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

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Introduction

- *Mycobacterium abscessus* (*Mab*) is the most multidrug-resistant, rapid growing mycobacteria, responsible for major pulmonary infections worldwide (1).
- Current regimens including parenteral administrations of cefoxitin (FOX) in combination with amikacin and clarithromycin raise compliance problems and are frequently associated with high failure and development of resistance.
- Intratracheal administration (nebulization) of FOX offers a biopharmaceutical advantage over intravenous administration (2).
- FOX is known to degrade *in vitro* (3). Consequently, time-kill assays performed up to more than a week and MIC interpretation over 3 days give a de facto misleading impression of the true extent of FOX activity.

Purpose

- To study the impact of FOX *in vitro* stability on time-kill curve data using pharmacokinetic/pharmacodynamic (PK/PD) type modeling approach.

Materials/Methods

M. abscessus CIP104536
FOX MIC: 8 mg/L

Time kill-kinetics analysis

Up to 8 days

Concentration measurement using LC-MS/MS

Bacterial count

Fig. 1: Schematic diagram of time kill-kinetics study with FOX concentration measurement over time

Materials/Methods

Ferro et al. (5) identified a FOX resistant (R) subpopulation pre-existing at time 0

growth inhibition model with single homogeneous bacterial population (S)

Fox is bacteriostatic against *Mab* (4)

✓ FOX Degradation → first order process ($t_{1/2}$: 1.5 days)

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

PK/PD type modeling approach using NONMEM

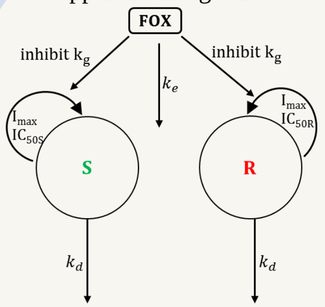


Fig. 2: Schematic diagram of final PK/PD type model

Results & Discussion

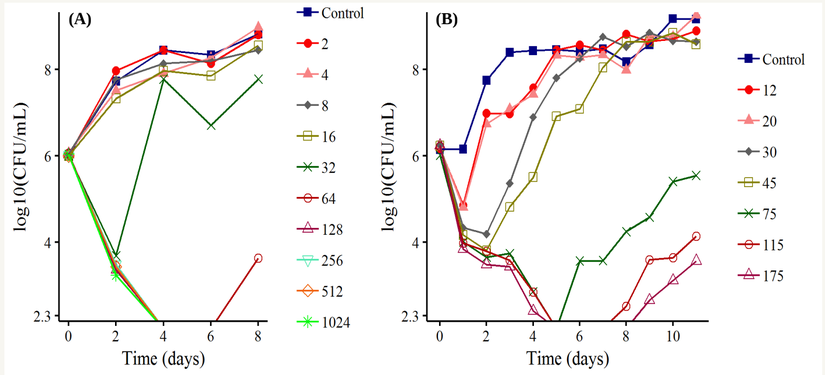
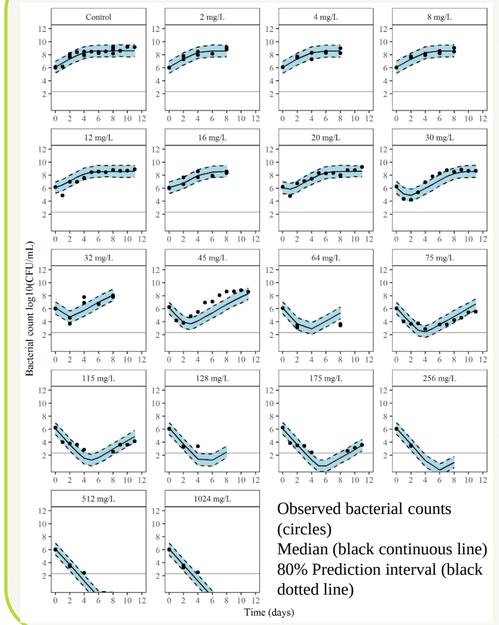


Fig. 3: FOX time-kill curves against *Mab*. Initial concentrations of FOX are in mg/L. (A) First set, (B) Second set

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

Results & Discussion



- ✓ Bacterial regrowth because of FOX degradation & existence of R subpopulation
- ✓ IC_{50S}: 16.2 mg/L ; IC_{50R}: 252 mg/L
- ✓ Maximum unbound Css = 5.5 mg/L in humans after an infusion of 2g over 8h, which is not enough to induce a decay of either subpopulation (6).
- ✓ FOX concentration > 300 mg/L may kill both subpopulations

Fig. 4: Visual Predictive Checks (VPCs) for the final PK/PD type model with correction for FOX degradation against *Mab*

Conclusion & perspective

- ✓ This study suggests that FOX dosing regimens used in clinic for the treatment of *M. abscessus* are not sufficient to reduce the bacterial burden.
- ✓ FOX by nebulization may allow to achieve high concentration at infection site.
- ✓ Also FOX in combination using nebulization could resolve this situation.

References

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6) Czaja et al., *Antim Agen chem*, 2014