Pharmacodynamics of F901318 against *Aspergillus fumigatus* in a rabbit model of invasive pulmonary aspergillosis

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• Invasive aspergillosis is a relatively common infection with mortality of 20-30%

• Triazole resistance in *Aspergillus fumigatus* is increasingly reported
  • Mortality is 88-100%
  • Treatment options poorly defined

• All antifungal agents have relative high rates of adverse events
F901318 is a new agent with a novel mechanism of action\textsuperscript{1}

\textsuperscript{1}Oliver et al PNAS 113(45) 2016
Preclinical PK-PD of F901318
Threshold (or time) dependent antifungal activity: Cmin or Cmin:MIC is the relevant dynamically linked variable

Hope et al 55th ICAAC San Diego
Aims of Current Study

1. Define the pharmacokinetics-pharmacodynamics (PK-PD) of F901318 against *Aspergillus fumigatus* NIH/4215 (MIC 0.03 mg/L) in a well characterised rabbit model of IPA

2. Identify the magnitude of the relevant pharmacodynamic index linked with a favorable outcome in rabbits and mice
Rabbit model of invasive pulmonary aspergillosis-1

- Male New Zealand White rabbits

- Central silastic venous catheter permits repeated atraumatic venous access
Rabbit model of invasive pulmonary aspergillosis-2

• Neutropenia induced with
  • Cytosine arabinoside 525 m² day⁻¹
  • Methylprednisolone 5 mg/kg day⁻¹

• Opportunistic bacterial infection prevented
  • Vancomycin 15 mg/kg/day
  • Gentamicin 5 mg/kg alternate days
  • Ceftazidime 75 mg/kg q12h
Experimental Design

- Immunosuppression
- Innoculation
- F901318 treatment

<table>
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<th>PK</th>
<th>0</th>
<th>24</th>
<th>48</th>
<th>72</th>
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PK: Pharmacokinetics
PD: Pharmacodynamics
F901318 Regimens & Study Endpoints

• F901318
  • Chosen on basis of preliminary tolerability studies with embedded PK
  • Vehicle control, 0.5, 2.5, 5, 10 mg/kg q12h orally

• F901318 plasma concentrations measured by HPLC

• Galactomannan measured by BioRad double sandwich ELISA according the the manufacturer’s instructions

• Cmin, GM at t=78 hr., and area under GM-time curve t=0 to t=78 hr. used as study endpoints
\[\begin{align*}
XP(1) & = B(1) - Ka \cdot X(1) \\
XP(2) & = Ka \cdot X(1) - \left(\frac{SCL}{V}\right) \cdot X(2) - Kcp \cdot X(2) + Kpc \cdot X(3) \\
XP(3) & = Kcp \cdot X(2) - Kpc \cdot X(3)
\end{align*}\]
Results - Controls
F901318 0.5 mg/kg q12h orally
F901318 5 mg/kg q12h orally
F901318 10 mg/kg q12h orally
GM at the end of the experiment vs. Cmin

Isavuconazole
Area under GM-time curve vs. Cmin
Conclusions

• F901318 induces a dose (and exposure) dependent decline in galactomannan in a severely neutropenic rabbit model

• Licensed regimen of isavuconazole in this model induces half-maximal reduction in GM

• Regimens of F901318 for Phase II & III must match or exceed isavuconazole
  • i.e. Cmin > 0.1-0.2 mg/L