Perspectives in Chagas Disease Treatment

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Delivery of care for patients with diagnosed Chagas disease encompasses 2 modalities: 1) the specific trypanocidal therapy with regulatory agencies—approved drugs; and 2) the management of clinical manifestations of the disease. In terms of the natural history of Chagas disease, current estimates indicate that up to 30% of infected patients develop the chronic form, which may be cardiac, digestive (megaesophagus and megacolon), or mixed. Undoubtedly among the clinical spectrum, the chronic Chagas cardiomyopathy represents the most severe form, in which patients evolve to advanced symptomatic and progressive heart failure with recurrent hospitalizations and poor quality of life, and nearly 60% of patients with chronic Chagas disease die between 7 months and 2 years after the onset of symptoms.

Management of heart failure, atrioventricular blocks and symptomatic bradycardia, ventricular arrhythmias, and thromboembolic events should follow usual recommendations from available guidelines, and they are not the primary scope of this paper. We herein discuss recent advances in the etiological treatment, including ongoing clinical investigations of available parasite eradication treatment in chronic Chagas cardiomyopathy, prevention of sudden cardiac death, and current perspectives in new drug development.

ETIOLOGICAL TREATMENT OF CHAGAS DISEASE

It is well recognized that the etiological treatment of Chagas disease is controversial, especially regarding its classes of recommendations and less robust levels of evidence, as well as the lack of reliable scientific evidence for efficacy and safety in the late chronic phase. There are only 2 trypanocidal drugs available, which indicates the long-lasting paucity of developing new therapeutic agents and emphasizes the neglected public health aspect of this disease, specifically in several regions from developing countries where it has an endemic behavior.

Currently, large randomized, adequately powered multicenter trials, with sufficient long-term follow-up and independent adjudication of clinically relevant outcomes have not been conducted to assess whether the parasiticide treatment effect yields a favorable impact on the natural history of the disease. Moreover, there has been a reasonably high degree of uncertainty regarding the accurate documentation of parasite eradication and complete cure of the disease due to the lack of reliable laboratory tests, although recent advances in diagnostic tests have been able to provide quantitative measurements of *Trypanosoma cruzi* DNA, which is potentially useful to follow-up parasitemia in patients undergoing specific chemotherapy [1,2].

Given the relevance of Chagas disease in terms of clinical manifestations, mortality risk, and high level of costs associated with delivery of care, particularly for the management of recurrent hospitalizations due to decompensated heart failure and eventually heart transplantation, as well as treatment of ventricular arrhythmias and atrioventricular blocks with permanent pacemakers and implantable cardioverter-defibrillator (ICD) implantation, the burden on financial resources of public health systems among Latin American countries is enormous.

Therefore, the Brazilian Society of Cardiology organized a task force with other South American and Inter-American Societies of Cardiology to write a consensus document, the I Latin American Guidelines for the Diagnosis and Treatment of Chagas Cardiomyopathy, which was released in 2011 [3]. Indeed, the participating Chagas disease experts reviewed and endorsed the current indications for the etiological treatment that had been previously issued by the World Health Organization in 1999 [4], in which the trypanocidal treatment was recommended to all eligible chagasic patients as long as it was prescribed by an experienced physician capable of performing careful clinical follow-up to assess for potential adverse reactions, tolerability, and post-therapy efficacy [5]. Based on those statements, 2 types of indications for the trypanocidal treatment were considered. First, the so-called consensual indications that include the following 4 scenarios: 1) all patients with acute infection phase, regardless of the mode of transmission; 2) chronic phase in children; 3) accidental contamination; and 4) reactivation due to immunosuppression. Second, nonconsensual indications were classified due to high uncertainty related to the late chronic infection phase and the indeterminate form in young individuals. It is worth noting that the trypanocidal treatment in patients with established chronic chagasic cardiomyopathy will remain controversial until large clinical trials reveal definitive results [6—8].

Trypanocidal drugs

Nifurtimox (nitrofuran). Nifurtimox was described in 1965 by Bayer (Hanover, NJ, USA), with its mechanism of action not fully clarified. Each tablet contains 120 mg of active substance, and the recommended dosages are 15 mg/kg/day for children and acute infection cases and 8 to 10 mg/kg/day for adults for 60 days, noting that the daily dose should be divided into 3 doses. This agent has gastrointestinal absorption and is metabolized via the cytochrome P450 system, with most excretion by the

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kidneys. Its side effects include anorexia, abdominal pain, nausea, vomiting, and weight loss. This agent is not available in Brazil.

Benznidazole (nitroimidazole). Benznidazole was developed by Roche (Indianapolis, IN, USA) in 1971, who maintained the production patent between 1980 and 2003 and further established production cooperation by sharing its technology over the following years, ultimately leading to current exclusive production by a Brazilian industry, the Laboratório Farmacêutico do Estado de Pernambuco (LAFEPE). The tablets contain 100 mg of active substance. Similar to nifurtimox, it has gastrointestinal absorption and also preferential renal excretion. Its recommended dose is 10 mg/kg/day for children and acute infection cases and 5 mg/kg/day for chronic cases for 60 days, with the daily dose being divided into 3 or 2 oral administrations. The maximum dose should be 300 mg/day. For adults weighing >60 kg, the total dose should be calculated, and the duration of treatment prolonged beyond the 60 days to complete the total dose as required. The most frequent side effect is exanthematous urticarial dermatitis, which occurs in up to 30% of the patients, commonly at the end of the first week of treatment. Patients tend to present favorable responses to usual antihistamines or even small oral doses of corticosteroids. Other significant side effects include polyneuropathy, usually at the end of the treatment, and anorexia, but these are less intense than that observed with nifurtimox therapy. Significant leukopenia and agranulocytosis are rare, but, when diagnosed, the treatment should be interrupted. It is important to highlight that those agents are contraindicated during pregnancy and in cases with kidney or liver failure.

The BENEFIT study

As mentioned, the indication for trypanocidal treatment in patients with established chronic Chagas cardiomyopathy remains controversial. Several researchers support that treatment based on the following: 1) experimental evidence that the etiological treatment attenuates the progression of cardiomyopathy; 2) observational studies in humans, although not definitive, but with clinically relevant outcomes, have reported a possible positive impact on the natural history of the disease, even in the nonadvanced phase of chronic Chagas cardiomyopathy; and 3) the relative paucity and low severity of the side effects, as compared with the potential benefit of short-term treatment (usually 2 months). In order to investigate the etiological therapy hypothesis in this clinically relevant condition, the BENEFIT (Benznidazole Evaluation for Interrupting Trypanosomiasis) study [6,7] was designed as a multicenter, randomized, double-blind, placebo-controlled clinical trial of 3,000 patients with chagasic cardiomyopathy in Latin America. Patient recruitment started in 2004 and included Argentina, Bolivia, Brazil, Colombia, and El Salvador. Patients were randomized to receive benznidazole (5 mg/kg per day) or matched placebo for 60 days. The pre-specified primary outcome was the composite of death, resuscitated cardiac arrest, sustained ventricular tachycardia, insertion of pacemaker or ICD, heart transplantation, and development of new heart failure, stroke, or systemic or pulmonary thromboembolic events. The average follow-up time was 5 years, and the study sample size trial was calculated to yield a 90% statistical power to detect a significant 25% relative risk reduction. The BENEFIT program also comprises a substudy evaluating the effects of benznidazole on parasite clearance and an echocardiography imaging substudy exploring the impact of etiological treatment on left ventricular function. This largest treatment trial yet conducted in Chagas disease yielded mixed results [9]. Trypanocidal therapy with benznidazole significantly reduced serum parasite detection (measured by polymerase-chain-reaction), but did not significantly reduce risk of the study's primary clinical cardiac outcome.

PREVENTION OF SUDDEN CARDIAC DEATH

Although both amiodarone and ICD therapy have been used and indicated for high-risk subjects, data from Chagas disease patients are scanty, and clinical evidence supporting these recommendations is mostly derived from results obtained in other cardiopathies. ICD is better than antiarrhythmic drug therapy for the primary and secondary prevention of all-cause mortality and sudden cardiac death in patients with either coronary artery disease or idiopathic dilated cardiomyopathy.

To answer the question regarding primary prevention of sudden cardiac death in Chagas heart disease patients, Martinelli et al. [10] designed the CHAGASICS study (Amiodarone Against ICD Therapy in Chagas Cardiomyopathy for Primary Prevention of Death; NCT01722942), aiming at assessing whether the ICD also has the protective effect for primary prevention in chronic Chagas cardiomyopathy. This is a randomized, open-label trial intended to enroll up to 1,100 patients with chronic Chagas cardiomyopathy and a Rassi risk score for death prediction of $\geq$10 points, and $\geq$1 episode of nonsustained ventricular tachycardia on 24-h Holter monitoring. Patients from 28 centers in Brazil have been enrolled and randomly assigned in a 1:1 ratio to receive an ICD or amiodarone (600 mg/day for 10 days, then 200 to 400 mg/day until the end of the study). The primary endpoint is all-cause death, and enrollment will continue until 256 patients have reached this endpoint. Key secondary endpoints include cardiovascular death, sudden cardiac death, hospitalization for heart failure, and quality of life. Patients will be followed for 3 to 6 years, and data analysis will be done on an intention-to-treat basis. This is the first large-scale trial to assess the benefit of ICD therapy for the primary prevention of death in patients with chronic Chagas cardiomyopathy and nonsustained ventricular tachycardia, who have a moderate to high risk of death. The trial started in October 2014 and its estimated completion date is October 2019.

COST-EFFECTIVENESS OF CHAGAS DISEASE INTERVENTIONS

Although drugs for treatment of Chagas disease have been developed, scanty data have been published in terms of estimated costs and expected benefits, specifically regarding vector control and drug treatment options. Furthermore, the estimated costs of hospitalizations due to decompensated heart failure of chagasic etiology are significantly higher than those related to other cardiomyopathies, representing an economic burden to lower income regions [11]. In order to investigate potentially attractive approaches to be implemented in Chagas disease public health programs, Wilson et al. [12] applied a Markov model to examine the cost-effectiveness of current and potential strategies for the eradication and treatment of Chagas disease in Latin America and the Caribbean. They concluded that the best approach for the control and treatment of Chagas disease in Latin American countries would be a combined strategy of vector control associated with new drug treatment, which would provide highly cost-effective beneficial effects on both morbidity and mortality [12].

NEW TREATMENT DEVELOPMENTS

Several clinical studies have shown that the Chagas disease pathogenesis goes beyond the parasite persistence per se; in other words, it essentially is characterized by an inflammatory disease coupled with imbalanced immune response. Therefore, the disease has been considered incurable and specific antiparasitic treatment has been neglected. However, recent studies using more sensitive methods demonstrated clear correlation between the inflammatory processes and the presence of the parasite, thus reinforcing the alternative hypothesis of required eradication of *T. cruzi* to cure the disease. On the other hand, despite a reasonably high percentage of cure in the acute infection phase, the percentage of successful cures as measured by parasite eradication rate is only achieved in a small proportion of patients at chronic stage, <20%, also with documented resistance in some *T. cruzi* strains.

Because of this relatively lower efficacy with benznidazole or nifurtimox, alternative drug design, development, or testing for new indications is warranted. As an example, similar to fungi biology, *T. cruzi* is completely dependent on the endogenously produced sterols that are vital for the parasite membranes, cell division, growth, and development processes. Therefore, the idea of screening the existing antifungal agents as potential drugs for specific etiological treatment of Chagas disease was very attractive due to long previous clinical utilization in general practice and better safety profile as compared with currently approved benznidazole or nifurtimox. Those antifungal drugs act by blocking ergosterol biosynthesis in fungi via inhibition of the cytochrome P450 enzyme, called sterol 14α-demethylase (CYP51). Indeed, research on clinical antifungal drugs for Chagas disease would be the most cost-efficient way to provide an immediate treatment, thus among the azoles approved for clinical systemic use (ketoconazole, itraconazole, posaconazole, fluconazole, and voriconazole), posaconazole has been extensively studied as potential new drug to treat chagasic patients with high in vivo activity against the infection caused by multiple, including several nitroderivative-resistant strains of *T. cruzi* [13].

One potential explanation for lower efficacy of benznidazole is low degree of hydrosolubility, therefore, Sesti-Costa et al. [14] tested the in vitro and in vivo effects of a ruthenium complex that combined the benznidazole with nitric oxide (RuBzNO2), which enhanced its solubility in water and increased its activity and reduced its toxicity. They found a high trypanocidal activity in vitro against both trypomastigotes and amastigotes but did not show cytotoxicity in mouse cells, enhancing the survival of treated mice due to reduction in heart damage with a more favorable impact than the same concentrations of benznidazole [14].

Another potential field to be explored is related to the supplementation of certain nutrients thought of as being involved in the progression of myocyte damage to chronic cardiomyopathy. Some observational and small studies have suggested the following aspects: selenium (Se) levels are related to the severity of the cardiomyopathy in chagasic patients; adequate Se diet is essential for mice survival at the acute phase of the experimental *T. cruzi* infection; and Se supplementation prevented the myocardial lesions at the acute phase in mice. Based on this rationale, the STCC study (Selenium Treatment and Chagasic Cardiopathy; NCT00875173) was designed as a superiority, double-blind, placebo-controlled, randomized clinical trial, aiming at investigating whether Se treatment via oral route is able to impair the progress of heart dysfunction in chagasic patients. The eligibility criteria are as follows: 1) Chagas disease diagnosis confirmed by serology; 2) segmental, mild, or moderate global left ventricular systolic dysfunction; and 3) age between 18 and 65 years. The intervention will be 100 μg of sodium selenite once daily for 365 consecutive days versus a placebo. The following are the primary outcomes to be measured: 1) the temporal trends on the left ventricular ejection fraction in the follow-up period; 2) reduction of heart disease progression rates, with progression defined as a 10% decrease in left ventricular ejection fraction; and 3) rate of hospital admissions attributable to cardiac arrhythmia, heart failure, or stroke due to Chagas disease. STCC will randomly allocate 130 patients to either the intervention or placebo group at a 1:1 ratio. Patient recruitment has just started, and the estimated study completion date is December 2020 [15].

SUMMARY

Current therapeutics in patients with Chagas disease comprises currently approved specific etiological drugs to eradicate the parasite *T. cruzi*, management of cardiac

manifestations particularly heart failure, and prevention of sudden cardiac death. Several limitations in the etiological treatment include low rates of parasitemia cure, specifically in the late stage of the disease; lack of adequately reliable laboratory tests to follow-up parasite eradication and respective serology; *T. cruzi* strains resistance to benznidazole and nifurtimox; side effects not rare and not mild; and neglecting behavior related to the disease in endemic regions and recently affected nations. The impact on public health systems is huge, particularly to developing countries in Latin America, with high burden of costs, premature deaths, and poor quality of life associated with limited financial resources and lack of interest in novel scientific research.

The BENEFIT trial demonstrated that treatment of patients with advanced Chagas infection and cardiomyopathy is unlikely to prevent progression of heart disease [16]. These results suggest that current treatment and future trials should focus on parasite eradication in younger patients who have earlier-stage disease.

Cost-effectiveness in Chagas disease interventions include continuous surveillance to maintain broad vector control and urgently warranted new drug developments to improve long-term efficacy in parasitemia negativization while reducing incidence and magnitude of side effects, as well as leading to slow progression to severe chronic cardiomyopathy, increased survival, and better quality of life.

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