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Editorial

A quick fix for Chagas disease therapy: a new trick using an old drug

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Charles Darwin described his experience of being a victim of the kissing bug with amazing details, including that it was painless and curious to watch the body of the arthropod changing from as flat as a wafer to a globular form in less than 10 minutes. Charles Darwin died in 1882, and it is speculated that that kissing bug attack may have infected him with the *Trypanosoma cruzi* parasite. It was only in the beginning of the 20th century that Carlos Chagas characterized the disease caused by this parasite and described its transmission cycle, and Chagas disease was named after him.

We now understand in more detail the progress of the disease in terms of clinical outcomes, which present as three distinct phases: acute, indeterminate chronic, and symptomatic chronic. The acute phase is characterized by high parasitemia that may be associated with a self-limiting febrile illness, although it is asymptomatic in the majority of cases. Once the immune system recognizes the parasite and responds to the infection, parasitemia is reduced to minimum levels, and the infected individual may remain asymptomatic for many years in the indeterminate chronic phase. For reasons yet to be understood, approximately one-third of those individuals will develop a cardiac manifestation, and not more than 5% will develop a digestive syndrome. In both cases, inflammation will lead to fibrosis in the muscle tissue, which progresses to cardiomyopathy, megacolon, or megaesophagus[1].

The recent characterization of *T. cruzi* dormancy[2], the role of the gut microbiome in disease progression[3], and the use of mass spectrometry techniques to characterize parasite metabolic activity in different regions of the heart[4] have all contributed to provide new insights about the disease pathogenesis. In addition, novel tools, including the CRISPR/Cas9 system[5], and genetically modified parasites that express luciferase and fluorescent protein reporters[6] enable the validation of new therapeutic targets and *in vivo* proof-of-concept efficacy using noninvasive methodologies to identify new drugs that are capable of treating the disease, which is the leading infectious cause of heart failure in Latin America. The first and only drugs used for treating Chagas disease were developed in the 1970s: nifurtimox and benznidazole. Both the drugs are nitroheterocyclic compounds that are reduced inside the parasite, generating reactive species that lead to the parasite's death. The efficacy of these drugs in achieving a cure in the acute phase is high, although they present two major problems. First, they can cause severe adverse effects, including dermatitis, digestive intolerance, peripheral neuropathy, and other minor symptoms, that altogether are the reason for 20%–50% of early treatment interruption[7], with benznidazole being better tolerated and most commonly used currently. Second, they have questionable efficacy in the chronic phase.

Because parasitemia during the chronic phase is minimal in immunocompetent individuals (close to detection limits), assessing treatment efficacy by direct parasite quantification is difficult. The most common and sensitive diagnostic methods rely on polymerase chain reaction (PCR) assay that detects parasite-specific deoxyribonucleic acid (DNA) or on serological assays that detects anti-*T. cruzi* antibodies. Owing to low levels of circulating parasites, negative PCR does not necessarily imply the absence of parasites. In addition, the detection of anti-*T. cruzi* antibody does not imply a current infection because antibody titers against some parasitic antigens are sustained at high levels even after a parasitological cure (absence of parasite), and it may take many years to observe a significant decay.

A clinical trial (BENEFIT) that enrolled Chagas disease patients in the symptomatic chronic phase with signs of cardiomyopathy observed, with limited statistical power, concluded that there was no significant difference in terms of clinical disease progression in the groups treated with placebo and benznidazole, although the latter confirmed a significant reduction in parasite detection by PCR during a 5-year follow-up[8]. Could the pathology have been prevented if the patients had received the treatment before manifesting cardiomyopathy? It is possible, but there are no data thus far

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to confidently answer that question, and it would take too long to test this hypothesis without a biomarker that can indicate anticipated cardiac or digestive pathology. Unfortunately, such a biomarker does not yet exist. The pharmaceutical industry is joining forces with academic groups and organizations, such as the Drugs for Neglected Disease Initiative, to develop novel compounds; however, unfortunately, there is currently no candidate in the clinical phase. Inhibitors of ergosterol biosynthesis (posaconazole and E1224) presented a safer profile than nitroheterocyclic compounds and thus were tested in phase II clinical trials, but their efficacy to eliminate parasites was not sustained according to PCR testing at 12 months after treatment[9].

A future, definitive treatment for Chagas disease may depend on combination therapy, addressing both parasites and inflammation responses to prevent or reverse fibrosis in symptomatic chronic patients; however, this is an enormous challenge. Although this new effective therapy is not a reality, treatment with currently available drugs may be improved. One way to remediate the adverse effects caused by benznidazole is simply by reducing the doses currently used. The mini-review article published in this issue of the *Revista da Sociedade Brasileira de Medicina Tropical* entitled ***The response to different doses of benznidazole in chronic phase in animal models with Chagas disease*** proposes that lower doses of benznidazole are still effective in eliminating parasites in animal models and thus could potentially reduce the toxicity and adverse effects in humans. This possibly increases the compliance and completion of treatment without affecting the antiparasitic efficacy of this drug.

In conclusion, even 109 years after Carlos Chagas characterized the disease, we still lack a definitive treatment for patients affected by the *T. cruzi* parasite, despite all recent advances in the overall knowledge about the disease. Hopefully, with the recent engagement of the pharmaceutical industry and academic sector, new treatment alternatives are on their way to patients. In the meantime, improving the safety of benznidazole appears to be a reasonable idea.

Conflict of interest

The author declares that there is no conflict of interest.

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