Towards a Paradigm Shift in the Treatment of Chronic Chagas Disease


There are an estimated 8 million chronic Chagas disease (CD) patients in Latin America (1), a large proportion of whom do not receive specific antiparasite treatment, and a growing infected population in the United States, Canada, and Europe (2). Antiparasitic treatment for Chagas disease (CD) is recommended universally for acute cases and for children up to 14 years old. The World Health Organization, however, also recommends specific antiparasite treatment for all chronic-phase Trypanosoma 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 (Nuevas Herramientas para el Diagnóstico y la Evaluación del Paciente con Enfermedad de Chagas/New Tools for the Diagnosis and Evaluation of Chagas Disease Patients), 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 the potential criteria for evaluation of treatment efficacy beyond parasitological cure. Etiological treatment should now be mandatory for all adult chronic Chagas disease patients.

Commentary

The views expressed in this Commentary do not necessarily reflect the views of the Editor or of ASM.

Traditional 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 specific antiparasite treatment for all chronic-phase Trypanosoma 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 (Nuevas Herramientas para el Diagnóstico y la Evaluación del Paciente con Enfermedad de Chagas/New Tools for the Diagnosis and Evaluation of Chagas Disease Patients), 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 the potential criteria for evaluation of treatment efficacy beyond parasitological cure. Etiological treatment should now be mandatory for all adult chronic Chagas disease patients.
ever, around 30% to 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 the progressive fibrotic cardiomyopathy of chronic cardiac CD (14). Evidence for chronic persistence of infective parasites after the acute infection, both in areas where T. cruzi is endemic and where it is not, includes vertical transmission or transfusion and transplant transmission, which only occur 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 immune-depressed patients or transplanted or HIV-infected individuals (17,18), by isolation of parasites through hemoculture of samples 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, the prevailing evidence indicates that parasite persistence is fundamental for triggering and sustaining pathogenic processes (25).

### WHAT IS CONSIDERED EFFICACY: A 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 the 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 the acute and chronic phase 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 nonrandomized studies have shown improved clinical and serological evolution for treatment with benznidazole compared with the same parameters in untreated chronic patients (26,33–37). Numerous subsequent studies and evidence supporting etiological treatment of chronic CD are summarized elsewhere (27), while Table 1 summarizes the results of etiological treatment in chronic patients from four nonrandomized studies (38). These latter studies demonstrate better clinical evolution in antiparasite-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 to 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) that should be completed by 2014 (41) and 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 and, hence, at the clinical endpoint for trial evaluation may not be the same as for those who have not yet developed cardiomyopathy when they are each given antiparasitic treatment.

### TREATMENT MONITORING

Antiparasitic treatment efficacy in Chagas disease can only be measured currently using anti-T. cruzi antibody titers 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 titers. However, a reduction in T. cruzi-specific antibody titers often takes many years, rendering measurement of treatment success insensitive and lengthy.

A long-term follow-up study using qualitative PCR before and after treatment with benznidazole, conducted in a country where CD is not endemic (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 to PCR

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**TABLE 1** Results of nonrandomized studies with etiological treatment for patients with chronic Chagas disease, showing the relationship between clinical and serological evolution

<table>
<thead>
<tr>
<th>1st author, yr (reference)</th>
<th>No. of patients:</th>
<th>No. of patients (treated/not treated) that had:</th>
<th>% of patients:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated</td>
<td>Not treated</td>
<td>EKG changes</td>
</tr>
<tr>
<td>Viotti, 1994 (33)</td>
<td>131</td>
<td>70</td>
<td>0/4</td>
</tr>
<tr>
<td>Gallerano, 2000 (35)</td>
<td>535</td>
<td>668</td>
<td>14/34</td>
</tr>
<tr>
<td>Viotti, 2006 (37)</td>
<td>283</td>
<td>283</td>
<td>5/16</td>
</tr>
<tr>
<td>Fabbro De Suasnábar, 2000 (34)</td>
<td>54</td>
<td>57</td>
<td>4/16</td>
</tr>
<tr>
<td>Avg</td>
<td></td>
<td></td>
<td>6/17</td>
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*Treatment was with benznidazole except for reference 35, which reports on 309 patients treated with alopurinol, 130 treated with benznidazole, and 96 treated with nifurtimox.*

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negative immediately after treatment. Additionally, sustained PCR-negative results were observed in 90% of treated patients after 1 year posttreatment. Standardized qualitative PCR for the assessment of the impact of parasitic load on the overall treatment response is now available (43) and is being used in ongoing preclinical and clinical studies. These studies will clarify the value of quantitative and qualitative *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 evaluating therapeutic efficacy. Following benznidazole treatment, there is a reduction of several markers, such as (i) anti-*T. cruzi* gamma interferon (IFN-γ)-producing cells (45), (ii) *T. cruzi* antigen-specific antibody titers detected using nonconventional serology (multiplex) (26), and (iii) seroreactivity against specific recombinant antigens (complement regulatory protein, recombinant *trans*-sialidase, or kinetoplastid antigen) (46,47).

The 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 and symptoms and complementary methods like 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 cell responses and IFN-γ production after treatment may correlate with the immune status prior to treatment and with the efficacy of treatment.

**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 (adverse drug reactions [ADR]). Severe adverse events, similar to the incidence of ADR like Stevens-Johnson syndrome for other drugs, occur in an estimated one in 3,000 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 aforementioned drugs. The 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, the 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 and the development of more effective antiparasitic drugs and, more importantly, has led to the 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 (Fig. 1) that 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 who are biased by the old paradigm.

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REFERENCES


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