27th ECCMID Vienna, Austria 22 – 25 April 2017
The congress of ESCMID

Session: OS173 Challenges in antifungal treatment

Category: 6d. Antifungal resistance & susceptibility testing

25 April 2017, 09:48 - 09:58
OS0850

A new in vitro endpoint of anidulafungin activity against Aspergillus fumigatus correlates with in vivo outcome

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Background: Assessment of *in vitro* activity of echinocandins against *Aspergillus* spp. is problematic because of the distinct mode of action against those species resulting in formation of aberrant hyphae without complete inhibition of growth. The minimal effective concentration (MEC) that is used to assess the *in vitro* activity of echinocandins is non-quantitative, subjective and cumbersome with no clear *in vivo* correlation. Other biomarkers like galactomannan and DNA have limited value. We, therefore, seek alternative *in vitro* endpoints to assess anidulafungin activity against *A. fumigatus* in an *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) model that correlated with *in vivo* outcome in animals.

Material/methods: Two clinical *A. fumigatus* isolates, a wild-type voriconazole-susceptible (AZN8196) and a voriconazole-resistant (V52-35) with identical anidulafungin CLSI MEC of 0.015 mg/L, previously tested in an animal model (Seyedmousavi *AAC* 2013), were studied in a previously optimized 2-compartment PK/PD dialysis/diffusion closed model (Siopi *JAC* 2014) using a 10^3cfu/mL starting inoculum inside a dialysis membrane (Float-A-Lyzer [FAL], SpectrumLabs, Netherlands). Anidulafungin animal dosages

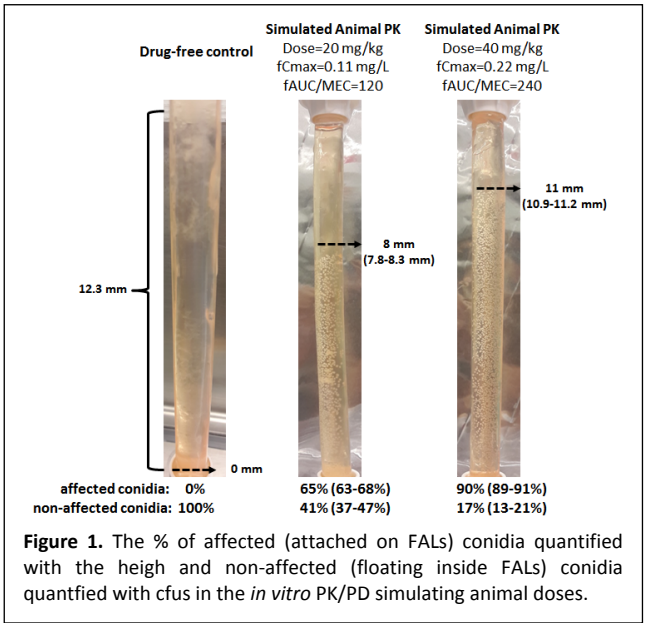

Figure 1. The % of affected (attached on FALs) conidia quantified with the heigh and non-affected (floating inside FALs) conidia quantfied with cfus in the *in vitro* PK/PD simulating animal doses.

of 5, 10, 20 and 40 mg/kg/od were simulated with animal serum *t*C_{max} 0.08, 0.11, 0.22 and 0.5 mg/L, respectively, and average half-life of 18h. Drug levels were measured with a bioassay. The % of non-affected by anidulafungin conidia floating inside the FAL was calculated microscopically (germinated vs non germinated conidia) and with time-kill assays (cfu counts). The % of affected by anidulafungin conidia attached on the FAL membrane was calculated based on the height of abnormal mycelia formed after 3 days divided by the total height (12.3mm) of FAL (see Figure 1). The *t*AUC_{0-24} (PK) was then associated with the % of affected conidia (PD) for each dose and isolate. The *in vitro* relationship of % affected conidia-*t*AUC/MEC was correlated with the *in vivo* survival-*t*AUC/MEC after 14 days of treatment.

Results: The % of non-affected conidia progressive decreased at higher anidulafungin concentrations whereas the opposite was observed for the % of affected conidia (see Figure 1) in such a way that the sum of these two % were close to 100% [98%(77-106) for AZN8196 and 97(80-114)% for V52-35]. The *in vitro* PK/PD relationship followed a sigmoid curve (R^2=0.85, Hillslope 1.74) similar to that of the animal model (R^2=0.85, Hillslope 1.38) (F test p value 0.68). The *in vitro* PK/PD target (95% CI) corresponding to 50% maximal activity (EC_{50}) was 150, close to the *in vivo* EC_{50} of 175 *f*AUC_{0-24}/CLSI MEC (F test p value 0.31).

Conclusions: The *in vitro* and *in vivo* efficacy of anidulafungin was dependent on drug exposure. The results of the *in vitro* PK/PD model were comparable with those obtained from the animal model, while a new surrogate marker of the abnormal hyphal growth caused by exposure to anidulafungin corresponding to *in vivo* survival was proposed.