Towards a paradigm shift in the treatment of chronic Chagas disease

R. Viotti\textsuperscript{a}, B. Alarcón de Noya\textsuperscript{b}, T. Araujo-Jorge\textsuperscript{c}, M. J. Grijalva\textsuperscript{d}, F. Guhl\textsuperscript{e}, M. C. López\textsuperscript{f}, J. M. Ramsey\textsuperscript{g}, I. Ribeiro\textsuperscript{b}, A. G. Schijman\textsuperscript{i}, S. Sosa-Estani\textsuperscript{i}, F. Torrico\textsuperscript{k}, J. Gascon\textsuperscript{l}

Latin American Network for Chagas disease NHEPACHA

(New Tools for the Diagnosis and Evaluation of Chagas Disease Patients)

a- HIGA (Hospital Interzonal General de Agudos) Eva Perón, Sección Chagas, Servicio de Cardiología, Buenos Aires, Argentina. b- IMT-UCV (Instituto de Medicina Tropical, Universidad Central de Venezuela), Venezuela. c- FIOCRUZ-IJC. (Fundação Oswaldo Cruz – Instituto Oswaldo Cruz, Programa Integrado de Doença de Chagas, Laboratório de Inovações em Terapias, Ensino e Bioprodutos), Brasil. d- CIEI-PUCE (Centro de Investigación de Enfermedades Infecciosas de la Pontificia Universidad Católica del Ecuador), Ecuador. TDI-OU (Tropical Disease Institute, Ohio University), USA. e- UA-CIMPAT (Centro de Investigaciones en Microbiología y Parasitología Tropical, Universidad de los Andes), Colombia. f- IPBLN-CSIC. (Instituto de Parasitología y Biomedicina Lopez-Neyra-Consejo Superior de Investigaciones Científicas), Granada, Spain. g- CRISP –INS (Centro Regional de Investigación en Salud Pública, Instituto Nacional de Salud Pública), México. h- DNDi (Drugs for Neglected Diseases Initiative). i- INGEBI (Instituto de Investigaciones en Ingeniería Genética y Biología Molecular, CONICET), Argentina. j- INP-ANLIS (Instituto Nacional de Parasitología "Dr. Mario Fatala Chaben” ANLIS Dr. Carlos G. Malbran). k- UMSS. (Universidad Mayor de San Simón), Bolivia. l- Barcelona Center for International Health Research (CRESIB), Hospital Clinic/IDIBAPS, Barcelona, Spain.

Corresponding author: Rodolfo Viotti, Telephone +5411 47640062,

rviotti@arnet.com.ar

(The views expressed in this Commentary do not necessarily reflect the views of the journal or of ASM.)
Abstract

Treatment for Chagas disease with currently available medications is recommended universally only for acute cases (all ages) and for children up to 14 years old. The World Health Organization, however, also recommends antiparasitic specific treatment for all chronic phase *T. cruzi*-infected individuals, even though in current medical practice this remains controversial, and most physicians only prescribe palliative treatment for adult Chagas patients with dilated cardiomyopathy. The present opinion, prepared by members of the NHEPACHA network (New diagnostic and treatment tools for Patients with Chagas Disease, in Spanish), reviews the paradigm shift based on clinical and immunological evidence and argues in favor of antiparasitic treatment for all chronic patients.

We review the tools needed to monitor therapeutic efficacy, and potential evaluation criteria for treatment efficacy, beyond parasitological cure. Etiological treatment should now be mandatory for all adult chronic Chagas disease patients.

**Key words:** Chagas disease; etiological treatment; treatment efficacy.
Introduction

There are an estimated eight million chronic Chagas disease (CD) patients in Latin America (1), a large proportion of whom do not receive specific anti-parasitic treatment, and a growing infected population in the United States, Canada and Europe (2).

Antiparasitic treatment for Chagas disease (CD) is recommended universally in most countries, for acute cases and for children up to 14 years old (3). Despite inclusion of chronic patients in guidelines, most doctors only prescribe symptomatic treatment of cardiomyopathy and digestive symptoms, avoiding antiparasitic drugs. At a meeting of clinical CD experts held in 1983, the use of etiological treatment for chronic stages was not recommended, pending more solid evidence of its efficacy (4), and of auto-immune mechanism involvement (5). Natural and elicited immunoglobulins and effector immune cells produced or modified during \textit{T. cruzi} infection, can directly or indirectly affect heart tissue. There is no evidence that any putative autoimmune mechanisms are primary causes of the chronic pathology, which may be secondary aggravating factors in the progression to cardiomyopathy (6). It is unclear, in addition, whether autoimmune reactions can be avoided if the infection is prevented or controlled (7), although it has been experimentally demonstrated that elimination of the parasite results in the reduction or elimination of autoimmune responses in the chronic phase of infection (8, 9).

In addition to neglecting adult chronic patient treatment by adopting the 1983 recommendations, lack of even a tentative recommendation had a negative impact on the chronic patients’ perceptions regarding their illness. These patients are labeled as “chagasic” and not simply as \textit{T. cruzi}-infected persons, leading to social stigma and negative economic and psychological effects from carrying a lethal, cureless and disabling disease (10). A similar conflict between infection and disease existed for AIDS and leprosy.
Chronic progression in both cases, similar to CD, evolves differentially in each patient, leading to a shift in current clinical management, to use pathogen-specific treatments (3). Scientific evidence regarding *Trypanosoma cruzi*’s (the parasite) role as stimulus and trigger for tissue damage has accumulated over the last two decades, providing a solid basis to reconsider antiparasitic treatment for chronic adult patients. The present viewpoint reviews evidence and presents arguments for anti-parasitic treatment of adult chronic patients, representing the opinion of clinical and biomedical scientists of the NHEPACHA network, and coincides with international guidelines which now recommend offering treatment to these patients (3, 11, 12).

**Pathogenesis of chronic Chagas disease: chronic persistence of the parasite?**

Following the acute phase of *T. cruzi* infection, CD patients evolve a chronic phase which is initially asymptomatic (indeterminate form of CD). This form of CD, is defined by *T.cruzi* infection (positive parasitological and/or serological tests), the absence of clinical disease symptoms, and normal EKG, thorax radiography, and colonic/esophageal imaging tests. However, around 30%-40% of chronically infected individuals will develop symptomatic disease over time (13). Biomarkers to follow each patient’s evolution are currently being developed, assessed and standardized. Several studies have highlighted the key role of myocardial inflammation in progressive fibrotic cardiomyopathy of chronic cardiac CD (14). Evidence for chronic persistence of infective parasites after the acute infection includes vertical transmission or transfusion and transplant transmission in endemic and non-endemic areas of *T.cruzi*, which only occurs if there are viable parasites in chronically infected mothers or blood/transplant donors (15, 16). In addition, chronic persistence is evident from clinical reactivations of immunedepressed patients, transplanted...
or HIV infected individuals (17, 18), by isolation of parasites through hemoculture from chronically infected patients, and by detection of parasites in bug feces following xenodiagnosis. Parasites can be detected most sensitively in blood and tissues using molecular techniques (19), and have been documented in cardiac inflammatory tissues (20).

The pathogenesis of chronic CD is currently considered multifactorial, with as yet poorly understood complex host-pathogen interactions. Several potential autoimmune mechanisms have been described (21), and good reviews and critiques of prevailing theories are available (22, 23). Although there is no doubt regarding the existence of an inflammatory immune response in CD, there is no conclusive experimental evidence that autoimmunity plays a significant role in its pathogenesis (7). Additional factors which may also play a role in chronic CD are microvascular disturbances, and neurogenic lesions producing dysautonomy (24).

Overall, prevailing evidence indicates that parasite persistence is fundamental for triggering and sustaining pathogenic processes (25).

What is considered efficacy: lower parasite burden or parasite clearance?

Although the treatment goal for infectious diseases is or should be pathogen elimination, there are other equally important therapeutic outcomes to be considered (26). Control and reduction of pathogen burden are well recognized strategies for some infections such as AIDS, which is now a classic example of a lethal infection which can convert into a chronically controlled disease with the administration of appropriate treatment.

Numerous studies in animal models and humans have reported the efficacy of parasitic treatment in both acute and chronic phases of CD (8, 9, 27, 28), with two
randomized studies having demonstrated the efficacy of benznidazole treatment in children (29, 30). Furthermore, other experimental studies have demonstrated a strong treatment impact on many immune response parameters, and these findings are consistent with parasite elimination or reduction (31, 32). One previous report and several subsequent non-randomized studies have shown improved clinical and serological evolution of treatment with benznidazole, as compared with untreated chronic patients (26, 33-37). Numerous subsequent studies and evidence supporting etiologic treatment of chronic CD is summarized elsewhere (27), while Table 1 summarizes the results of etiologic treatment in chronic patients from four non-randomized studies (38). These latter studies demonstrate better clinical evolution in anti-parasite treated patients. An association between clinical evolution and negative seroconversion has also been analyzed in these previous studies, as in a recent publication that reported 107 chronic adult patients with cure criteria (39).

Two randomized trials are in the process of comparing benznidazole versus placebo in chronic patients. The first including patients with or without mild heart disease conducted in Argentina (TRAENA) and terminated in 2012, is currently being analyzed (40). The other is a multicenter study (BENEFIT) which should be completed by 2014 (41), that will provide evidence regarding the evolution of advanced or mild heart disease in chronic patients treated with antiparasitic drugs. The evolution of individuals with irreversible myocardial damage given anti-parasitic treatment, and hence clinical endpoint for trial evaluation, may not be the same as for those who have not yet developed cardiomyopathy.

**Treatment monitoring**

Anti-parasitic treatment efficacy in Chagas disease can only be measured currently...
using anti-\textit{T. cruzi} antibody titres and/or by parasite detection in blood. A therapeutic failure is defined by the persistence of the parasite, detected using different methods such as PCR, while treatment success would be measured by the absence or reduction of antibody titres. However, a reduction in \textit{T. cruzi} specific antibody titres often takes many years, rendering measurement of treatment success insensitive, and lengthy.

A long-term follow-up study using qualitative PCR prior to and post-treatment with benznidazole, conducted in a non-endemic country (42), demonstrated two key findings. Sixty-eight percent of adults with chronic Chagas disease were PCR positive prior to treatment, and of these, 100% converted immediately post-treatment to PCR-negative. Additionally, sustained PCR-negative results were observed in 90% of treated patients after one year post-treatment. Standardized qualitative PCR is now available for the assessment of the impact of parasitic load on overall treatment response (43), and is being used in ongoing preclinical and clinical studies. These studies will clarify the value of quantitative and qualitative \textit{T. cruzi} DNA measurements for monitoring therapeutic response and their association with clinical outcomes (40, 41).

Changes in various biochemical (44), and nonconventional serological and immune parameters detected shortly after benznidazole treatment may also be used for therapeutic efficacy. Following benznidazole treatment, there is a reduction of several markers such as (1) anti-\textit{T. cruzi} interferon \(\gamma\)-producing cells (45), (2) \textit{T. cruzi} antigen specific antibody titres using non-conventional serology (Multiplex) (26), and (3) seroreactivity against specific recombinant antigens (complement regulatory protein or a recombinant form of trans-sialidase or kinetoplastid specific antigens) (46, 47).

Tools available to assess treatment impact in adult chronic patients, although not always accessible in the medical practice, can be summarized as follows:
Clinical stability, which has low sensitivity but high significance, should be evaluated using clinical signs, symptoms and complementary methods such as EKG and echocardiogram and should always accompany the other markers for treatment efficacy.

Seroconversion using conventional serology is often long-term or incomplete, although it continues to be a standard for follow-up.

Changes in specific anti-*T. cruzi* T cells responses after treatment and interferon-γ production may correlate with immune status prior to treatment and its efficacy.

**Adverse effects of antiparasitic treatment**

Both benznidazole and nifurtimox, the only drugs currently available for treatment, can have variable adverse effects. Adults are more affected than children, and a proportion of treated individuals must discontinue treatment due to severe adverse events (ADR).

Severe adverse events, similar to the incidence for other drugs such as Stevens-Johnson syndrome, occur in an estimated one in 3000 treated patients (48). Using a rabbit model, a high dose of benznidazole can provoke an increased risk of lymphoma. However, in humans, and with the doses used for Chagas treatment, no such risk has been detected, in adult cohorts with long-term follow-up (49).

Strict supervision of patients is required to manage ADR with the afore-mentioned drugs. Risk of adverse effects and lack of experience in ADR prevention and management, especially in adults, often affects physician compliance for treatment (physician opposition). The development of more effective and safe drugs is a clear target for
improved patient outcome, and for clinical management. Fortunately, currently available
drugs can be used in all *T. cruzi* infected adults at least until 50 years of age, with careful
follow-up by attending clinical staff.

Conclusions

Chagas is a major neglected disease. For years, the hypothesis that chronic Chagas
disease has an autoimmune origin has held back basic research, development of more
effective antiparasitic drugs and more importantly, failure to treat most chronic adult
patients. The lack of recognition of the important role of parasite persistence for the
development of lesions and clinical presentations is only one of the current barriers to more
effective clinical management of CD. From an integrated perspective, appropriate follow-
up care for chronic patients and the development of clinical trials for new drug candidates
will require appropriate early follow-up and surrogate markers for cure. The evidence-
based paradigm shift (Figure 1) which supports etiological treatment of chronic patients,
will require the development of novel marker tools. Whereas there has been clear
recognition of the shift in the treatment paradigm by academia for several years, public
health and clinical care communities have lagged in recognizing and adopting this
evidence. The greatest challenge now is how to change the mindset and habits of health
professionals, biased by the old paradigm.

Conflicts of interest

We declare that we have no conflicts of interest.

Role of the funding source

None


**Table 1.** Results of non-randomized studies with etiological treatment for patients with chronic Chagas disease. Relationship between clinical and serological evolution.*

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treated (T) N</th>
<th>Untreated (NT) N</th>
<th>EKG changes T vs. NT</th>
<th>Progression of cardiomyopathy T vs. NT</th>
<th>Reduction of risk progression (%)</th>
<th>Negative seroconversion T (%)</th>
<th>Negative seroconversion NT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viotti et al. (1994) (42)</td>
<td>131</td>
<td>70</td>
<td>0/4</td>
<td>2/17</td>
<td>88</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Gallerano et al. (2000) (44)</td>
<td>535</td>
<td>668</td>
<td>14/34</td>
<td>4/18</td>
<td>78</td>
<td>5</td>
<td>Data not available</td>
</tr>
<tr>
<td>Fabbro et al. (2007) (43)</td>
<td>54</td>
<td>57</td>
<td>4/16</td>
<td>-</td>
<td>75</td>
<td>37</td>
<td>Data not available</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,003</strong></td>
<td><strong>1,078</strong></td>
<td><strong>6/17</strong></td>
<td><strong>3/16</strong></td>
<td><strong>78</strong></td>
<td><strong>19</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>

*benznidazole except for reference 44 (309 treated with allopurinol, 130 with benznidazole and 96 with nifurtimox.*
Figure 1. Comparison of concepts belonging to the “old” and to the "new" paradigm for chronic Chagas disease.
Old Paradigm

- Autoimmune origin of chronic myocarditis (5, 7, 20)
- Absence of T cell in tissues
- Lack of relationship between acute and chronic stages of the disease, with 30% of heart disease progression because non-established causes (95)
- Severe manifestations of cardiomyopathy progression, autonomic, autonomic denervation, disorders of microcirculation (33, 51, 52)
- Indication of antiparasitic treatment (53, 54)

New Paradigm

- Inflammatory immune response triggered and sustained by the parasite (25)
- Finding of T cell 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, 10, 23)
- The parasitic persistence is postulated as the main mechanism of progression toward cardiomyopathy (14, 24, 25)
- Antiparasitic treatment (51, 11, 27, 29, 30, 33-39)