“PK/PD” type of modelling approach to support time-kill data interpretation of cefoxitin for the treatment of *Mycobacterium abscessus*

ISAP, 12\textsuperscript{th} April 2019

Shachi MEHTA

INSERM U1070, Pharmacology of antimicrobial agents
Poitiers, France.
Introduction

Objective

In vitro study and PK/PD type modeling approach

Conclusion

✓ Nontuberculosis mycobacteria
✓ Pulmonary infections

Mycobacterium abscessus

Koh W et al. 2002
Griffith et al. 2007
Introduction

Objective

In vitro study and PK/PD type modeling approach

Conclusion

• **General treatment:**
Tri-antibiotic combination:
one **macrolide + two antibiotics**
from amikacin, cefoxitin, imipenem
and linezolid (by ATS)

✓ Nontuberculosis mycobacteria
✓ Pulmonary infections

*Koh W et al. 2002
Griffith et al. 2007*
Introduction

Mycobacterium abscessus

✓ Nontuberculosis mycobacteria
✓ Pulmonary infections

Objective

In vitro study and PK/PD type modeling approach

Conclusion

- **General treatment:**
  Tri-antibiotic combination:
  one **macrolide** + **two antibiotics**
  from amikacin, cefoxitin, imipenem and linezolid (by ATS)

- Treatment: long, costly, often associated with drug related toxicity and rapid development of drug resistance

Koh W et al. 2002
Griffith et al. 2007
Introduction

Objective

In vitro study and PK/PD type modeling approach

Conclusion

Cefoxitin

✓ β-lactam antibiotic
✓ Time-dependent activity
Introduction

Objective

In vitro study and PK/PD type modeling approach

Conclusion

Cefoxitin

✓ β-lactam antibiotic
✓ Time-dependent activity

Few challenges during in vitro experiments

Rominski et al. 2017
Introduction

Objective

In vitro study and PK/PD type modeling approach

Conclusion

Cefoxitin

✓ β-lactam antibiotic
✓ Time-dependent activity

Few challenges during in vitro experiments

✓ not stable over time

Rominski et al. 2017
Introduction

Objective

In vitro study and PK/PD type modeling approach

Conclusion

Cefoxitin

✓ β-lactam antibiotic
✓ Time-dependent activity

Few challenges during in vitro experiments

✓ not stable over time
✓ MIC determination after 3 days – misleading!

Rominski et al. 2017
Introduction

Objective

In vitro study and PK/PD type modeling approach

Conclusion

Cefoxitin

✓ β-lactam antibiotic
✓ Time-dependent activity

Few challenges during *in vitro* experiments

✓ not stable over time
✓ MIC determination after 3 days – misleading!
✓ Time-kill kinetics assay for longer period > 1 day

Rominski *et al.* 2017
Introduction

Objective

In vitro study and PK/PD type modeling approach

Study in vitro pharmacodynamics of FOX

Study in vitro FOX degradation over time

PK/PD type modeling approach to correct for degradation

Rominski et al. 2017
Experimental Design

**Mycobacterium abscessus**
CIP104536

**Time kill kinetics assay**

**Sampling up to 8 days**

**Bacterial count**

**PK/PD type modeling approach**

**Cefoxitin**

**Concentration measurement using LC-MS/MS**

**In vitro study and PK/PD type modeling approach**
FOX degradation

$t_{1/2} = 1.5$ days
First order degradation

Concentrations: mg/L
**FOX time kill kinetics assay**

**MIC: 8 mg/L**

Concentrations: mg/L
FOX time kill kinetics assay

MIC: 8 mg/L

✓ No effect for initial FOX concentration < MIC
✓ An initial CFU decay followed by regrowth > MIC
✓ Regrowth depends on the increasing FOX initial concentration

Concentrations: mg/L
Why Regrowth?
**Experimental Design**

Growth inhibition model with single homogeneous bacterial population (S)

FOX is bacteriostatic against *M. abscessus*

---

**In vitro study and PK/PD type modeling approach**

Lefebvre *et al.* 2016
Ferro *et al.* 2016

Schematic diagram of final PK/PD type model
Experimental Design

Ferro et al. identified a FOX resistant (R) subpopulation pre-existing at time 0.

Growth inhibition model with single homogeneous bacterial population (S)

FOX is bacteriostatic against *M. abscessus*

Schematic diagram of final PK/PD type model

Lefebvre *et al.* 2016
Ferro *et al.* 2016
**Introduction**

**Objective**

In vitro study and PK/PD type modeling approach

**Conclusion**

Experimental Design

Ferro et al. Identified a FOX resistant (R) subpopulation pre-existing at time 0

Growth inhibition model with single homogeneous bacterial population (S)

FOX is bacteriostatic against *M. abscessus*

---

Growth inhibition model two subpopulation S & R and FOX degradation ($k_e$)

PK/PD type modeling approach using NONMEM

Schematic diagram of final PK/PD type model

Ferro et al. Identified a FOX resistant (R) subpopulation pre-existing at time 0

FOX is bacteriostatic against *M. abscessus*
Introduction
Objective
Results
Conclusion

In vitro study and PK/PD type modeling approach

Observed bacterial counts (circles)
Median (black continuous line)
80% Prediction interval (black dotted line)

Czaja et al. 2014
## Results

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Estimation (%RSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGINOC (\log_{10}\text{CFU/mL})</td>
<td>6.1 (1%)</td>
</tr>
<tr>
<td>(K_g) ((\text{day}^{-1}))</td>
<td>4.3 (6%)</td>
</tr>
<tr>
<td>(B_{\text{max}}) ((\log_{10}\text{CFU/mL}))</td>
<td>9.05 (1%)</td>
</tr>
<tr>
<td>(K_d) ((\text{day}^{-1}))</td>
<td>2.83 (7%)</td>
</tr>
<tr>
<td>(I_{\text{max}})</td>
<td>1 (fixed)</td>
</tr>
<tr>
<td>(IC_{50S}) ((\text{mg/L}))</td>
<td>16.2 (11%)</td>
</tr>
<tr>
<td>(IC_{50R}) ((\text{mg/L}))</td>
<td>252 (20%)</td>
</tr>
<tr>
<td>(K_e) ((\text{day}^{-1}))</td>
<td>0.438 (fixed)</td>
</tr>
<tr>
<td>MUTF</td>
<td>-9.66 (6%)</td>
</tr>
<tr>
<td>(\gamma)</td>
<td>4.8 (39%)</td>
</tr>
</tbody>
</table>

**Czaja et al. 2014**

Observed bacterial counts (circles)
Median (black continuous line)
80% Prediction interval (black dotted line)
Results

In vitro study and PK/PD type modeling approach

IC50S

IC50R
A PK/PD type model: to predict the time-course of effects under different dosing regimens after correction for cefoxitin degradation
A PK/PD type model: to predict the time-course of effects under different dosing regimens after correction for cefoxitin degradation
