DRUGS FOR CHAGAS AND LEISHMANIASIS

A brief, and probably skewed, overview from a translational perspective

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Disclaimer

I do not have any potential conflicts of interest to disclose

My opinions are my own and do not necessarily agree with those of my employer(s) or anybody else...
What are Neglected Diseases?

**No universally accepted definition**

- Prevalent among impoverished and marginalized populations in the developing world
- Insufficient incentives for private or public sector to invest in research and development of drugs or vaccines
- Not adequately addressed nationally and internationally
Who is affected?

• Neglected diseases impair or permanently disable a large number of people
• but cause comparatively few deaths, and many have a silent chronic progression
• Neglected diseases mostly affect children and women (particularly in pregnancy)
Who is affected? CHILDREN !!

Chagas disease

- Caused by the parasite *Trypanosoma cruzi*
- Transmitted by blood-sucking insect vectors, transfusions and **vertical transmission**
- >8 million infected people in the Americas
- >50,000 people die each year of Chagas disease complications
- Economic losses >6 billion U$S/year
Chagas disease - vectors
CHAGAS DISEASE

• The infection occurs mostly in children by vectorial or congenital route
• The majority of children are asymptomatic
• If untreated, CD leads to cardiac morbidity years or decades after infection
• CD is endemic in Latin America but, due to migration, infected patients have been found in USA, Europe, Australia, Japan
Benznidazole formulation problem

100 mg

1/8 = 12.5 mg

WARNING: CHOKING HAZARD - Small Not for children under 3 yrs
Leishmaniasis

Sandfly Stages
1. Sandfly takes a blood meal (injects promastigote stage into the skin)
2. Promastigotes are phagocytized by macrophages or other types of mononuclear phagocytic cells
3. Promastigotes transform into amastigotes
4. Amastigotes multiply in cells of various tissues and infect other cells

Human Stages
5. Sandfly takes a blood meal (ingests macrophages infected with amastigotes)
6. Ingestion of parasitized cell
7. Amastigotes transform into promastigote stage in the gut
8. Divide in the gut and migrate to proboscis

= Infective Stage
= Diagnostic Stage

CDC
SAFER • HEALTHIER • PEOPLE™
# Leishmaniasis

## Leishmania taxonomy

<table>
<thead>
<tr>
<th>Region</th>
<th>Complex</th>
<th>Species</th>
<th>Clinical Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old World</td>
<td><em>Leishmania donovani</em></td>
<td><em>L. donovani</em></td>
<td>CL, VL, PKLD, ML (rare)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>L. infantum</em></td>
<td>CL, VL (children), PKLD, ML (rare)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>L. chagasi</em></td>
<td>CL, VL (children), PKLD, ML (rare)</td>
</tr>
<tr>
<td></td>
<td><em>Leishmania tropica</em></td>
<td><em>L. tropica</em></td>
<td>CL, ML (rare), VL (rare)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>L. major</em></td>
<td>CL, ML (rare)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>L. aethiopica</em></td>
<td>CL, DCL</td>
</tr>
<tr>
<td>New World</td>
<td><em>Leishmania mexicana</em></td>
<td><em>L. mexicana</em></td>
<td>CL, DCL (rare)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>L. amazonensis</em></td>
<td>CL, DCL, ML, VL (rare), PKLD (rare)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>L. venezuelensis</em></td>
<td>CL, DCL (rare)</td>
</tr>
<tr>
<td></td>
<td><em>Leishmania (Vianna) braziliensis</em></td>
<td><em>L. braziliensis</em></td>
<td>CL, ML, VL</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>L. guyanensis</em></td>
<td>CL, ML</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>L. panamensis</em></td>
<td>CL, ML</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>L. peruviana</em></td>
<td>CL</td>
</tr>
</tbody>
</table>
## Leishmaniasis - Treatments

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Regimen</th>
<th>Marketinga</th>
<th>Clinical Efficacy</th>
<th>Resistance</th>
<th>Toxicity</th>
<th>Cost/Course</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentavalent antimonials</td>
<td>20 mg/kg iv or im daily for 28–30 days</td>
<td>Albert David (SSG); GSK (Pentostam); Sanofi Aventis (Glucantine)</td>
<td>35%–95% (depending geographic area)</td>
<td>As high as 60%</td>
<td>Frequent, potentially</td>
<td>Generic price: $52</td>
<td>Quality control, Resistance in India</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>0.75–1 mg/kg iv for 15–20 doses (daily or alternate days)</td>
<td>Bristol Meyers Squibb (Fungizone); Generic companies</td>
<td>&gt;97% all regions</td>
<td>Not documented</td>
<td>Frequent</td>
<td>Generic price:</td>
<td>Nephrotoxicity, In-patient care needed, Need for slow iv</td>
</tr>
<tr>
<td>Liposomal Amphotericin B</td>
<td>10–30 mg/kg; Total dose iv; usually 3–5 mg/kg/dose; Single dose (10 mg/kg) in India</td>
<td>Gilead (AmBisome)</td>
<td>Not documented</td>
<td>Uncommon and mild; Nephrotoxicity</td>
<td>Preferential price: $780</td>
<td>Commercial price: ~10x</td>
<td>Price, Need for slow iv</td>
</tr>
<tr>
<td>Miltefosine</td>
<td>2–2.5 mg/kg/d orally daily over 28 days</td>
<td>Paladin (Impavid)</td>
<td>Asia: 94% (India); Africa: single first study (93% in HIV(-))</td>
<td>Readily obtained</td>
<td>Common, usually mild</td>
<td>Preferential price: $150</td>
<td>Patient compliance, Possibly teratogenic</td>
</tr>
<tr>
<td>Paromomycin sulfate</td>
<td>15 mg/kg im daily for 21 days (India only)</td>
<td>IOWH/Gland Pharma</td>
<td>Asia: 95% (India); Africa: 15 mg/kg; 64% (Sudan); 20 mg/kg: 80% (Sudan)</td>
<td>Readily obtained</td>
<td>Uncommon, Efficacy variable</td>
<td>~$15</td>
<td>Preference for resistance (?)</td>
</tr>
</tbody>
</table>

*Table 1: The main drugs currently used for treatment of visceral leishmaniasis*
Leishmania – miltefosine

For Humans

For Dogs

WARNING: CHOKING HAZARD - Small parts. Not for children under 3 years.
Leish – amphotericin B, antimonials, paromomycin
New drugs are needed, but they need to be:

- Orally available
- Effective (at least as good as available treatments)
- Rapid action (i.e. short treatments)
- Appropriate, and safe, for children!
- And for pregnant women!!
- Affordable...
Drug development - preclinical

Compounds (molecules, natural products, etc)

Disease model(s) (in vitro, in vivo, etc)

Lead compounds (a lot less!)

Compound modification

Pre-clinical evaluation
- Pharmacokinetics
- Toxicity

Price tag: 1.3 billion dollars!!

90% ATTRITION

CLINICAL STUDIES
Where is big pharma?

- Development costs of a new drug >1B
- These costs include opportunity costs, abandoned projects, marketing...
- Marketing, marketing, marketing...
- NTDs have unattractive socioeconomic characteristics
Why is big pharma not interested?

They can’t really pay much...
What other options are out there?

**Academic drug development**

- Drug development very difficult and expensive
- Academia has very limited compound portfolios
- Limited experience and skills in transitioning from one development phase to the next
- Too often focused on one "miracle" drug, that gets killed off when costs (or toxicity) are actually evaluated
- Very slow to “let go” of ineffective drugs

Public – private partnerships and NGOs can help a lot here! (such as DNDi does)
Disease models

• Many animal models can give insights into parts of the PKPD process
• But it’s important to remember that the objective is not to cure mice, rats or dogs…
• The only accurate animal model is the human model!
Academic drug development

- Transfer from lead compound to a drug in clinical trials is not easy
- Drug development has about 90% attrition rate in the CLINICAL TRIALS stage!
- But if you don’t get there, your drug will never help anyone

- Let go!
PHARMACOKINETICS

“What the body does to the drug”
Drug Metabolism and Pharmacokinetics (DMPK)

**Pharmacokinetics**: “what the body does to the drug”

- **Absorption**
- **Distribution**
- **Metabolism**
- **Excretion**

Can be evaluated by *in vitro* techniques and in animals to predict (to some extent...) human pharmacokinetics

- **Toxicity** (not really pharmacokinetics... pharmacodynamics)

⇒ **ADMET**
Drug Metabolism and Pharmacokinetics (DMPK)

- **Absorption:** Dissolution models, monolayer permeability, animal bioavailability, simulation,…
- **Distribution:** protein binding, lipid-water partition, animal studies (radiolabelled drug),…
- **Metabolism:** In vitro CYP studies, microsomes, ex vivo organ perfusion, animal drug metabolism
- **Excretion:** animal models, simulation, in vitro drug transport, …
- **Toxicity** (not really pharmacokinetics... pharmacodynamics)
PK -> Pharmacodynamics (PKPD)

Relevance to Chagas or Leishmaniasis????
TRANSLATIONAL MEDICINE
(WHAT CAN WE LEARN FROM HUMAN TRIALS?)
TRANSLATIONAL MEDICINE

• Interdisciplinary branch of medicine
• *Translates* clinical observations or findings to basic research (e.g. disease models) to try to find new solutions that can then be brought back to clinical research (and patient treatment)

“bench to bedside”

*(actually,)*

*bedside to bench, and back to bedside*
Drug development - preclinical

- Compounds (molecules, natural products, etc)
- Disease model(s) (in vitro, in vivo, etc)
- Lead compounds (*a lot less*)
- Compound modification

Pre-clinical evaluation
- Pharmacokinetics
- Toxicity

TRANSLATIONAL MEDICINE

CLINICAL STUDIES
Human model

- Where should the drug go?
- How high should it be?
- How long should it stay there?
- How fast should it clear the infection?
- What effects we don’t like to have?
- What effects we don’t like but accept as part of the treatment?
Population Pharmacokinetic Study of Benznidazole in Pediatric Chagas Disease Suggests Efficacy despite Lower Plasma Concentrations than in Adults

Jaime Altcheh, Guillermo Moscatelli, Guido Mastrantonio, Samanta Moroni, Norberto Giglio, Maria Elena Marson, Griselda Ballering, Margarita Bisio, Gideon Koren, Facundo García-Bournissen

Published: May 22, 2014 • DOI: 10.1371/journal.pntd.0002907

Clinicaltrials.gov registry # NCT00699387
Steady state concentrations (popPK)

All children had a positive treatment response, with negative *T. cruzi* qPCR
Overall good correlation with PCR results

A significant drop in Elisa titers seen after 3-6 months.

Seroconversion in most patients at 12 months.
**T. cruzi ELISA**

**Age <2 y**
- Overall good correlation with PCR results
- A significant drop in Elisa titers seen after 3-6 months.
- Seroconversion in most patients at 12 months.

**Age >3 y**
- Some drop in Elisa titers after 3-6 months.
- Large intra and inter-patient variability
- No seroconversion after 80 months
BNZ – Children

- Benznidazole concentrations in children were significantly lower than those reported in adults (treated with comparable mg/kg doses).
- In spite lower plasma concentrations, children responded well to the treatment, and had a low incidence of ADRs.
- If these results are confirmed, dose reduction of benznidazole in adults should be explored.
Prevention of congenital Chagas through treatment of girls and women of childbearing age

Guillermo Moscatelli/*, Samanta Moroni, Facundo García-Bournissen, Griselda Ballering, Margarita Bisio, Héctor Freilij, Jaime Altcheh

Department of Parasitology and Chagas, Ricardo Cutiérrez Children’s Hospital, Buenos Aires, Argentina

Trypanocide Treatment of Women Infected with Trypanosoma cruzi and Its Effect on Preventing Congenital Chagas

Diana L. Fabbro, Emmaria Danesi, Veronica Olivera, Maria Olenka Codebó, Susana Denner, Cecilia Heredia, Mirtha Streiger, Sergio Sosa-Estani

Published: November 20, 2014  •  DOI: 10.1371/journal.pntd.0003312
BNZ & POSACONAZOLE ADULTS

Figure 2. Efficacy End Points.
The intention-to-treat analysis included all patients who underwent randomization; the per-protocol analysis included patients who completed treatment and follow-up. Patients who were lost to follow-up were excluded from the per-protocol analysis unless rt-PCR testing after the end of the treatment period was positive.

Randomized Trial of Posaconazole and Benznidazole for Chronic Chagas’ Disease

Israel Molina, M.D., Jordi Gómez i Prat, M.D., Fernando Salvador, M.D., Begoña Treviño, M.D., Elena Sulleiro, M.D., Núria Serre, M.D., Diana Pou, M.D., Silvia Roure, M.D., Juan Cabezos, M.D., Lluís Valerio, Ph.D., Albert Blanco-Grau, M.D., Adrián Sánchez-Montalvá, M.D., Xavier Vidal, Ph.D., and Albert Pahissa, Ph.D.
E1224 & BENZNUDIAZOLE

Proportion of treatment success by treatment group - survival curve

- Placebo: 9% success
- Benznidazole: 84% success
- E1224 High Dose (4-Week): 11% success
- E1224 High Dose (8-Week): 31% success
- E1224 Low Dose (8-Week): 9% success
E1224 & BENZNIDAZOLE

% Positive PCR vs TIME, per Treatment Group

% Positive PCR

Days

treatment_group
- Placebo
- Benznidazole
- E1224 High Dose (4-Week)
- E1224 High Dose (8-Week)
- E1224 Low Dose (8-Week)
Chagas translational medicine lesson

• Antifungals (CYP 51 inhibitors at least) are not particularly good for treatment of Chagas disease...
• Screening (in vitro) and animal models should incorporate this knowledge
• New approaches may still have potential (e.g. combinations)

• Back to the drawing board!
MILTEFOSINE TRIALS - FAILURES

Figure 1. Kaplan-Meier Survival plot for relapse per age group.
doi:10.1371/journal.pone.0100220.g001

Figure 2. Observed miltefosine end-of-treatment (EOT) concentrations among children and adults, by body weight. Adults are individuals aged ≥12 years, and children are individuals aged <12 years. The solid line shows a fitted polynomial smoothed regression line. For comparability, only observed concentrations within 7 days of EOT were included here.
Leishmaniasis translational medicine lesson

• No matter how effective in animal models, studies in humans will need adjustments
• Children will need even more adjustments
• Children are not small adults...
• Or big mice...
• And they have more rights than dogs do to have a liquid formulation!!
DISCUSSION

• Drug development, particularly from an academic perspective, should be viewed as an iterative process.
• Data from clinical trials and clinical observations can inform the drug development process.
• Animal and in vitro models can help refine knowledge and select drugs that address clinical problems.
• New compounds with potential should be evaluated for clinical testing as soon, and as often, as possible provided safety data is reassuring.
• Drug combinations have a still untapped potential in Chagas disease and Leishmaniasis.
Thank you very much!

Facundo Garcia Bournissen
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