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Review

Course of serological tests in treated subjects with chronic *Trypanosoma cruzi* infection: A systematic review and meta-analysis of individual participant data

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ABSTRACT

Objective: To determine the course of serological tests in subjects with chronic *Trypanosoma cruzi* infection treated with anti-trypanosomal drugs.
Methods: A systematic review and meta-analysis was conducted using individual participant data. Survival analysis and the Cox proportional hazards regression model with random effects to adjust for covariates were applied. The protocol was registered in the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO; CRD42012002162).
Results: A total of 27 studies (1296 subjects) conducted in eight countries were included. The risk of bias was low for all domains in 17 studies (63.0%). Nine hundred and thirteen subjects were assessed (149 seroreversion events, 83.7% censored data) for enzyme-linked immunosorbent assay (ELISA), 670 subjects (134 events, 80.0% censored) for indirect immunofluorescence assay (IIF), and 548 subjects (99 events, 82.0% censored) for indirect hemagglutination assay (IHA). A higher probability of seroreversion was observed within a shorter time span in subjects aged 1–19 years compared to adults. The chance of seroreversion also varied according to the country where the infection might have been acquired. For instance, the pooled adjusted hazard ratio between children/adolescents and adults for the IIF test was 1.54 (95% confidence interval 0.64–3.71) for certain countries of South America (Argentina, Bolivia, Chile, and Paraguay) and 9.37 (95% confidence interval 3.44–25.50) for Brazil.
Conclusions: The disappearance of anti-*T. cruzi* antibodies was demonstrated along the course of follow-up. An interaction between age at treatment and country setting was found.

Contents

Introduction

Chagas disease is a potentially life-threatening endemic illness in the Latin America region (Bulla et al., 2014; Pérez-Molina and Molina, 2018). It is caused by a protozoan parasite called *Trypanosoma cruzi*. This parasite has been classified into six genetic variants with approximate geographical distribution in domestic and wild transmission cycles (Zingales et al., 2012). It is mainly transmitted through vectors (namely triatomine bugs) in impoverished rural areas (Houweling et al., 2016; Pérez-Molina and Molina, 2018). Blood transfusion and congenital transmission are other mechanisms for acquiring the disease. Alternative mechanisms are accidental, oral, and via organ transplantation (Dias and Amato Neto, 2011; Ministerio de Salud de la Nación, 2012).

The duration and clinical presentation of the initial acute phase of the infection may be variable, depending on the patient's age, immunological status, presence of comorbidities, and the transmission pathway. It usually lasts a few months and may be symptomatic (prolonged febrile syndrome, asthenia, hepatosplenomegaly, and other characteristic but less frequent signs, such as Romaña sign and 'chagoma' of inoculation) or asymptomatic (Ministerio de Salud de la Nación, 2012).

Most subjects who do not receive specific treatment during the acute phase go on to develop a chronic infection. If untreated, the chronic phase usually continues for the subject's lifetime, and 30% to 40% of patients will progress to the chronic phase with a cardiac, digestive, neurological, or mixed form at 15 to 30 years after the initial infection. Progressive heart failure and sudden death are the main causes of death in patients with chronic Chagas heart disease (Ministerio de Salud de la Nación, 2012; Pérez-Molina and Molina, 2018).

Several systematic reviews on the effectiveness of treatment in chronically infected subjects have been published (Villar et al., 2014; Fuentes et al., 2012; Pérez-Molina et al., 2009; Vallejo and Reyes, 2005). The current recommendation of the World Health Organization (WHO) is to offer anti-trypanosomal drugs (benznidazole or nifurtimox) to subjects with chronic *Trypanosoma cruzi* infection, particularly those who are asymptomatic (Bulla et al., 2014). Based on current techniques and their attributes, the general consensus is that treatment success is confirmed by conversion from a positive to a negative serological state (seroreversion), while treatment failure is demonstrated through a positive molecular or parasitological test. The assessment of the response to treatment is uncertain in a large number of subjects because of the long span needed to demonstrate the disappearance of anti-*T. cruzi* antibodies (de Lana and Martins-Filho, 2009; Viotti et al., 2014).

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