Enfermedad de Chagas, mejor presente, futuro expectante

Eliminación de enfermedades por kinetoplástidos, H2020

X CONGRESO SEMTSI, Bilbao, España, Octubre 22-25, 2017

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Jefe Programa Clínico de Chagas

DNDi
Drugs for Neglected Diseases initiative
Chagas disease: Physiopathology

Parasite

Specific immune response to the parasite

Microvascular

Pathology

Inflammation
GOAL OF TIMELY DIAGNOSIS AND TREATMENT

CURE INFECTION

PREVENT MORBIMORTALITY

PERSONAL AND FAMILY WELLBEING

AVOID CONGENITAL TRANSMISSION

REDUCE DISEASE BURDEN
Guidelines for antitrypanosomal treatment with benznidazole or nifurtimox

Varying strengths of recommendation (A-E) and levels of evidence (I-III)

- All patients undergoing the acute phase (A I; A II)
- Children and young adult patients undergoing the chronic phase (A I)
- Women of childbearing age (A II)
- Adults undergoing the chronic phase (B II; C II)
- Laboratory or surgical accidents (B III)
- Organ transplant recipients or donors (A III)

Oral; 60 days
Timeline of side effects of benznidazole and nifurtimox

Gastrointestinal

Hematological

Peripheral Neurotoxicity

Dermal

CNS Toxicity

Liver toxicity

Day 1
Start

Day 60
End

Day 30
Middle

Monitoring Adverse Events/Drug Tolerance
- Weekly contact with the patient
- Laboratory testing

Typical completion rates
- adults = 83%
- neonates = 100%

Assessing response to etiological treatment

**PRIMARY CRITERIA**

- Demonstration of no clinical progression
- Wellbeing (clinical evolution)

**SECONDARY CRITERIA**

- Failure: Detecting parasite presence using molecular tests (PCR)
  - Time range: end of treatment to month/years post-treatment
- Success: serological negativization
  - Acute phase: Follow-up for 24 months post-tx
  - Chronic phase: Long-term follow-up, every 1-3 years.
Clinical studies in the 60’s and 70’s

Acute Phase: Decrease antibodies and parasitaemia

Chronic Phase: Remain antibodies and Decrease parasitaemia

Chronic Phase: Better response on the south than Central west of Brasil
Preclinical and Clinical studies in the 90’s

Treatment with Benznidazole during the Chronic Phase of Experimental Chagas’ Disease Decreases Cardiac Alterations
Simone Garcia,1,2 Carolina O. Ramos,3 Juliana F. V. Senra,1 Fabio Vilas-Boas,3 Mauricio M. Rodrigues,4 Antonio C. Campos-de-Carvalho,5 Ricardo Ribeiro-dos-Santos,5 and Milena B. P. Soares5

Figure 2. Kaplan–Meier curves of cumulative percentage of patients who changed clinical group.

Long-Term Cardiac Outcomes of Treating Chronic Chagas Disease with Benznidazole versus No Treatment
A Nonrandomized Trial
Randomized clinical trials to assess treatment against *T. cruzi* infection in the 90s

Figure 1: Decrease in the percentage of children with reactive serology against *Trypanosoma cruzi* (indeterminate phase of Chagas' disease) by enzyme immunoassay using the F2000 test after treatment with benzimidazole or placebo in Salta, Argentina, 1993–1995.

Figure 2: Percentage of children with a positive serodiagnosis 48 months after treatment with benzimidazole or placebo in Salta, Argentina, 1993–1995.

Figure 2: AT ELISA results at trial entry (●) and at end of follow-up (○) for 50 benzimidazole-treated and 54 placebo-treated children who completed trial treatment. Between horizontal line cut-off, values below this indicate seronegativity.
A NEW PARADIGM IN THE 21ST CENTURY

Review Article
Therapy of Chagas Disease: Implications for Levels of Prevention

Sergio Sosa-Estani,1,2,3 Lisandro Colantonio,4 and Elsa Leonor Segura1,2

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3 Instituto de Efectividad Clínica y Sanitaria (IECS), Dr. Emilio Ravignani 2024, 1414 Buenos Aires, Argentina
4 Departamento de Salud Pública, Facultad de Medicina, Universidad de Buenos Aires

Acute Phase
Old Paradigm

- Autoimmune origin of chronic myocarditis (5,7,21)
- Absence of T. cruzi in tissues
- Lack of relationship between acute and chronic stages of the disease, with 30% of heart disease progression due to non-established causes (50)
- Several mechanisms of cardiomyopathy progression: autoimmune, autonomic denervation, disorders of microcirculation (33,51,52)
- No indication of antiparasitic treatment (53,54)

Acute and Chronic Phase
New Paradigm

- Inflammatory immune response triggered and sustained by the parasite (25)
- Finding of T. cruzi in tissues (19,20)
- Linking acute and chronic stages of disease, correlation with the host’s immune status, and reactivation of the infection by immunosuppression (14,15-18,23)
- The parasitic persistence is postulated as the main mechanism of progression toward cardiomyopathy (14,24,25)
- Antiparasitic treatment (3,11,27,29,30,33-39)

FIG 1 Comparison of concepts belonging to the old and the new paradigms for chronic Chagas disease. Relevant references are given in parentheses.
<table>
<thead>
<tr>
<th><strong>Chagas Disease – TPP 2015</strong></th>
<th><strong>Acceptable</strong></th>
<th><strong>Ideal</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target population</strong></td>
<td>Chronic indeterminate</td>
<td>Chronic indeterminate and Acute</td>
</tr>
<tr>
<td><strong>Geographic Distribution</strong></td>
<td>All regions</td>
<td>All regions</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>Non-inferior to benznidazole standard dose* in all parasitological areas</td>
<td>Superior to benznidazole standard dose in different phases of disease (acute and chronic) (parasitological)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Superior to benznidazole* in the frequency of definitive treatment discontinuations due to medical indication (clinical and laboratory)**</td>
<td>Superior to benznidazole* in the frequency of definitive treatment discontinuations due to medical indication (clinical and laboratory)**</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Pregnancy</td>
<td>No contraindications</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>No genotoxicity**; no pro-arrythmic potential</td>
<td>No genotoxicity; no teratogenicity; no pro-arrythmic potential</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>No clinically significant interaction with anti-arrythmic and anticoagulant drugs</td>
<td>No clinically significant interaction with other drugs</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Oral/Parenteral (short POC)***</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Age-adapted</td>
<td>Age-adapted</td>
</tr>
<tr>
<td><strong>Stability</strong></td>
<td>3 years, climatic zone IV</td>
<td>5 years, climatic zone IV</td>
</tr>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>Oral - any duration</td>
<td>&lt;30 days</td>
</tr>
<tr>
<td></td>
<td>Parenteral - &lt;7 days</td>
<td></td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Lowest possible</td>
<td>≤ current treatment cost</td>
</tr>
</tbody>
</table>

* As per WHO recommendation; ** No genotoxicity is a condition only for NCEs; *** Need for parenteral treatment for severe disease.
Randomized Trial of Benznidazole for Chronic Chagas’ Cardiomyopathy


Results:
Tripanocide effect: $p< 0.05$
Clinical evolution: $p> 0.05$

2854 randomized

1431 BNZ
84% took $\geq 75\%$ of target dose
Discontinuation 192
(13.4%)
Lost to follow-up (n=8)
99.5% Complete Follow-up

1423 Placebo
90% took $\geq 75\%$ of target dose
Discontinuation 51
(3.6%)
Lost to follow-up (n=7)
99.5% Complete Follow-up

Mean FU 5.4 yrs.
Trypanocide Treatment of Women Infected with *Trypanosoma cruzi* and Its Effect on Preventing Congenital Chagas

Diana L. Fabbro¹, Emmaria Danesi², Veronica Olivera¹, Maria Olenka Codebó³, Susana Denner¹, Cecilia Heredia³, Mirtha Streiger¹, Sergio Sosa-Estani²,³.

(RR congenital transmission in treated mothers = 0.04, IC:95%: 0.012 - 0.166; p<0.05)

Randomized Trial of Posaconazole and Benznidazole for Chronic Chagas’ Disease

Benznidazole and Posaconazole in Eliminating Parasites in Asymptomatic *T. Cruzi* Carriers

The STOP-CHAGAS Trial

E1224: DNDi

Proof of Concept for a Safe, Effective and Affordable New Therapy for Chagas Disease

E1224 matching placebo (double-blind) N = 46
Benznidazole tablets (open-label) N = 46
E 1224 short dose arm (double-blind) N = 46
E 1224 high dose arm (double-blind) N = 46
E 1224 low dose arm (double-blind) N = 46

8 weeks treatment (60 days for BZN)
10 months additional follow-up

EOT M12 M6 M4

Fexnidazole Phase II
DNDi

Proof-of-Concept Dose Ranging Study
Evaluation of Dose and duration

20 patients/arm
Stopping rules: futility and safety
Cardiac and liver safety surveillance
SUMMARY OF RECENT RCTs

- Posaconazole (monotherapy or in combination) and E1224 (monotherapy) were effective during treatment and relapsed after EOT (demonstrated by PCR Positive).

- Fexinidazole (suspended for safety issues) was effective during treatment with sustained response (100%) at 12 months FUP.

- Benznidazole was effective during treatment with sustained response (~80%) at 12 months FUP.

- PCR proved useful for assessing treatment response to anti-trypanosomal drugs.
Strategies for Improving Efficacy and Tolerability

- BNZ is an effective drug
  ... but
- Efficacy gap
  - About 80% exhibit sustained response on PCR at 12 months
- Tolerability gap
  - 15-20% do not complete treatment
    - Majority due to ADRs

- Reduce BNZ exposure
  - Improve tolerability while maintaining efficacy
  - *Does not address the efficacy gap
- Combination therapy
  - Improve efficacy while maintaining or improving tolerability
  - *May not address the tolerability gap
BENDITA overall design

- Adults (18 – 50 years old) at Chronic Indeterminate CD stage
- 210 subjects - 30 patients/arm

Follow-up at 10 wk, 12 wk, 4M, 6M, 12 M

Primary endpoint at 6M
Follow-up until 12M

Partners
CEADES
ISGlobal
INGEBI
INP

- Screening period
- Futility stopping rule
- 10 and 12-week interim analysis (safety and efficacy)

Follow-up at 10 wk, 12 wk, 4M, 6M, 12 M

Primary endpoint at 6M
Follow-up until 12M

2 months treatment phase
FEXI 012 overall design

- Futility stopping rule
- 12-week interim analysis (safety and efficacy)

**Screening period**

**Randomization**

- Fexi 600 mg 10 days
- Fexi 1200 mg 3 days PBO 7 days
- Fexi 600 mg 3 days Fexi 1200 mg 4 days PCO 3 days

**10 days treatment phase**

**Follow-up at 1-4; 6; 10; 12 wk, 4M, 6m, 12 M**

**Primary endpoint at 4M**

**Follow-up until 12M**

- Adults (18 – 50 years old) at Chronic Indeterminate CD stage
- 45 subjects - 15 patients/arm

**Partners**
- ISGlobal
- Hosp Vall d’Hebron
- Hop Clinic
- Hop Moises Broggi
- Hosp Univ Valencia
- INGEBI

DNDi
Drugs for Neglected Diseases initiative
Chagas Disease – R&D strategy

POC PHASE 2 studies
BENDITA (N: 210)
3 Arms New Reg Bz
2 Arms Combo New Reg Bz - E1224
LPI 29/7/17 : 210

FEXI 012 (N: 45)
3 Arms new Reg Fexinidazole
FV/FP OCTOBER 2017

PHASE 3 study
Select best NCE (1-2 among 5 arms)
Efficacy and Safety – Confirmatory

- New Regimen BZN in combination E1224, and/or
- Fexinidazol
- Using a new Set of BMKs

Go/No-Go

Registration in Endemic Countries (US and EMA)
Chagas Disease – R&D strategy
New Regimen of BZ monotherapy

**PHASE 2 studies**
POA and POC – Exploratory in adult, chronic indeterminate CD

- BENDITA Study (DNDi), N: 210 (assessing 3 new regimens of BZ monotherapy)
  - Bolivia
- **LPI 29/7/17 : 210**

- BERENICE Study (EU FP7), N: 240 (assessing 2 new regimens of BZ monotherapy)
  - Argentina
  - Brasil
  - Colombia
  - Spain
- **FV/FP JULY 2017**

Consistent/Inconsistent Results

IMPLEMENTATION NEW REGIMEN OF BENZNIDAZOLE
Figure 1. Flow of inclusion of studies on biological markers for evaluating.
Chagas Disease – R&D strategy - Biomarkers

- **Non-human primates**
  - PCR (TBRI)
  - Anti-alpha-GAL Ab (TU)
  - Multiplex Recomb Ag (UGA)

- **Humans**
  - PCR Clinical Validation
  - ApoA1 fragments (Proteomic platforms. McGill U)
  - Multiplex Recomb Ag (UGA)
  - F29 (NHEPACHA)
  - K11-H70 (NHEPACHA)
  - PFR2-peptido 3973 (NHEPACHA)
  - Anti-alpha-GAL Ab (NHEPACHA)
  - Ab3 Ag (InfYnity Biomarkers)

**Assessment of treatment failure**

**Selection of a minimum set of BMKs among 7 candidates to assess treatment success**
- Protocol LT FUP RCTs
- Set Biomarkers Phase 3
OUTLOOK FOR 2020 BEYOND....

- NEW TRYPANOCIDE CHEMOTHERAPY

- TRYPANOCIDE CHEMOTHERAPY PLUS IMMUNOTHERAPY (?)

- TRYPANOCIDE CHEMOTHERAPY PLUS MODULATION OF PHYSIOPATHOGENESIS (?)

- TRIPANOCIDE CHEMOTHERAPY PLUS IMMUNOTHERAPY PLUS MODULATION OF PHYSIOPATHOGENESIS (?)
R&D and Access

Increased access to current regimens based on benznidazole and nifurtimox

POC FEXI 012
P 2: 3 arms

POC BENDITA
P 2: 6 arms

POC BERENICE
P 2: 3 arms

New Treatment
P 3: 1-2 among 5 arms

New regimen bz monotherapy
P4: 1 among 4 arms

New treatment
P 4:1 among 1-2 arms

New regimen bz monotherapy Implementation

Implementation
NCE

H 2    2018
H 1    2019
H 2    2019
H 1    2020
H 2    2020
H 1    2021
THANK YOU!!!

https://www.dndi.org/