Chagas disease: 115 years of neglect

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In 1908, Carlos Chagas, a Brazilian physician and researcher identified a protozoan in the gut of triatomines in the town of Lassance, in Minas Gerais state, Brazil. 1 year later, after conducting experimental work with the vectors and small mammals, he identified a 2-year-old girl with symptoms and described the first case of the disease that would be later named after him. Chagas disease is a silent zoonotic disease caused by *Trypanosoma cruzi*, a parasite with a remarkable life cycle, which can cause severe symptoms that range from cardiac alterations to digestive and neurological symptoms. In this issue, we publish a Series on Chagas disease in collaboration with *The Lancet Microbe*. The Series consists of five papers and sheds light on the current and future landscapes of Chagas disease in the Americas region, covering a range of topics including epidemiology in the Americas, climate change impact in North America, an overview of disease progress and severity, advancements and challenges in diagnosis, and obstacles in vaccine development and therapy. Despite some progress in disease control, Chagas still affects 6–8 million people in the Americas, and is spreading to countries outside the region due to human mobility. Treatment is limited as only two drugs are available, benznidazole and nifurtimox, both of which are nitroimidazole derivatives. Treatment efficacy increases with early diagnosis and younger age, but there are important challenges associated with treatment in adults, including treatment discontinuation (9–31% of cases), duration (with 60-day treatment for both drugs with dose variation depending on the type of drug), and tolerability to side effects. Although highly effective in the acute stage, with up to 80% of adult patients presenting a serological cure, drug efficacy diminishes in the chronic stage. Management of symptoms during treatment is also important, as 30–40% of patients with chronic disease present with cardiac and gastrointestinal symptoms and a multidisciplinary team is required for treatment and symptom control. Moreover, for adults with indeterminate phase or chronic cardiomyopathy, treatment is complicated and relies on symptom management.

The ideal scenario is an effective universal drug providing a parasitological cure for both the acute and chronic phases. However, *T cruzi* is a genetically diverse complex parasite that poses a challenge for discovering new treatments. This parasite has a diploid genome with 22,000 coding sequences that can target parasite invasion and antigenicity, and is grouped into seven discrete typing units with a broad geographic distribution throughout the Americas. These genetic lineages are associated with different disease outcomes, various levels of virulence and drug resistance, and variable frequency by region with overlapping distributions. Moreover, one must consider that *T cruzi* is a master of disguise and evades the host's immune response infecting nearly any cell type. To further complicate, the parasite undergoes a dormant stage during the chronic phase, another strategy to evade the host's immune system. The dormant-stage parasites, called amastigotes, replicate at a very slow rate and have reduced susceptibility to drugs, becoming metabolically inactive and compromising the efficacy of the treatment and the identification of new molecules, making this parasite a complex candidate for new treatments.

Despite the challenges, some promising new therapy candidates have been proposed. A proof-of-concept, phase 2 trial of oral fexinidazole in adults with the chronic form reported early and complete *T cruzi* clearance sustained for 12 months. However, the trial had to be terminated early due to safety events. Another treatment candidate is AN15368, tested in vitro and in vivo in non-human primates. This drug achieved a uniform cure of infection in non-human primates with long-term infection, an important finding for new treatment candidates. Although in the very early days, the two candidates suggest a great advance in the development of new, more effective options for Chagas disease, especially for patients with chronic disease. The MULTIBENZ trial is an international, randomised, double-blind, phase 2b trial comparing the parasitological efficacy and safety of 3 different benznidazole regimens in adults with chronic Chagas disease. The regimens consisted of group 1 (a control treatment of benznidazole 300 mg for 60 days), group 2 (low dose treatment of benznidazole 150 mg for 60 days), and group 3 (short treatment with 400 mg of benznidazole for 15 days). Sustained parasitological negativity was the same between the control and experimental groups, with lower discontinuation of the treatment among groups. The authors found that discontinuation was 14% in the control group, 9% in the low-dose group, and 2% in the short-treatment group. These findings pose some possibilities for a new treatment regimen with higher adherence and lower cost, while new drug candidates are still in the early stages.

115 years have passed since Chagas disease was discovered, without any change in the disease treatment. A *2019 Lancet* Editorial discussed tackling some of the same challenges which we continue to face. Efforts must

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be made not only to contain the disease but to actively treat patients with drugs that provide full parasite clearance. With the climate crisis and human actions, Chagas disease is no longer contained in the endemic countries but has spread to other non-endemic locations in many regions of the world. A holistic health-care strategy is important with collaboration among different teams, by providing funding for all levels of research to accelerate the development of new drug candidates. Offering patients a cure should be an urgent priority.

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