Translational PKPD modeling framework to assess the predictive performance of a preclinical visceral leishmaniasis hamster model

UPPSALA UNIVERSITET

Thomas P.C. Dorlo[1,2], Louis Maes[3], Mats O. Karlsson[1], Stéphanie Braillard[4], Charles Mowbray[4]

1. Uppsala University, Sweden; 2. Utrecht University, the Netherlands; 3. University of Antwerp, Belgium; 4. Drugs for Neglected Diseases initiative, Geneva, Switzerland

Introduction

Visceral leishmaniasis (VL) is a parasitic **neglected tropical disease** in which parasites reside and replicate within human host macrophages in spleen, liver or bone marrow. Preclinical efficacy of novel compounds against VL is typically assessed by **reduction of splenic or hepatic intra-macrophageal** *Leishmania* parasite burden in a Golden hamster infection model. Selection of adequate clinical dosing regimens based on these experiments is difficult, since the predictive value of this model remains unassessed and correlation with clinical exposure-response remains unestablished.

Objective

Develop a translational framework to model available preclinical PK and PD data of the oral anti-leishmanial drug miltefosine, derive appropriate PKPD targets, and assess their translational relevance by comparing PK target attainment in human VL patients.

Methods

- **Miltefosine plasma PK data in Golden hamsters** were pooled from 3 different studies:
  1. Single dose p.o. study, dose levels: 5, 10, 20, 40 mg/kg, 12 hamsters
  2. Two multiple dose (5 day) p.o. studies: 10, 40 mg/kg q.d., 24 hamsters
- Population PK analysis: NONMEM v7.3, PsN and Xpose.
- Various structural, variability, covariate and error models were assessed (FOCE-I). Non-linearities were evaluated.

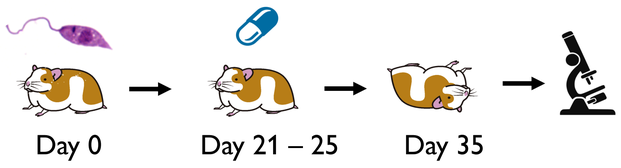
- **PD data** were available from 2 separate studies using hamsters infected with *Leishmania infantum*:
  1. Study 1: 0, 5, 10, 20 mg/kg q.d. for 5 days
  2. Study 2: 20 mg/kg b.d. and 40 mg/kg q.d. for 5 days
- Terminal endpoint: **Leishman-Donovan Unit (LDU)** determined by microscopy counting in liver and spleen at **14 days post start of treatment**:

$$LDU = \frac{Leishmania\ amastigotes}{Macrophages} \times Weight_{tissue}$$

- Exposure-response curves for LDU were fitted using 4-parameter log-logistic model (drc-package in R):

$$E = E_{max} + \frac{E_{min} - E_{max}}{1 + \exp(y(\log(X) - \log(EX_{50})))}$$

- Various simulated summary PK parameters ($AUC_{0\text{-}14d}$, Time>IC_{50}, Time>IC_{90}, *etc.*) for both total and fraction unbound (*f*) were evaluated as exposure-covariate (X).
- Fraction unbound miltefosine: (1) hamster: 1.72%; (2) human: 1.16%; (3) RPMI medium: 1% (to derive free IC50).
- In vitro intracellular IC50 and IC90 values (for *L. infantum*) that were used: 4.10 µg/mL (n=160) and 7.30 µg/mL (n=160), resp.



PK Results

- 1-compartment model with standard allometric scaling fitted the data adequately, but revealed **various non-linearities** (Table 1 and Figure 1).

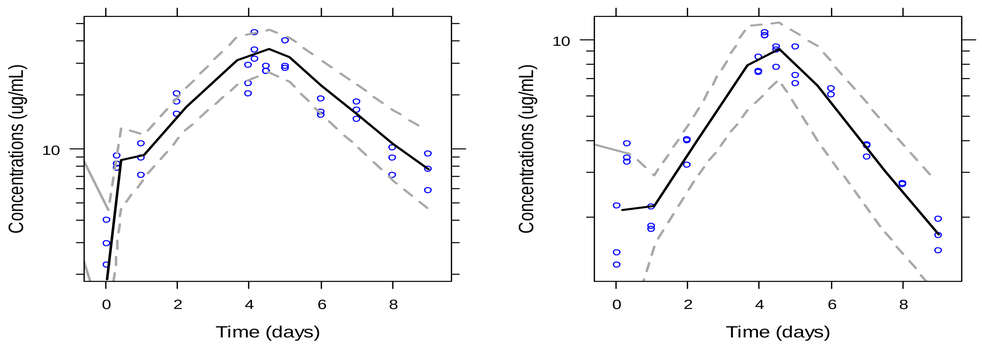


Figure 1. Example visual predictive checks showing the 90% prediction interval and median of simulations versus the observed data for one of the multidose studies, 5 days of miltefosine 10 mg/kg (left) or 40 mg/kg (right).

Conclusions

- **First PKPD relationships for miltefosine quantified in *Leishmania infantum*-infected hamsters**
- **$fAUC_{0\text{-}EOT}$ E99% target attainment in human VL patients corresponded to clinical outcome**
- **Translational framework may be valuable tool to establish best preclinical model and targets for visceral leishmaniasis and help designing future first-in-human clinical trials.**

Parameter	Estimate	Relative standard error	95% CI	Shrinkage
CL/F (L/day/kg)	1.04	2.8%	0.983-1.097	
V/F (L/kg)	1.85	5.3%	1.657-2.043	
ka (/day)	30.8	55.8%	-2.912-64.512	
Proportional residual error (%)	14.2	8.1%	0.119-0.165	
Additive residual error (µg/mL)	0.167	20.5%	0.1-0.234	
Covariate effects				
Effect of time on CL/F (power-function)	-0.439	7.5%	-0.503--0.375	
Effect of dose on ka (power-function)	-0.677	26.9%	-1.034--0.32	
Between-subject variability (BSV)				
BSV CL/F (%)	10.0%	13.6%		21.4%
BSV ka (%)	48.6%	12.9%		7.9%

Table 1. PK parameter estimates with precisions.

PD – Preclinical exposure-response

- Exposure-response curves for various simulated PK parameters ($AUC_{0\text{-}14d}$, Time>IC50, etc.) for both total and free miltefosine were successfully fitted.
- **No clear distinction between PK predictors** or PKPD relationships based on the 'goodness' of fit (AIC or RSE). Fig. 2 shows fitted curves for free exposure metrics.
- **PKPD targets** corresponding to 50%, 95% and 99% effect (E50, E95 and E99), i.e. reduction of parasite burden (LDU), were derived from each preclinical PKPD relationship.

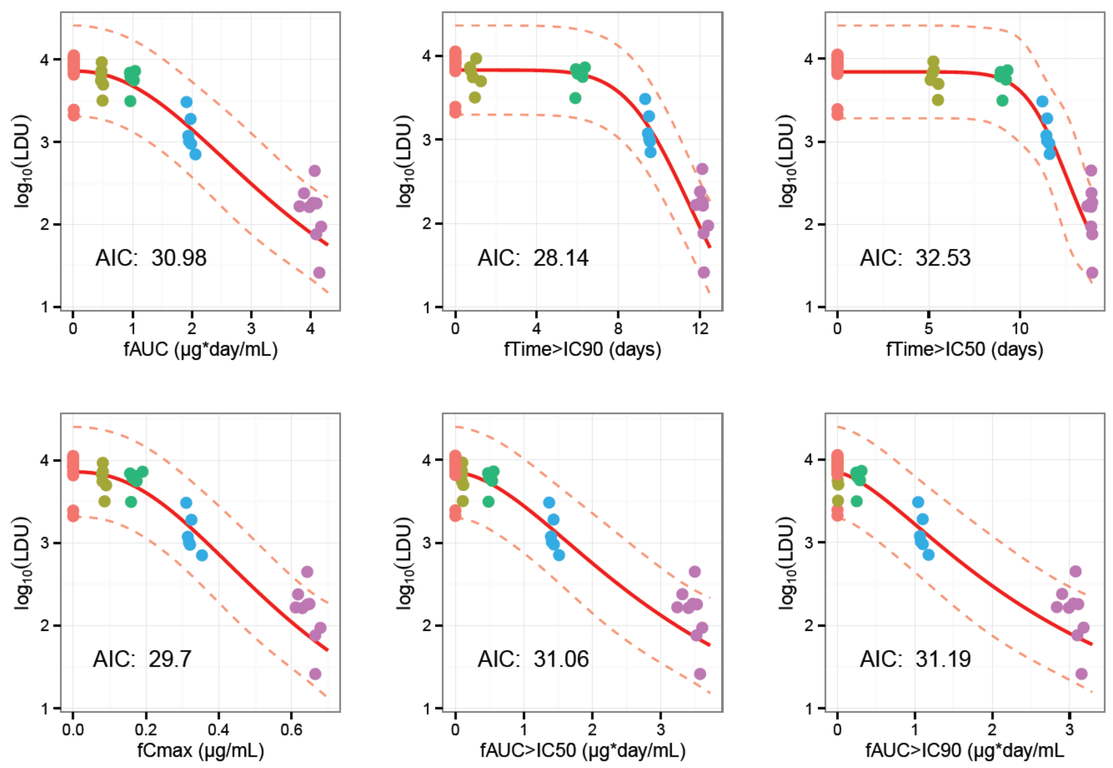


Figure 2. Exposure-response curve fits based on simulated PK parameters. Placebo, 5, 10, 20 and 40 mg/kg/day for 5 days.

Target attainment in human patient population

- Target attainment assessed in **human VL patient cohort in Africa** (n=48, 2.5 mg/kg/day miltefosine 28 days), with cure rate of 72% (CI 60-85).
- Several PKPD indices showed over-attainment (~100%), while $fAUC_{0\text{-}EOT}$ E99% corresponded well in relation to clinical outcome.

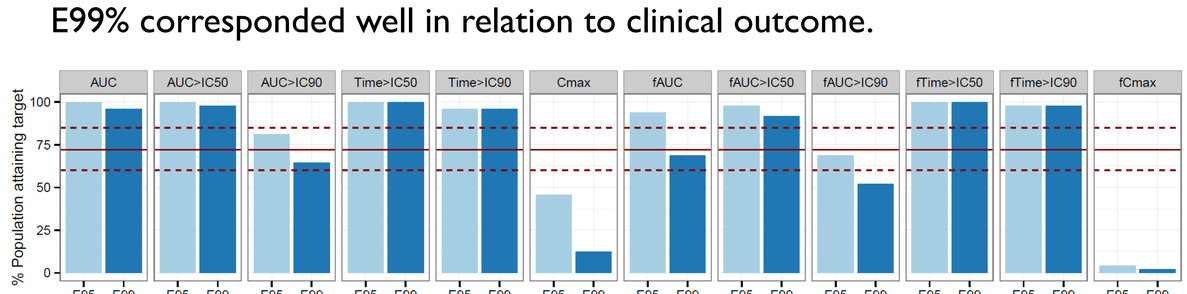


Figure 3. Target attainment in human miltefosine-treated VL patients (n=48, East Africa), the red line indicates the cure rate in this cohort (+CI, broken lines)