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DRUG EVALUATION

An evaluation of benznidazole as a chagas disease therapeutic

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ABSTRACT

Introduction: As benznidazole is the first-line treatment for patients with Chagas disease, rational chemotherapy strategies are required based on the critical analysis of the evidence on the relevance and applicability of this drug at different disease stages.

Areas covered: The authors discuss the current understanding of benznidazole-based chemotherapy for Chagas disease, focusing specifically on epidemiology, pharmacokinetics, mechanism of action, clinical recommendations, cure criteria, and therapeutic efficacy in different phases of the disease.

Expert opinion: Benznidazole shows high bioavailability after oral administration. Benznidazole at 5–8 mg/kg/day and 5–10 mg/kg/day for 30–60 days are consistent clinical recommendations for children and adults, respectively. A high correlation between negative parasitological, serological, and polymerase chain reaction (PCR) assays in long-term post-therapeutic follow-up has been consistently used to evaluate therapeutic efficacy. These methods support the evidence that the success of benznidazole-based chemotherapy is closely correlated with the phase of infection in which the treatment is administered. The greater therapeutic efficacy is obtained in acute infections, gradually worsening as the infection becomes chronic. When therapeutic failure is confirmed by any diagnostic assay, benznidazole treatment does not always ensure better long-term prognosis, and Chagas cardiomyopathy may develop as well as in untreated patients.

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1. Introduction

American trypanosomiasis or Chagas disease is a neglected tropical anthropozoonose caused by the parasite protozoan *Trypanosoma cruzi*. At least seven million people are infected by this parasite and 25 million people are at risk of infection worldwide [1,2]. Chagas disease is endemic in Latin America, and most cases of infection are reported in areas with low socioeconomic development [1]. In the last decades, this disease has been more consistently detected in non-endemic areas, and at least 181,181 cases in Europe and 350,000 cases in North America were recently confirmed [3,4]. While oral and vector routs are responsible for most cases of *T. cruzi* infection in endemic countries, blood donation and transplantation of infected organs, congenital transmission (mother to fetus), and laboratory accidents are the main routes of infection in non-endemic countries [5].

The Chagas disease develops into acute and chronic stages. Acute infections are asymptomatic in about 95% of the cases and are characterized by high parasitemia easily detectable by direct microscopic observation of *T. cruzi* trypomastigotes in fresh blood [4,6]. About 5–10% of patients die in the acute phase and those who survive progress to the chronic phase of the disease [7,8]. Due to low or undetectable parasitemia, the diagnosis of chronic infections are based on conventional serological methods and polymerase chain reaction (PCR)-based molecular methods, which exhibit more acceptable profiles of sensitivity and specificity compared to conventional parasitological methods [5,9].

About 70% of *T. cruzi*-infected patients develop a chronic indeterminate infection, which is asymptomatic. Conversely, 30% of patients evolve to a chronic symptomatic disease, developing mega syndromes (megacolon and megaesophagus) and Chronic Chagas cardiomyopathy (CCC), the main causes of morbidity and mortality in Chagas disease [1,10]. Complex and multifactorial processes are involved in the pathogenesis of mega syndromes and CCC, especially parasite persistence, autonomic denervation, microvascular insufficiency, oxidative damage, and autoimmunity [4,10]. The mega syndromes are caused by the parasitism and persistent inflammation in the digestive organs, determining severe loss of smooth muscle cells and destruction of intramural parasympathetic neurons [11,12]. Esophagus and colon dilatation, thickening of their walls, segmental disturbances of peristalsis of the digestive tract, dysphagia, regurgitation, and constipation are the main manifestations of mega syndromes [11,12].

Chronic Chagas cardiomyopathy (CCC) is the most severe and incapacitating manifestation of Chagas disease that occurs years or decades after acute infection [5,10]. CCC develops as a dilated cardiomyopathy in response to extensive heart microstructural remodeling associated with cardiomyocyte

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