigatus* isolates with anidulafungin CLSI MEC of 0.06 mg/L and different susceptibility to voriconazole were studied: one wild-type susceptible without mutations in the *cyp51A* gene (AFM8196) and one resistant strain harboring the TR/L98H mutation (AFM5235) with voriconazole CLSI MICs of 0.12 and 2 mg/L, respectively. Human standard dosages of 4 mg/kg for voriconazole and 100 mg for anidulafungin were simulated in a newly developed *in vitro* PK simulation model. In particular, the mean, lower and upper 95% confidence interval limits of the free drug levels were calculated the based on voriconazole and anidulafungin protein binding of 58% and 99%, respectively and previously reported total maximum concentrations (C_{max}) in human serum (Purkins *et al* AAC 2002, Liu *et al* AAC 2013). Thus, time-concentration profile of voriconazole and anidulafungin with fC_{max} of 1.5, 0.35, 3 mg/l and 0.08, 0.01, 0.16 mg/L and half-lives 6h and 24h, respectively were simulated alone and in all 3x3 combinations. The model was inoculated with a conidial suspension (10^3 CFU/mL) and incubated at 37°C for 72 hours, while voriconazole and anidulafungin were injected alone and in combination in both compartments every 12 and 24h, respectively. Drug levels were determined by microbiological diffusion assays and fungal growth by measuring galactomannan concentrations using a commercially available sandwich-ELISA. Pharmacodynamics were also assessed with real-time PCR.

Results: The *in vitro* simulated steady state drug pharmacokinetics were close to the target values observed in human plasma. Anidulafungin alone resulted in minimal (fC_{max} 0.35, 1.5 and 3 mg/l, respectively. The combination was indifferent at all dosing regimens except at the lowest fC_{max} of 0.35 mg/l of voriconazole and 0.01-0.08 mg/l of anidulafungin where synergy was found for the susceptible AFM8196 (12%-14%) and the resistant AFM5235 (20-22%) isolate. PCR conidial equivalents of monotherapies were reduced down to $3\log_{10}$s when the two drugs were combined confirming the enhanced killing of combination.

Conclusion: The combination of voriconazole+anidulafungin was indifferent for combinations with serum concentrations equal or higher than the average levels observed in patients and synergistic for combinations with subtherapeutic serum concentrations.