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

Maria Siopi*, Johan Mouton1, Spyros Pournaras3, Joseph Meletiadis4

1University General Hospital Attikon; Clinical Microbiology Laboratory

2Erasmus University Medical Center; Department of Medical Microbiology and Infectious Diseases

3Medical School, University of Athens; Department of Microbiology

4Clinical Microbiology Laboratory, Attikon University Hospital, Athens, Greece; Department of Medical Microbiology and Infectious Disease, Erasmus MC

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 $10^3$cfu/mL starting inoculum inside a dialysis membrane (Float-A-Lyzer [FAL], SpectrumLabs, Netherlands). Anidulafungin animal dosages
of 5, 10, 20 and 40 mg/kg/od were simulated with animal serum $fC_{\text{max}}$ 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 $fAUC_{0-24}$ (PK) was then associated with the % of affected conidia (PD) for each dose and isolate. The in vitro relationship of % affected conidia-$fAUC$/MEC was correlated with the in vivo survival-$fAUC$/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 $fAUC_{0-24}$/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.