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

Session: OS173 Challenges in antifungal treatment

Category: 6c. Antifungal drugs & treatment

25 April 2017, 09:24 - 09:34
OS0848

Pharmacodynamics of F901318 against Aspergillus fumigatus in a rabbit model of invasive pulmonary aspergillosis (IPA)

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Background: F901318 is a novel antifungal agent with potent activity against *Aspergillus* spp. Studies in mice suggest that Cmin:MIC is the pharmacodynamic index that best links drug exposure with the observed antifungal effect. In a murine model of IPA Cmin of 0.5-1 mg/Lis associated with near maximal reduction of serum galactomannan concentrations. The safety, tolerability and pharmacokinetics of F901318 have been determined in Phase I clinical studies, and Phase II studies are under way. PK-PD justification for the regimen(s) for those studies is required.

Material/methods: A well-characterised persistently neutropenic rabbit model of invasive pulmonary aspergillosis was used. Neutropenia was induced with Ara-C and methylprednisolone and commenced on day -2. Vancomycin was added to drinking water and ceftazidime and gentamicin were used for antibacterial prophylaxis. Rabbits were infected via endobronchial instillation of 1 x 10^8 conidia. Treatment commenced 24 hours post inoculation. F901318 was administered orally every 12 hours. Dosages of 0.5, 2.5, 5 and 10 mg/kg Q12h were used. Plasma concentrations of F901318 were determined on day 1 and day 7 at predose, 0.5, 1, 2, 4 and 12 hours post dose. The primary

pharmacodynamic endpoint was serum galactomannan concentrations that were measured throughout the experimental period. All rabbits were treated for 7 days and sacrificed at 192 hours post inoculation. A mathematical PK-PD model was fitted to the entire PK and PD dataset using a population methodology to enable the relationship between dose, drug exposure and the resultant effect on galactomannan concentrations to be established. The model was then used to establish the relationship between Cmin and both the area under the galactomannan-time curve and the galactomannan concentrations at the end of the experiment.

Results: F901318 was well tolerated in rabbits with no evidence of drug related toxicity. All rabbits survived to the end of the experiment. There was a dose-dependent decline in galactomannan with near maximal antifungal activity observed with a regimen of 5 mg/kg q12h. The fit of the mathematical model was highly acceptable. The relationship between Cmin and the area under the galactomannan-time curve is shown in the figure. A Cmin of ~0.5 mg/L resulted in near-maximal suppression of serum galactomannan concentrations.

Conclusions: F901318 is a potent anti-Aspergillus agent. A Cmin of 0.5 mg/L is a pharmacodynamic target that resulted in near maximal suppression of galactomannan in a persistently neutropenic rabbit model of IPA. This target exposure has been produced in healthy volunteer repeat dose studies and can be used to design clinical regimens for Phase II and III studies.