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

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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-macrophagial 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, PAn 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:

  \[ LDU = \frac{Leishmania \text{ amastigotes}}{\text{Macrophages}} \times \text{Weight}_{\text{tissue}} \]

- Exposure-response curves for LDU were fitted using 4-parameter log-logistic model (drc-package in R):
  \[ E = E_{\text{max}} + \frac{E_{\text{min}} - E_{\text{max}}}{1 + \exp(y(\log(X) - \log(EX_{50}))} \]
- Various simulated summary PK parameters (AUC0-14d, Time\(>\)IC50, Time\(>\)IC90, 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 \(\mu\)g/mL (n=160) and 7.30 \(\mu\)g/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).

Conclusions

- First PKPD relationships for miltefosine quantified in Leishmania infantum-infected hamsters
- \(fAUC_{0\rightarrow EOT}\) 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.

Table 1. PK parameter estimates with precisions.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Relative standard error</th>
<th>95% CI</th>
<th>Shrinkage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F (L/day/kg)</td>
<td>1.04</td>
<td>2.8%</td>
<td>0.981-1.097</td>
<td></td>
</tr>
<tr>
<td>V/F (L/kg)</td>
<td>1.85</td>
<td>5.3%</td>
<td>1.657-2.043</td>
<td></td>
</tr>
<tr>
<td>ka (day(^{-1}))</td>
<td>30.8</td>
<td>55.8%</td>
<td>-2.912-64.512</td>
<td></td>
</tr>
<tr>
<td>Proportional residual error (%)</td>
<td>14.2</td>
<td>8.1%</td>
<td>0.119-0.165</td>
<td></td>
</tr>
<tr>
<td>Additive residual error ((\mu)g/mL)</td>
<td>0.147</td>
<td>20.5%</td>
<td>0.1-0.234</td>
<td></td>
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<tr>
<td>Covariate effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Effect of time on CL (power-function)</td>
<td>-0.439</td>
<td>7.5%</td>
<td>-0.503-0.375</td>
<td></td>
</tr>
<tr>
<td>Effect of dose on ka (power-function)</td>
<td>-0.677</td>
<td>26.9%</td>
<td>-1.034-0.32</td>
<td></td>
</tr>
<tr>
<td>Between-subject variability (BSV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSV CL/F (%)</td>
<td>10.0%</td>
<td>13.6%</td>
<td>21.4%</td>
<td></td>
</tr>
<tr>
<td>BSV V/F (%)</td>
<td>48.6%</td>
<td>12.9%</td>
<td>7.9%</td>
<td></td>
</tr>
</tbody>
</table>

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).

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 \(fAUC_{0\rightarrow EOT}\) 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 (+CL, broken lines).