Challenges in Developing a New Treatment for Chagas Disease

Sergio Sosa-Estani, MD, MPH, PhD
Head Service of Epidemiology
National Center for Research on Endemic Diseases/ANLIS “Dr. Carlos G. Malbrán
Ministry of Health, Argentina
Carlos Chagas  Salvador Mazza
T. Cruzi Transmission

<table>
<thead>
<tr>
<th>Transmission Mechanism</th>
<th>w/o Control</th>
<th>w/ Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vector-borne transmission</td>
<td>&gt;80%</td>
<td>10%</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>16%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Congenital</td>
<td>2%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Other mechanisms:</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>(i.e. oral, organ transplant, laboratory accident)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Initiatives for interrupting vectorial and transfusional transmission of Trypanosoma cruzi
Trend of epidemiological indexes of Chagas’ disease in Latin America, 1990-2000
Rates x 1000 inhabitants

Prevalencia 35 19
Incidencia 2,5 1
Mortalidad 0,045 0,025

Migration Flows from Latin America Chagas’ disease

Current Recommendations for Specific Treatment against *T. cruzi* Infection

- All patients in the acute phase
- Children and young patients in the chronic phase
- Laboratory or surgical accidents
- Organ transplant recipients or donors

- Chronic phase, indeterminate or incipient cardiac form in adults may be considered for treatment, although with limited evidence
Side Effects: Timeline

Gastrointestinal
Dermal

Hematological
Liver toxicity

Peripheral Neurotoxicity

Day 1
Start

Day 30
Middle

Day 60
End

Tolerability Monitoring
• Weekly contact with the patient
• Laboratory testing

Adults

Neonates
Treatment of children: there are no adequate formulations for pediatric use

Product sheet with problem

New approaches
Solution: UNR Argentina
Suspension: LAFEPE Brazil
Adapted tablet size: DNDi/LAFEPE Brazil

1/16 doses each 12 hs ???
Some concerns with tablet fragmentation

- Improper dosages
- Drug may not disperse uniformly when grinded and suspended in liquids
- Potential impact on:
  - Pharmacokinetics
  - Safety
  - Efficacy
Different parameters to take into account for a new formulation or new presentation

- Ease of administration (preparation and dosing)
- Accuracy of dose administered
- Flexibility of dose
- Stability of the preparation
- Acceptability/suitability of the preparation
- Excipients acceptability
- Manufacturing and financial implications
Some alternatives

Liquid formulations
- Syrup
- Reconstitutable dry suspensions

Solid formulations
- Immediate release tablets
- Effervescent, soluble or dispersible tablets
- Chewable tablets
- Orodispersible dosage forms
- Multiparticulate preparations

Tuleu C, School of Pharmacy University of London
Registered drugs with anti-\textit{T. cruzi} activity

- Posaconazole (antifungal)
- Bisphosphonates (osteoporosis)
- Miltefosine (antineoplastic, antiprotozoal)
- Clomipramine (tricyclic antidepressant)
- Liposomal amphotericin (antifungal, antiprotozoal)
Evaluation of Combination Treatment

Objectives

- Different types of combination treatments depending on the main objectives of the treatment:
  - Improvement of efficacy
  - Delay of development of resistance to the individual components of the combination
    - With low levels of resistance, low prevalence and deficiencies in laboratory testing: impact of resistance to antiparasitic agents is insidious.
    - Unless clinical drug trials are conducted, resistance and its impact often go unrecognized
  - Improvement of safety profile
  - Reduction of dose and duration of treatment regimens
    - Side effects of Bz and Nftx are both dose and time-dependent
Evaluation of Combination Treatment

Pragmatic decision for short term evaluation:

Combination of registered compounds (Benznidazole/Nifurtimox) with drugs with demonstrated activity in Chagas’ disease
Animal studies - Combination studies

Combination candidates

Benznidazole + Nifurtimox +

Itraconazole
Ravuconazole
Posoconazole
TAK 187
Miltefosine
Evaluation of library of existing compounds

Priorities:

- Determine IC50s for hits from existing libraries
- Toxicology/pharmacology review of hits
- Proceed to \textit{in vivo} models as monotherapy if justified
- Prioritize partner drugs from existing libraries and current Chagas therapy
- Assay for additive/synergistic effects in vivo
- Review of hits as scaffolds for lead optimization
How to assess a treatment during chronic phase?

- **Immunological tests**
  - Serological tests - Commercially Available
    - Need long follow up to demonstrate efficacy
  - Serological tests - Not commercially available, tested as useful
    - Need shorter time of follow up, but > 3 years
    - Need validation
  - Specific cellular response (under research)

- **Parasitological tests**
  - Direct tests (low sensitivity)
  - Xenodiagnosis (only in centers of reference, low sensitivity)
  - Hemoculture (available, low sensitivity)
  - PCR (higher sensitivity, currently under standardization, new techniques quantitative PCR with rapid developments)
Need for clinical research

Etiological treatment

- To develop and assess new formulation or presentation of old drugs
- To assess new application of drugs for other indications
- To develop novel drugs
- To develop new tools to assess efficacy of current and new treatments in short time
  - To validate and standardize PCR test
Needs for clinical research

Other issues

• To develop new tools to diagnose congenital *T. cruzi* infection at the time of delivery

• To find and assess markers of evolution of disease

• To gather evidence for selection of interventions in case management
They are waiting for...

the researcher to research,
the politician to decide,
and the health worker to do
Thank you !!

ssosa@msal.gov.ar