
**EFFICACY OF BENZNIDAZOL TREATMENT IN
TRYPANOSOMA CRUZI INFECTED CHILDREN:
A RANDOMIZED DOUBLE BLIND CLINICAL
TRIAL CONDUCTED IN CENTRAL BRAZIL**

Andrade ALSS,¹ Fabio Zicker,² Silva AS,³ Oliveira RM,³ Luquetti AO,³ Almeida IC,⁴ Travassos LR,⁴ Rassi A,⁵ Rassi AG,⁵ Andrade JG,³ Andrade SS,³ Siqueira Jr JB,³ Spadeto AI,³ Martelli CMT³

A field trial to assess the efficacy of Benznidazole was conducted between 1991-95 in the municipalities of Posse, Simolândia and Guarani de Goiás, Central Brazil, sponsored by TRD/OMS. In this report, we present a summary of the main results of the trial and some comments about monitoring ECG abnormalities during this period. Detailed of study design, methods were published previously (Andrade et. al. 1996; Andrade et al, 1997).

In brief, the trial design included a *T. cruzi* serological baseline survey of 1,990 schoolchildren carried out in 1991 using various serologic tests (IHA, IIF, ELISA and AT ELISA). 129 seropositive children were eligible and were randomly allocated to receive Benznidazol (BZ - 60 days course) or Placebo (PL) preparation in a double blind controlled trial with 38 months follow-up. The outcome for efficacy was the disappearance of specific antibodies (negative seroconversion) by the end of 3-years-follow-up. The secondary endpoint was the reduction of antibody titres on repeated serological tests. Full compliance was obtained for 87% of the participants, BZ (n=58) and PL (n=54). Minor side effects were recorded in a small proportion of individuals and only one exclusion was due to adverse effect.

The criteria for seropositivity is: Indirect immunofluorescence (IIF) - a reciprocal titre of 40 or more; ELISA index - 1.2 or more; Indirect

¹ Pan American Health Organization - WHO

² Special Programme for Research and Training in Tropical Diseases (TDR) - WHO

³ Instituto de Patologia Tropical e Saúde Pública - Universidade Federal de Goiás

⁴ Universidade Federal de São Paulo

⁵ Faculdade de Medicina - Universidade Federal de Goiás

haemagglutination (IHA)– reciprocal titre of 16 or more; Chemoluminescent ELISA (AT ELISA) – values greater than 1.0.

All tests were performed blindly without the knowledge of the previous serological results at the WHO Reference Laboratory for Chagas' disease serology, Federal University of Goiás (Dr. Luquetti AO). The AT ELISA was carried out at Universidade Federal de São Paulo under the supervision of Dr. Almeida IC. For this study not only the 3-year follow-up but the intermediate end-points of the trial were tested in order to determine the serum pattern among participants.

Baseline results – Children enrolled in the trial had similar age and sex distribution. Also serological, haematological, and biochemical results were similar in the two groups. Although all children were free of symptoms, ECG recorded at baseline showed that 13 children had ECG abnormalities, 9 had complete right bundle branch block (CRBBB) which indicates premature development of Chagas's disease cardiomyopathy

Monitoring effect on serology

Chemoluminescent ELISA was positive at the beginning of the trial. At the end of follow-up, 37 (58%) of the 64 benznidazole treated and 3 (5%) of those who received placebo were negative for *T. cruzi* antibodies. The efficacy of benznidazole treatment was 55.8% (95% CI 40.8-67.0). At the end of follow-up, children who received BZ had five-fold lower geometric mean titres by indirect immunofluorescence than placebo-treated. There was also a clear time-trend toward seronegativity in the treated group when compared to the placebo one that maintained the same levels of antibody response during the whole monitoring period.

The trial showed that a 60-day course of benznidazole treatment in early chronic *T. cruzi* infection was safe and 55.8% effective in producing seronegative conversion of specific antibodies. The results are very encouraging and justify the recommendation of treatment for seropositive children as public health policy.

Ethical issues

The seropositive participants originally from the placebo group were treated with Benznidazole after the trial was finished and the results justified the recommendation of treatment. In this adolescent cohort side-effects were slight (nausea, anorexia, stomach-ache) reported for 6% of the individuals. During the 60-day treatment, cutaneous maculopapular rash and pruritus was

reported by 28% of the patients. No patient had to stop drug-intake because of side-effect. Participants with ECG alterations were examined by a specialist and treatment and follow-up were recommended accordingly.

Final Remarks

This study disclosed a high prevalence of early development of cardiac lesions among symptom free children/adolescents detectable by conventional ECG in a population-based perspective. In this sense, the lag-time between infection and disease may be much shorter than previously thought. There was also an early patterns of cardiac evolution among these *T. cruzi* infected children. 3-years-follow-up was not enough to answer whether Benznidazole treatment in early chronic infected children avoid cardiac damage involvement. The prognosis of cardiac lesions will be further explored in risk factor analysis, relating probable age-at-infection, parents and siblings serology and ECG findings. However, a long-term follow-up of these patients and genetic and molecular biology investigations under study may add valuable information about disease progression.

During the 3-years follow-up there was a decreasing trend in seropositive findings due to an increase in seronegative conversion among treated patients in paired and unpaired analyzes. Therefore, this study answered two important questions: (a) seronegative conversion was higher among treated patients while the antibody levels were stable among untreated individuals during the 3-years-follow-up; (b) 3-years-follow-up seems sufficient to assess cure at individual basis. Although conventional serology showed decrease in antibodies titres during the monitoring period these tests do not seem to be specific enough to assess cure rates. The correlation between the levels of antibody response in different tests and what are the possible risk factors for resistant to treatment are issues that we are addressing in data analysis on progress.

This study was sponsored by the UNDP/World Bank/WHO/Special Programme for Training in Tropical Disease/TDR and by the Brazilian Council For Science and Technology development.

References

1. Almeida IC, Rodrigues EG, Travassos LR. Chemoluminescent immunoassays: discrimination between the reactivities of natural and human patients antibodies from eukaryotic pathogens, *Trypanosoma cruzi* and *Paracoccidioides brasiliensis*. *J Clin Lab Anal.* 8:424-31.
2. Andrade ALSS, Zicker F, Oliveira RM, Silva AS, Luquetti AO, Travassos LR, Almeida IC, Andrade SS, Andrade JG, Martelli CMT. Randomized trial of efficacy of benznidazole in treatment of early *Trypanosoma cruzi* infection. *Lancet*, 384: 1047 – 1413, 1996

3. Andrade ALSS, Zicker F, Rassi A, Rassi AG, Oliveira RM, Silva AS, Andrade SS, Martelli CMT. Early electrocardiographic abnormalities in *Trypanosoma cruzi* seropositive children. *Am. J. Trop. Med. Hyg.* 1998 (accepted for publication).
4. Zicker F, Almeida Netto JC, Zicker SEM, Oliveira RM, Smith PG, *Trypanosoma cruzi* infection and electrocardiographic findings among manual workers. *Int. J. Epidemiol.* 19: 182-186.