Efficacy of voriconazole-liposomal amphotericin B combination against azole-resistant Aspergillus fumigatus in an in vitro pharmacokinetic-pharmacodynamic model

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Background: A recent randomized clinical trial showed that voriconazole-anidulafungin combination therapy may improve outcome of voriconazole monotherapy against invasive aspergillosis when drugs were combined at standard dosages (Marr e al Ann Intern Med. 2015). Whether alternative dosages can maximize efficacy of combination therapy particularly against azole-resistant isolates is unknown. We therefore investigated the activity of voriconazole-anidulafungin combination against voriconazole-susceptible and -resistant *Aspergillus fumigatus* using different doses of anidulafungin in an *in vitro* pharmacokinetic-pharmacodynamic model.

Material/Methods: Four clinical *A. fumigatus* isolates with anidulafungin CLSI MEC 0.008 mg/L and voriconazole CLSI MICs 0.12-2 mg/L were tested in a pharmacokinetic-pharmacodynamic model (Siopi AAC 2015). Free human serum drug concentration-time profiles were simulated for nine combination regimens of voriconazole (fCmax 3/1.5/0.3 mg/L, t1/2 6h dosed q12) and anidulafungin (fCmax 0.16/0.08/0.01 mg/L, t1/2 24h dosed q24) (Liu AAC 2014). Drug levels were determined by microbiological diffusion assays and fungal growth by measuring galactomannan production using a commercially available sandwich-ELISA. *In vitro* interactions were assessed with Bliss independence model and response surface was modeled using the canonical-mixture nonlinear global response-surface E\textsubscript{max}-based model (Meletiadis AAC 2007). The % of patients attained the pharmacodynamic target associated with 50% of maximal efficacy (E\textsubscript{50}) was calculated for 10,000 simulated patients treated with 4 mg/kg of voriconazole alone and together with 100, 50 and 25 mg of anidulafungin as a combination therapy and for isolates with different voriconazole MICs. The optimal total target serum levels were determined taking into account the protein binding of each drug.

Results: The combination was mostly independent against voriconazole-susceptible isolates at intermediate and high drug exposures, whereas synergistic interactions (8-16%) were found at low
Stronger synergy (20-80%) was observed for isolates with high voriconazole MICs at intermediate and low drug exposures, while at higher drug concentrations independence was found. At the highest anidulafungin exposure ($t_{C_{max}}=0.16$ mg/L), antagonistic effects (-5~-12%) were observed. The $E_{50}$ attainment rates for isolates with voriconazole MICs 0.5, 1, 2 and 4 mg/L were 97%, 72%, 9% and 0% for voriconazole monotherapy and increased to 100%, 86%, 34% and 2% for combination therapy with 100mg anidulafungin, respectively. The highest $E_{50}$ attainment rates were found for combination therapy with 25 mg of anidulafungin (100%, 99%, 79% and 16%, respectively). The serum target levels required to attain the $E_{50}$ were two-fold reduced from 3 $t_{C_{min}}$/MIC in voriconazole monotherapy to 1.5 $t_{C_{min}}$/MIC in combination therapy providing that anidulafungin $t_{C_{max}}$ will be between 6 and 10 mg/L.

**Conclusions:** The combination of voriconazole-anidulafungin is beneficial particularly for patients with sub-therapeutic serum concentrations infected with voriconazole-resistant *A. fumigatus* isolates. The lower dose of 25 mg of anidulafungin may increase efficacy of combination therapy.