Translational PK M&S for the assessment of duration of contraceptive cover after use of miltefosine for the treatment of visceral leishmaniasis

Thomas Dorlo, Manica Balasegaram, Nines Lima, Peter de Vries, Jos Beijnen, Alwin Huitema
Visceral Leishmaniasis (VL)

- Neglected tropical disease
- Poor rural areas – **India & Sudan**
- Intracellular parasite within macrophages

Visceral Leishmaniasis (VL)

- Neglected tropical disease
- Poor rural areas – **India & Sudan**
- Intracellular parasite within macrophages

Visceral Leishmaniasis (VL)

- Neglected tropical disease
- Poor rural areas – India & Sudan
- Intracellular parasite within macrophages

Miltefosine

- Only oral drug currently available for VL
- Monotherapy regimen:
  - 2.5 mg/kg for 28 days
- Extremely long elimination half-life
  - t½: first 5-7 days and terminal of 31 days\(^{[1,2]}\)
- Shorter combination regimens under development

Reproductive toxicity of miltefosine

- First-line in India – regional elimination programme
- Toxicity: GI-related & **reproductive toxicity**
- Feto- & embryotoxicity rabbits & rats – **teratogenicity** rats only (∆ 1.2 mg/kg/day for 10 days during gestation) \[1\]

---

\[1\] Paladin Labs/WHO, Application Essential Medicine List (2010)  
\[2\] Sindermann et al, TRSTMH (2003)  
\[3\] WHO TRS 949 (2011)  
Reproductive toxicity of miltefosine

- First-line in India – regional elimination programme
- Toxicity: GI-related & reproductive toxicity
- Feto- & embryotoxicity rabbits & rats – teratogenicity rats only (≥ 1.2 mg/kg/day for 10 days during gestation)\(^1\)
- Guidelines: 2 or 3 months post-treatment contraception for women of child-bearing potential on 28-day regimen\(^2,3\)
- But miltefosine can be detected until 5 months post-treatment?\(^4\)

Reproductive toxicity of miltefosine

• First-line in India – regional elimination programme
• Toxicity: GI-related & reproductive toxicity
• Feto- & embryotoxicity rabbits & rats – teratogenicity rats only (≥ 1.2 mg/kg/day for 10 days during gestation)[1]
• Guidelines: 2 or 3 months post-treatment contraception for women of child-bearing potential on 28-day regimen[2,3]
• But miltefosine can be detected until 5 months post-treatment?[4]
• Ethical dilemma: Costs & adherence vs risk malformation

Aim & approach

**Dose conversion** from animal teratogenicity studies (NOAEL)

Human Equivalent Dosage (HED)

Human Equivalent Exposure (HEE)

Suggest rational & optimal **durations of post-treatment contraceptive cover**
Population PK model

Developed based on PK data from Indian children (9-25 kg), Indian adults (25-48 kg) & European adults (60-105 kg)[1,2]

Fat-free mass (FFM) & fixed allometric scaling

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Estimate</th>
<th>RSE (% of Estimate)</th>
<th>BSV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption ($k_a$)</td>
<td>$h^{-1}$</td>
<td>0.416</td>
<td>(11.5%)</td>
</tr>
<tr>
<td>Clearance (CL/F)</td>
<td>$L/day$</td>
<td>3.99</td>
<td>(3.5%)</td>
</tr>
<tr>
<td>Central compart ($V_2/F$)</td>
<td>$L$</td>
<td>40.1</td>
<td>(4.5%)</td>
</tr>
<tr>
<td>Periph compart ($V_3/F$)</td>
<td>$L$</td>
<td>1.75</td>
<td>(18.3%)</td>
</tr>
<tr>
<td>Intercompart. Clearance ($Q/F$)</td>
<td>$L/day$</td>
<td>0.0375</td>
<td>(8.2%)</td>
</tr>
<tr>
<td>Residual variability</td>
<td>%</td>
<td>34.3</td>
<td>(3.7%)</td>
</tr>
</tbody>
</table>

Population PK model

Developed based on PK data from **Indian children** (9-25 kg), **Indian adults** (25-48 kg) & **European adults** (60-105 kg)[1,2]

**Fat-free mass (FFM) & fixed allometric scaling**

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Estimate</th>
<th>RSE</th>
<th>BSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption ($k_a$)</td>
<td>$h^{-1}$</td>
<td>0.416(11.5%)</td>
<td>18.2%</td>
</tr>
<tr>
<td>Clearance (CL/F)</td>
<td>$L/day$</td>
<td>3.99 (3.5%)</td>
<td>32.1%</td>
</tr>
<tr>
<td>Central compart ($V_2/F$)</td>
<td>$L$</td>
<td>40.1 (4.5%)</td>
<td>34.1%</td>
</tr>
<tr>
<td>Periph compart ($V_3/F$)</td>
<td>$L$</td>
<td>1.75 (18.3%)</td>
<td>NE</td>
</tr>
<tr>
<td>Intercompart. Clearance (Q/F)</td>
<td>$L/day$</td>
<td>0.0375 (8.2%)</td>
<td>NE</td>
</tr>
<tr>
<td>Residual variability</td>
<td>%</td>
<td>34.3 (3.7%)</td>
<td>NE</td>
</tr>
</tbody>
</table>


No PK data from females!
Anthropometric data

• Collected at MSF hospital in Bihar, India
• Total of 2247 VL patients

465 females of child-bearing potential (12-45 yrs)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median value (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25 (16–31)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>38 (34–42)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>148 (144–152)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>17.3 (15.8–18.8)</td>
</tr>
<tr>
<td>Fat-free body mass (kg)</td>
<td>27.1 (24.6–29.5)</td>
</tr>
</tbody>
</table>
Monte Carlo PK simulations for Indian females

285 days
Monte Carlo PK simulations for Indian females

- 5 day regimen: 158 days
- 7 day regimen: 176 days
- 10 day regimen: 196 days
- 28 day regimen: 258 days

LLOQ
Dose conversion: animal to human

• Rat reproductive **NOAEL**: 0.6 mg/kg for 10 days\(^1\)
• BSA normalisation\(^2,3\) & total dose

Dose conversion: animal to human

• Rat reproductive **NOAEL**: 0.6 mg/kg for 10 days[^1]

• BSA normalisation[^2,^3] & total dose

• **Human equivalent dose** (HED):
  
  0.6 mg/kg for 10 days in rat = 6 mg/kg total in rat
  
  = 36 mg/m² in rat = **45 mg total HED**

Dose conversion: reproductive safety threshold exposure limit

• Monte Carlo simulations of HED in 465 Indian female VL patients:
  – Median AUC\(_{0-\infty}\) (90% PI): 245 µg·day/mL (140 – 467)

• Species-specific sensitivity to reproductive toxicity?

Dose conversion: reproductive safety threshold exposure limit

• Monte Carlo simulations of HED in 465 Indian female VL patients:
  – Median $\text{AUC}_{0-\infty}$ (90% PI): 245 $\mu$g·day/mL (140 – 467)

• Species-specific sensitivity to reproductive toxicity?

• Animal-to-human safety factor of 10$^{[1,2,3]}$

• Final human threshold exposure limit: 24.5 $\mu$g·day/mL

Post-treatment contraceptive cover of 1, 2, 3 and 4 months
Post-treatment contraceptive cover of 1, 2, 3 and 4 months
Post-treatment contraceptive cover of 1, 2, 3 and 4 months

Threshold exposure limit: $\text{AUC} < 24.5 \, \mu\text{g} \cdot \text{day}/\text{mL}$
Simulations: Exposure post-EOC

Monte Carlo simulations \( n = 465 \text{ females} \) (500x)

\[ \text{AUC}_{\text{EOC-∞}} \quad (\mu g* mL/day) \]

- 5 days
- 7 days
- 10 days
- 28 days

- 1 month
- 2 months
- 3 months

\( PI: \) prediction interval; \( EOC: \) end of contraception
Simulations: Exposure post-EOC

Monte Carlo simulations $n = 465$ females (500x)

$\text{PI}: \text{prediction interval; EOC: end of contraception}$
Simulations: Probability

**Comparison to the exposure threshold limit:**

<table>
<thead>
<tr>
<th>Miltefosine regimen</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
<th>4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 days</td>
<td>4.3%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>7 days</td>
<td>18.2%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>10 days</td>
<td>54.6%</td>
<td>0.198%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>28 days</td>
<td>93.6%</td>
<td>5.42%</td>
<td>0.581%</td>
<td>&lt;0.1%</td>
</tr>
</tbody>
</table>

EOT, end of therapy.
Interpretation

• Incidence of **congenital malformation (CM)**
  – India: 0.2-3.6% - limited evidence[^1]
  – Europe: 2.44%[^2]

• Approx 1/10th of CM due to environmental factors[^3]

• Probability of exposure above chosen threshold should be less than CM-incidence due to environmental factors < 1/10th of 2.44%

[^1]: Swain et al, Indian pediatrics (1994)  
# Simulations: Probability

Probability of exposure above the reproductive safety threshold exposure limit for the indicated number of months on contraception after EOT

<table>
<thead>
<tr>
<th>Miltefosine regimen</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
<th>4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 days</td>
<td>4.3%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>7 days</td>
<td>18.2%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>10 days</td>
<td>54.6%</td>
<td>0.198%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>28 days</td>
<td>93.6%</td>
<td>5.42%</td>
<td><strong>0.581%</strong></td>
<td>&lt;0.1%</td>
</tr>
</tbody>
</table>

EOT, end of therapy.

**Probability of exposure <0.244%**
Simulations: Probability

Probability of exposure above the reproductive safety threshold exposure limit for the indicated number of months on contraception after EOT

<table>
<thead>
<tr>
<th>Miltefosine regimen</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
<th>4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 days</td>
<td>4.3%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>7 days</td>
<td>18.2%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>10 days</td>
<td>54.6%</td>
<td>0.198%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>28 days</td>
<td>93.6%</td>
<td>5.42%</td>
<td>0.581%</td>
<td>&lt;0.1%</td>
</tr>
</tbody>
</table>

EOT, end of therapy.

**Probability of exposure <0.244%**

Longer than current guidelines, but shorter than approach based on LLOQ (>5 months)
Simulations: Probability

<table>
<thead>
<tr>
<th>Miltefosine regimen</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
<th>4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 days</td>
<td>4.3%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>7 days</td>
<td>18.2%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>10 days</td>
<td>54.6%</td>
<td>0.198%</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>28 days</td>
<td>93.6%</td>
<td>5.42%</td>
<td>0.581%</td>
<td>&lt;0.1%</td>
</tr>
</tbody>
</table>

EOT, end of therapy.

**Probability of exposure <0.244%**
Discussion: Teratogenic risk management

Other examples:

- **Isotretinoïn**
  - Endogenous levels Vit A
- **Ribavirin**
  - Turnover-time erythrocytes (site accumulation)
- **Leflunomide**
  - Based on undetectability (LLOQ!)\(^1\)

Concentration-effect relationship?

\(^1\) Brent RL. Teratology (2001)
Discussion:
Limitations of our study

• Reproductive tox studies in small set of animals
• Animal-to-human dose conversion
  – Similar PK in animals (mouse, rat, dog, human)
  – Distribution into cell membranes
  – No evidence interspecies metabolic differences

→ Animal-to-human safety factor (10x)
Conclusion

• **M&S:**
  - Simulate PK in a **unique & vulnerable population**
  - Non-parametric probability estimations with full variability

• **More rational teratogenic risk management**

• **Contraceptive cover recommendations:**
  - 4 months for miltefosine monotherapy (e.g. oral or intra-uterine)
  - 2 months for shorter combination regimens (e.g. depot medroxyprogesterone acetate)
Acknowledgements

Slotervaart Hospital / the Netherlands Cancer Institute
Dept. Pharmacy & Pharmacology
Alwin Huitema
Jos Beijnen

Academic Medical Center / University of Amsterdam
Center for Tropical & Travel Medicine
Peter de Vries

Drugs for Neglected Diseases initiative (DNDi)
Geneva, Switzerland
Manica Balasegaram

Médecins Sans Frontières
Operational Center Barcelona-Athens
Nines Lima

Field and capital teams in India
Sakib Bursa, Avinash Sadashivaiah, Gaurab Mitra,
Marta Gonzalez, Mattia Novella and Bjorn Nissen
The full paper describing the work presented here was recently accepted for publication in *Journal of Antimicrobial Chemotherapy*:


http://jac.oxfordjournals.org/content/early/2012/05/10/jac.dks164
http://dx.doi.org/10.1093/jac/dks164