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Current drug therapy and pharmaceutical challenges for Chagas disease

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ABSTRACT

One of the most significant health problems in the American continent in terms of human health, and socioeconomic impact is Chagas disease, caused by the protozoan parasite *Trypanosoma cruzi*. Infection was originally transmitted by reduviid insects, congenitally from mother to fetus, and by oral ingestion in sylvatic/rural environments, but blood transfusions, organ transplants, laboratory accidents, and sharing of contaminated syringes also contribute to modern day transmission. Likewise, Chagas disease used to be endemic from Northern Mexico to Argentina, but migrations have earned it global. The parasite has a complex life cycle, infecting different species, and invading a variety of cells – including muscle and nerve cells of the heart and gastrointestinal tract – in the mammalian host. Human infection outcome is a potentially fatal cardiomyopathy, and gastrointestinal tract lesions. In absence of a vaccine, vector control and treatment of patients are the only tools to control the disease. Unfortunately, the only drugs now available for Chagas' disease, Nifurtimox and Benznidazole, are relatively toxic for adult patients, and require prolonged administration. Benznidazole is the first choice for Chagas disease treatment due to its lower side effects than Nifurtimox. However, different strategies are being sought to overcome Benznidazole's toxicity including shorter or intermittent administration schedules—either alone or in combination with other drugs. In addition, a long list of compounds has shown trypanocidal activity, ranging from natural products to specially designed molecules, re-purposing drugs commercialized to treat other maladies, and homeopathy. In the present review, we will briefly summarize the upturns of current treatment of Chagas disease, discuss the increment on research and scientific publications about this topic, and give an overview of the state-of-the-art research aiming to produce an alternative medication to treat *T. cruzi* infection.

Contents

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1. Introduction

Neglected Tropical Diseases are a group of 17 parasitic infections that affect people living with low income mainly in developing countries, causing large physical, economic and health problems in patients and their communities. According to the World Health Organization (WHO), these infections include dengue, rabies, trachoma, human African trypanosomiasis (sleeping sickness), leishmaniasis, leprosy, Chagas disease, Buruli ulcer, echinococcosis, lymphatic filariasis, onchocerciasis, schistosomiasis, dracunculiasis (Guinea worm disease), foodborne trematodiases, taeniasis/cysticercosis, soil-transmitted helminth infection, and yaws (WHO, 2013). American trypanosomiasis, also called Chagas disease after the Brazilian physician Carlos Chagas who described the infection in 1909, is a vector-borne infection caused by the protozoan parasite *Trypanosoma cruzi* (Chagas, 1909). It was originally found throughout South and Central America, but owing to migrations it has been recorded in every continent. The endemicity of the disease is a complex phenomenon that roots in history, when sedentary and grain accumulation developed in ancient human populations facilitating their interaction with vectors (Brenière et al., 1998; Aufderheide et al., 2004; Coura, 2007) and in the modern economic and social scenery of Latin America (Dias et al., 2014; WHO, 2002). Chagas disease represents one of the most significant health problems in the American continent in terms of human health (i.e., number of people infected with and dying from it), socioeconomic impact, and geographic distribution. Even though the incidence of new infections decreased in Brazil and other countries due to urbanization and improved living conditions, an estimated number of 8 million people remains infected (WHO, 2013).

In its natural life cycle, *T. cruzi* is transmitted by reduviid insects to vertebrates while they sleep. While feeding, infected reduviids (Order Hemiptera, Family Reduviidae, Sub-Family Triatominae) defecate on the sleeping vertebrate and parasites present in the feces (metacyclic trypomastigotes) enter the host through skin abrasions provoked by scratching the bite. Due to this complex life cycle that can be sustained in both sylvatic and urban environments, *T. cruzi* oral transmission has been reported in rural areas in close association with the sylvatic cycle. One of the main sylvatic reservoirs is *Didelphis* spp., marsupials that have anal glands where all *T. cruzi* stages can be found (epi, trypo and amastigote forms). With these glands' secretions, oppossums can contaminate with parasites fruits and utensils used to prepare juice in sylvatic/rural environments in the Amazon region (Shikanai-Yasuda et al., 1991; Roque et al., 2008; Coura, 2015; Barbosa et al., 2015). Crushing infected bugs among the fruits and ingestion of raw or undercooked meat has also been reported as a source of oral outbreaks (Pereira et al., 2010; Cardoso et al., 2006). Oral transmission is usually manifested as acute Chagas, and it has been demonstrated that metacyclic trypomastigotes invade the gastric mucosal epithelium (Camandaroba et al., 2002; Pinto et al., 2008; Pinto Dias, 2006; Yoshida, 2009). A comparison between oral and gastric infections in mice showed that oral infections induced higher levels of parasitemia, mortality, liver lessions, and pro-inflammatory cytokines (INF-γ and TNF-α) than gastric infections (Barreto-de-Albuquerque et al., 2015). Similarly, intragastric infections showed slower development of parasitemia, with lower peaks, as well as lower mortality than intraperitoneally infected mice (Castellanos-Domínguez et al., 2015), demonstrating that the initial site of parasite entrance strongly affects the host immune response and disease outcome.

Human infection results in a myriad of clinical symptoms arising from the initial deposition of infective trypomastigotes, occasionally originating swelling or "chagoma" at the site of infection (WHO, 2002). The development of Chagas' disease varies considerably and there are marked differences between individuals and geographic localities. This suggests that genetic differences on both the parasite and the host (Trischmann and Bloom, 1982; Anon., 1992; Silva et al., 1992; Williams-Blangero et al., 2012) are important for disease outcome, which is characterized by three phases. In the early, acute phase of infection trypomastigotes circulate in blood (parasitemia), and infect cells where they transform into the asexually-multiplying amastigotes. When the cell containing amastigotes is broken, parasites are released to the blood and infect other cells in a cycle lasting a few weeks. During this period there are unspecific symptoms (fever, allergic reactions, and more rarely acute heart failure or meningoencephalitis). Acute Chagas disease can be life threatening if acute myocarditis develops, but it can also be a non-specific febrile illness that in some cases resolves spontaneously without diagnosis or therapy (WHO, 2002). The acute phase might be fatal in children, but most patients survive to enter a prolonged, asymptomatic indeterminate phase where parasites reach and establish in their target organs, forming amastigote nests (Estani et al., 1998). Chronic Chagas disease progresses at a relatively slow pace and 70% of chronic patients have no further evidence of disease. Only 30% develop chronic Chagasic cardiomyopathy or mega-organs—esophagus, liver or intestines- decades later (WHO, 2002). Chronic Chagasic cardiomyopathy (CCC) is characterized by heart hypertrophy and dilatation, which cause severe arrhythmias and progressive systolic dysfunction (Pearson et al., 2003). Severe inflammation of the myocardium (myocarditis) was found to be positively associated with parasite persistence and interstitial fibrosis (Benvenuti et al., 2008). Destroyed myocardial cells are also found, with lymphocyte, plasma cell, and macrophage infiltration often forming "microabscesses" that later heal by fibrosis. Mega-organ disease is associated with destruction of the myenteric plexus in the gastrointestinal tract (Pearson et al., 2003). Inflammatory infiltrate cells and their cytokine and chemokine expression in CCC heart lesions are well characterized. Moreover, given the fact that only 20–40% of patients develop CCC (Rassi et al., 2009; Bern, 2015; Organization WH, 2015), and the importance of inflammatory mechanisms in its development, it is expected to find genetic polymorphisms and susceptibility markers to CCC in genome-wide association studies (Cunha-Neto and Chevillard, 2014).

A consequence of research about Chagas disease has been the description and study of its causative agent, *T. cruzi* (Domain: Eukarya, Phylum: Euglenozoa, Class: Kinetoplastea, Order: Tripanosomatida, Family: Tripanosomatidae, Genus: *Trypanosoma*,