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# Limitations of currently available Chagas disease chemotherapy

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*Trypanosoma cruzi* infection or Chagas disease was discovered more than 100 years ago by Carlos Chagas[1]. Today, it affects eight million people in a total of 21 countries of Latin America and, due to immigration, the infection is also present in non-endemic countries like Australia, Canada, Spain and the United States. In recent years, chronic imported forms of Chagas disease in immigrant populations have grown in Spain. Moreover, several cases of congenital transmission have been reported[2,3,4]. Although the infection kills more than 15,000 people each year, it is still classified as a neglected tropical disease[5]. Since the 1960s only benznidazole and nifurtimox have been available for clinical use, despite new chemotherapy approaches such the inhibitors of ergostherol synthesis[6].

Treatment with these trypanocidal drugs in the acute phase leads to regression of clinical symptoms and parasitological cure, diminishing the death rate. Nifurtimox and benznidazole cure around 80% of the acute *T. cruzi* infections. Early treatment increases the possibilities of success, and so treatment must be begin as early as possible[7,8,9]. Nevertheless, while specific treatment with these drugs has been recommended for the acute phase of the disease and in congenital infection, the effectiveness of benznidazole and nifurtimox in eradicating *T. cruzi* during the chronic stage remains unclear[10], mainly because of the lack of reliable tests and biomarkers to evaluate parasite elimination. At present, it is recommended that all infected patients be treated.

Since seroconversion occurs several years after treatment and a long-term follow up of the patients is required, several studies have been conducted to evaluate parasitological cure using PCR in chronic cases. Our group performed the first PCR follow-up survey in patients with Chagas disease in a European country, where the absence of triatominal vectors rules out the possibility of reinfection[11]. In that study, early PCR negative conversion was observed in all patients 90 days post-treatment, which was deemed to reflect the effectiveness of the treatment to clear parasites better than serology. Moreover, PCR allowed treatment failure to be ratified – in our case in 6.9% of the patients, who shifted to positive at the end of the follow-up period. Although PCR is a sensitive and specific tool for the early detection of the parasite's susceptibility to treatment, a negative PCR result does not necessarily indicate parasitological cure of the patients in the absence of other markers.

The major limitation of benznidazole and nifurtimox is the high incidence of side effects. In a previous and in the current issue, we report the side effects of these antiparasitic agents in the treatment of Chagas disease (Carrilero et al.[12] and Murcia et al. in the letter to the editor[13]). Carrilero et al.[12] describes a prospective survey of the side effect of benznidazole treatment in a cohort of chronic Bolivian patients, who were treated at the Unit of Tropical Medicine of the Virgen de la Arrixaca Hospital in Murcia (Spain). In this study, 373 patients received treatment with benznidazole, 5-7 mg/kg body weight per day in pediatrics and 100 mg three times a day in adults for 60 days. Of these, 150 (40.2%) presented adverse reactions.

Of the two currently available compounds, benznidazole is the most frequently used because of its better safety record. The treatment was less toxic in children and adolescents, while mildly intense side effects, defined by the authors as those which did not interfere with the patient's daily activity or did not require treatment, occurred in the most of the patients who suffered adverse reactions (99 of 150 = 66%). Nevertheless, regardless of the different measures that were taken into account to avoid the interruption of treatment, it was found that 21 of 373 patients (5.6%) had to suspend the treatment due to the side effects and of these, 12 did so following a extreme adverse reaction, which entailed a risk or produced sequels, highlighting the high toxicity of this drug. In the referred to article, we describe some well defined adverse reactions to benznidazole, such us cutaneous hypersensitivity, gastrointestinal intolerance, articular problems, fever and neurological disorders, including polyneuritis, headache, vertigo, insomnia and asthenia. Of these, in accordance with the findings of previous studies, dermatological side effects and

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digestive intolerance were the most frequent; however, some patients showed less common side effects such as renal failure. Surprisingly, three cases of migratory arthritis were observed.

The side effects profile of nifurtimox is no better than that of benznidazole. Thus, in addition to some systemic side effect described for benznidazole, nifurtimox has also been associated with anorexia, weight loss and other central nervous system disorders like disorientation, forgetfulness, spasm and convulsive seizure. In the letter to the editor13 in this issue, we describe nifurtimox tolerance in only 26 treated patients with Chagas disease (8-10 mg/kg in 3 daily doses for 90-120 days), of whom 16 (61.5 %) presented adverse reactions. In spite of this high percentage of patients showing side effect, none had to suspend the treatment. The most frequent side effect was digestive intolerance (nausea, vomiting, epigastralgy and dysphagia), followed by anorexia and forgetfulness. However, this is a preliminary study and, taking into account the low number of patients treated with nifurtimox, among the adverse reactions found in this cohort, some would be expected to change in frequency if a higher number of patients were included in the study.

Trypanosomal therapy with the current drugs is indicated in children and in adults in chronic phase with no clinical manifestations or with mild cardiac or digestive symptoms, in order to improve prognosis.

In non-endemic countries where health services are not familiar with Chagas disease a better knowledge of the side effects of trypanosomiasis treatment is essential for management of the disease.

Due to the limitations associated with the therapeutic use of benznidazole and nifurtimox, new drugs showing higher trypanocidal activity in both the acute and chronic stages of the disease and fewer side effects are urgently needed. In this respect, inhibitors of ergostherol synthesis, such as ketaconazole, itraconazole, posaconazole or amiodarone, are the most promising candidates for Chagas disease chemotherapy. In order to increase the effectiveness of the treatment, the combined use of anti-*T.cruzi* drugs with synergistic effects has been proposed. Drug synergy helps reduce the dosage of each compound, thus diminishing side effects[14]. Moreover, hybrid compounds with a dual action mechanism consisting of nitrofuran activity and ergostherol biosynthesis inhibition have been obtained[15].

In addition to the search for new compounds, future research should include a search for markers with a predictive value for diagnosis and follow up after treatment, which would allow therapeutic efficacy to be assessed. In these sense, among *T. cruzi* specific antigens, KMP-11 is capable of distinguishing between the clinical stages of infected patients (acute vs. chronic) and Chagas patients from healthy persons[16]. Nevertheless more studies are necessary to confirm the usefulness of these antigens as potential tools for follow up and cure.

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## TRANSPARENCY DECLARATIONS

None to declare

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