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Opinion

Trypanocidal Treatment in Chronic Chagas Disease: Critical Evaluation of Cure Criteria

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Chagas disease (CD), caused by *Trypanosoma cruzi (T. cruzi)* infection, is a neglected tropical disease that continues to pose a significant public health threat in Latin America. According to data from the World Health Organization, an estimated 6–7 million people across 21 Latin American countries are currently infected with *T. cruzi*. In the 1980s, the implementation of vector, and transfusion control programs successfully reduced disease transmission rates in these countries. However, several challenges have arisen, including new outbreaks of orally transmitted CD in endemic regions and the potential for vertical transmission, even in nonendemic areas. The focus of integrated surveillance and healthcare interventions has shifted toward a substantial population of individuals already infected with *T. cruzi*, with a significant portion at risk of developing chronic Chagas heart disease, a leading cause of morbidity and mortality. With the rapid pace of globalization, CD cases are no longer confined to Latin America. A growing number of immigrants carrying CD have relocated to nonendemic countries in the Northern Hemisphere, presenting a new challenge in the fight against this disease.[1]

Patients with CD, an important endemic illness in Latin American countries, often go with their condition unnoticed within the national and regional healthcare systems. Consequently, only a small number of those affected receive accurate and timely diagnosis and treatment with trypanocidal drugs, leaving the vast majority without access to this crucial healthcare benefit. The natural progression of CD reveals four distinct clinical conditions after the acute phase: indeterminate form, cardiac form, digestive form, and mixed form (involving both cardiac and digestive form). The indeterminate form generally exhibits a favorable long-term prognosis, while the consequences of the digestive form can be treated. However, the cardiac form is the primary driver of disease morbidity and mortality, with the potential for progression toward a severe cardiac disease with cardiovascular clinical events that significantly affect patients' quality of life and survival.

Prior to the mid-1990s, there was insufficient evidence to support the use of trypanocidal drugs for treating patients with chronic CD. Prior research was based on the paradigm that the main pathophysiological mechanism involved an imbalanced immune response resulting in autoimmune manifestations and subsequent heart disease.[2] Furthermore, histopathological studies of cardiac tissue in chronic patients did not identify *T. cruzi*, which further reinforced the theory of autoimmunity. It was only through longitudinal observational clinical studies and the introduction of molecular diagnostic tools such as polymerase chain reaction (PCR) that the concept of autoimmunity as the sole factor was debunked, and the parasite itself became directly associated with the physiopathogenic mechanism of chagasic heart disease.[3] Consequently, it was not until the early 21st century, a century after the discovery of the disease and three decades after the emergence of the only two effective trypanocidal drugs, nifurtimox and benznidazole,[4] that treatment for chronic patients began. Prior to this, etiological treatment was mandatory only during the acute phase or in cases of disease reactivation with high parasitemia. Over the last decade, guidelines have been developed to standardize the indications for treatment.[5] Currently, trypanocidal treatment is recommended for chronic patients in specific situations, including children, teenagers, women of childbearing age, and young adults (up to 50 years of age) with the indeterminate form or early stages of heart disease.[5]

Despite the advancements in medical and pharmaceutical technologies, the current etiological treatment for CD still relies on drugs developed in the 1960s and 1970s.[4] It is crucial to emphasize that these drugs have a high incidence of adverse effects.[6] This factor leads to treatment discontinuation in approximately 10% of patients who fail to complete the recommended 60-day treatment period.[7] Preclinical studies have been conducted to explore alternative therapies, aiming to identify new candidates that are safer, more effective, cost-effective, and less prone to drug resistance.[8] In clinical trials, new drugs have been evaluated, however, none of them have demonstrated superior efficacy to the existing ones when used as monotherapy. Therefore, the current approach involves considering the combination of new drugs with benznidazole and/or the repurposing of drugs with potential trypanocidal effects.[9,10]

Following the initial infection, individuals with CD consistently exhibit positive serology for *T. cruzi* throughout their lives, while

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Abbreviations: CD, Chagas disease; PCR, polymerase chain reaction; *T. cruzi*, *Trypanosoma cruzi*.

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parasitemia is typically undetectable in over half of the cases. Clinically, the progression of CD is slow, taking years to manifest symptoms and signs of cardiac involvement. This interplay between serological, parasitological, and clinical factors significantly influences the assessment of the response to trypanocidal treatment. Therefore, it becomes essential to establish criteria for recovery that encompass these three dimensions, considering their distinct patterns of change over time.

In the short term, PCR is utilized to assess the therapeutic response of trypanocidal drugs in CD.[11] Clinical trials investigating the therapeutic response to benznidazole or nifurtimox involve patients who initially tested positive by PCR, and their treatment outcome is determined by maintaining a consistently negative PCR result.[9] In the majority of instances, negative PCR results become evident shortly following the conclusion of etiological treatment, typically within 60 days. However, over a follow-up period of up to 3 years, these results may exhibit fluctuations. As a result, the definition of parasitological cure requires the continual absence of parasitic presence for a duration exceeding three years.[12] Achieving this negative PCR outcome is considered a parasitological cure, indicating patient recovery. In medium and long-term follow-up studies, patients treated with trypanocidal drugs exhibit a progressive decline in serological titers over time. Research conducted in adults suggests that seroreversion rates occur within a span of 5 to 10 years following treatment, and eventually reaching a sustainable seronegative state, which signifies a serological cure.[13,14]

Another important question arises. Despite the evidence of parasitological and/or serological cure, does this condition guarantee us that the patient will evolve better than the untreated one? When considering clinical aspects, the methods used to evaluate parasitological or serological responses may not be applicable. Patients with electrocardiographic or echocardiographic abnormalities do not see a regression of these alterations after undergoing trypanocidal treatment.[15] Therefore, in chronic CD, the crucial factor for patient prognosis lies not in the resolution of symptoms and signs but in decreasing the risk for subsequent cardiovascular events and progression to the cardiac form. In this specific context, the criterion for clinical cure is established.[16]

Nevertheless, there are significant factors to be considered when assessing the longitudinal clinical response in CD. First, the duration of observation plays a crucial role, as longer follow-up periods provide stronger corroborating evidence.[16] Second, the age of patients at the time of trypanocidal treatment is an important consideration. Younger individuals derive greater benefits from trypanocidal treatment, as they have a higher probability of progressing to the cardiac form.[17] Additionally, the optimal management of concurrent comorbidities and comprehensive care contributes to a more favorable therapeutic response following trypanocidal treatment.[18]

Within the framework of monitoring cure, various biomarkers have been investigated in CD to evaluate the short-term therapeutic response.[19] However, only a limited number of these biomarkers can reliably determine treatment effectiveness. In addition to the conventional serological biomarkers, which involve the detection of antibodies against *T. cruzi* antigens, specific IgG subclasses, and changes in their levels and patterns have been analyzed.[20] Furthermore, quantitative parasitological and genotyping biomarkers have been examined, not limited to qualitative parasitological markers.[21] In terms of clinical assessment, cardiac biomarkers such as the electrocardiogram, which depicts the characteristic pattern of disease progression toward the cardiac form, have been considered.[16] Furthermore, echocardiographic evaluation can identify cardiac damage and ventricular myocardial systolic and diastolic dysfunction levels.[22] In the clinical context, serum troponin, brain natriuretic peptide, and cardiac fibrosis markers are also utilized.[23] Moreover, inflammatory biomarkers like C-reactive protein, cytokines, and chemokines can offer insights into inflammatory processes and treatment responses.[24]

In summary, existing scientific evidence confirms that the assessment of etiological treatment in CD can be based on parasitological, serological, and clinical criteria. While various types of biomarkers have been examined in relation to therapeutic response to trypanocidal treatment, their widespread acceptance as criteria for cure has not yet been established.

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Conflict of interest

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