CARTAS AL EDITOR

Are imidazolic drugs effective in the treatment of chronic Chagas cardiomyopathy?

To the editor: In 1909 Carlos Chagas described American Trypanosomiasis (AT), or Chagas disease. Today this disease is still a major threat to public health in Latin American countries. In 1991 the World Health Organization reported that approximately 18 million people were infected, and another 100 million were potentially at risk.[1] Since then, the Health Ministries of Argentina, Brazil, Bolivia, Chile, Paraguay, and Uruguay created the South Cone Initiative to eliminate vectorial and transfusional Chagas disease transmission by year 2010. This initiative has spread to other South and Central American countries. The accomplishments so far are remarkable: some countries have been declared free of vectorial transmission, and others are very close to reaching this goal.[2]

In our country Chagas disease was neglected for many years and is now considered an emerging disease posing a serious public health problem because it is a poverty-linked condition in subtropical and tropical zones, both in rural villages and in the poor outskirts of big cities. In the former, vectorial transmission is the rule; in urban settings, uncontrolled blood donation has become a potentially important infection transmission pathway. Estimates reveal that no less than 1.5 million people are infected, 10% of whom already have or will develop a chronic symptomatic condition. In addition, transmission also occurs among children under 10 years of age, with 70 000 new cases per year. The majority of them are not recognized because the disease is not known by the general population nor by practitioners. Furthermore, there are no diagnostic tools available in the clinical laboratory; parasitemia and serological responses are not sought in everyday medical practice and even chronic chagasic cardiopathy remains unrecognized at many tertiary care facilities throughout Mexico.[3,4]

Since 1992 the health authority included Chagas disease as a mandatory notification condition;[5] however, this regulation had no practical consequences. Furthermore, the same ordinance recommended medical treatment using either nitrofuran or imidazolic parasiticidal drugs. Unfortunately, these drugs are not available in the market and their availability is limited throughout the health system. Treatment is thus unavailable in most cases. We feel it is time to review some aspects of Chagas disease management in the context of chronic disease treatment.

Trypanocidal drugs have been used in the treatment of Chagas disease since the 1960, when nitrofuran, and later imidazolic drugs, were introduced after a 50-year history of therapeutic failures.[6] Both nitrofuran and imidazole derivatives (nifurtimox and benznidazol, respectively) induce a well-recognized therapeutic response, limited to acute and early chronic trypanosomal infections, and achieving a recovery rate of about 76 percent.[7]

The proven efficacy of benznidazol and nifurtimox in the treatment of acute phase Chagas disease is not the same in later stages.[8-10]

We researched the evidence and found 47 papers, which studied different aspects of drug therapy of chronic chagasic cardiopathy (CCC). Only six published papers addressed the treatment of overt CCC; only one of them used a double-blind randomized placebo-controlled clinical trial, the rest were case-cohort studies or clinical case series studying patients suffering from CCC.[11]

Double-blind placebo-controlled clinical trials for benznidazol show no conclusive results.[12] Open studies, which lacked a sound methodological design revealed no solid conclusions. Some of them loosely suggest that treatment in people below 40 years of age may improve their clinical condition, a recommendation difficult to sustain, since these individuals may well have been suffering from a subclinical "disease".[7,12-16] Under the best conditions, treatment, hopefully, will slow heart abnormalities. This expectation is not supported by validated data and represents mostly "clinical experience".

Evidential support for such a therapeutic approach is not enough and represents conspicuously negative data. It challenges treatment with oxidative stress-inducing drugs, such as those mentioned above, which were conside-

red the mainstream of pharmacological treatment.

At present, after reviewing the evidence we can assert, without hesitation, that CCC has no etiologic antiparasitic treatment if the generally available nitrofuran or imidazolic drugs are recommended. Further research on the pathophysiology of CCC is necessary, as well as to establish whether chronic tissue parasitism is an important issue in the disease's progression in order to look for drugs which would control parasites from the tissues and therefore avoid organ damage.

Pharmacological research is now considering the use of other trypanocidal drugs focusing on parasite metabolic routes which are not shared with host cells, such as glycolitic pathways, diphosphonates as modifiers of pyrophosphate metabolism, or drugs which modify sterol biosynthesis in protist parasites. Hopefully, some of these new drugs will be available for clinical trials in the near future.

M en C Maité Vallejo,
Dr Pedro A. Reyes.
Instituto Nacional de Cardiología "Ignacio Chávez"
Dirección de Investigación.
preyes44@yahoo.com.mx.

References

1. World Health Organization. Control of Chagas disease. Report of a WHO expert committee. Ginebra: WHO, WHO Technical report series No. 811, 1991.
2. Schofield CJ, Dias JC. The Southern Cone initiative against Chagas disease. Adv Parasitol 1999;42:1-27.
3. Guzmán-Bracho C. Epidemiology of Chagas disease in Mexico: An update. Trend Parasit 2001;17:372-376.
4. Dumonteil E. Update on Chagas disease in Mexico. Salud Publica Mex 1999;41:322-327.
5. Secretaría de Salud. Norma técnica No 348, para la prevención y control de la tripanosomiasis en la atención primaria a la salud. México, DF: Diario Oficial de la Federación, 17 enero 1992.
6. Brener Z. Chemotherapy of *Trypanosoma cruzi* infection. Arch Pharmacol Chemother 1975;13:13-44.
7. Cancado JR. Long-term evaluation of etiological treatment of Chagas disease with benznidazole. Rev Inst Med Trop S Paulo 2002;44:29-37.
8. Andrade SS, Guimaraes J. Randomized trial of efficacy of benznidazole in treatment of early *Trypanosoma cruzi* infection. Lancet 1996;348(23):1407-1413.
9. Sosa S, Segura EL, Mariano A, Velázquez E, Porcel BM, Yampotis C. Efficacy of chemotherapy with benznidazole in children in the indeterminate phase of Chagas disease. Am J Trop Med Hyg 1998;59(4):526-529.
10. Stoppani AOM. Quimioterapia de la enfermedad de Chagas. Medicina 1999;59(supl II):147-165.
11. Reyes P, Vallejo M. Trypanocidal drugs for late stage, symptomatic Chagas disease (Cochrane Protocol). In: The Cochrane Library. Oxford: Update Software, 2003.
12. Rodriguez-Coura J, De Abreu LL, Percy H, Wilcox F, Petana W. Estudo comparativo controlado com emprego de benznidazole, nifurtimox e placebo, na forma crónica da doenca de Chagas, em uma área de campo com trasmissao interrompida. I. Evaluacao preliminar. Rev Soc Bras Med Trop 1997;30:139-144.
13. Viotti R, Vigliano C, Armenti H, Segura E. Treatment of chronic Chagas disease with benznidazole: Clinical and serological evolution of patients with long-term follow-up. Am Heart J 1994;127:151-162.
14. Fabro D, Arias E, Streiger M, Placenza M, Ingaramo M, Del Barco M *et al.* Evolutive behavior towards cardiomyopathy of treated (nifurtimox or benznidazole) and untreated chronic chagasic patients. Rev Inst Med Trop S Paulo 2000;42:99-109.
15. Braga MS, Lauria-Pires L, Arganaraz ER, Nascemento RJ, Teixeira ARL. Persistent infection in chronic Chagas disease patients treated with anti-*Trypanosoma cruzi* nitroderivatives. Rev Inst Med Trop S Paulo 2000; 42: 157-161.
16. Lauria-Pires L, Braga MS, Vexenat AC, Nitz N, Simoes-Barbosa A, Tinoco DL. Progressive chronic Chagas heart disease ten years after treatment with anti-*Trypanosoma cruzi* nitroderivatives. Am J Trop Med Hyg 2000;63:111-118.