Treatment of *Trypanosoma cruzi* Infection in the Undetermined Phase. Experience and Current Guidelines of Treatment in Argentina

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The goals of specific treatment against *Trypanosoma cruzi* infection, at an individual level, are to eliminate the parasite, to diminish the probability of developing illness (Chagas disease), and to hinder the chain of *T. cruzi* transmission as actions for the control of vectorial and non vectorial transmission (Sosa Estani 1993). Around 1930, investigations began in Argentina to obtain an effective drug against *T. cruzi*. Of all the substances evaluated, only nifurtimox (1972) and benznidazol (1974) have been accepted by the Ministry of Health as anti-*T. cruzi* drugs. Both drugs began to be assessed on the acute phase, and later, on the chronic phase of the disease.

THE EXPERIENCES

In patients treated with nifurtimox following recommended guidelines, xenodiagnoses turned negative for 88 to 100% of the cases evaluated up to 123 months after treatment, although in the chronic patients, serology rarely became negative. Some researches found negativization to occur between 28 and 38% of the cases (Cerisola 1969, Boca Tourres 1969, Cançado 1969, Cichero et al. 1969).

Until 1983, in Argentina, it was recommended to treat exclusively patients in the acute phase of Chagas disease, because in the undetermined and chronic phases, conventional serology persisted reactive, in spite of negative xenodiagnoses. However, different authors (Cichero et al. 1969, Cançado 1969, Rubio & Donoso 1969, Schenone et al. 1969, Ferreira 1969, 1990, Cerisola 1977), concluded that these drugs were also effective in the undetermined phase. This was inferred based on the evaluation of parasitemia through xenodiagnoses, which became undetectable or decreased. It must be stressed that in most cases serology persisted reactive (Rubio & Donoso 1969, Schenone et al. 1969, Cerisola 1977). Some of these authors indicated a decrease of serologic titers (Ferreira 1969, Viotti et al. 1994, de Andrade et al. 1996, Sosa Estani et al. 1998). Some authors suggested the possibility that lack of parasitic clearance was the cause of reactive serology. It was also suggested that the difference of antibodies (Abs) involved in the conventional serology and those Abs that unite to the circulating forms of the parasite would influence the serological evaluation of the specific treatment (Krettli & Brener 1982, Krettli et al. 1984).

In 1994, Viotti et al. in an eight year follow-up of adult and young patients non treated or treated with benznidazol, showed that 23% of the controls had unfavorable changes in their electrocardiograms (ECGs). Those alterations were seen in 5% of the treated patients ($p < 0.05$). However among those that maintained a reactive serology, the alterations of the ECGs were observed in 29% of the control patients and 2% of the patients treated with benznidazol. The authors concluded that specific treatment has a protective effect during the chronic phase of the infection.

Between 1991 and 1995 a controlled clinical trial was carried out to evaluate the effectiveness of treatment with benznidazol in children during the undetermined phase of Chagas disease (Sosa Estani et al. 1998). After a four year follow-up, this study demonstrated a significant decrease on the titers of Abs in patients that received benznidazol, while changes were not observed in those that received placebo. In patients that showed reactivity against the recombinant antigen (Ag) F29 (Porcel et al. 1996), negativization of serology at the end of the follow-up was 62.1% among children treated with benznidazol and 0% among those that received placebo. After seven years of follow-up, the negativization in children treated with benznidazol was around 69% (manuscript in preparation). Other authors found similar results

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using Ags not currently used in conventional serology (Galvão et al. 1993, Gazzinelli et al. 1993, Krautz et al. 1995, de Andrade et al. 1996). Xenodiagnoses at the end of the follow-up was positive in 4.7% of patients treated with benznidazol and 51.2% among control children ($p<0.05$). Our study concluded that the effectiveness was over 60%, and that children infected with *T. cruzi* that inhabited rural areas may be successfully treated with benznidazol in an outpatient modality. There are good opportunities of administering specific treatment, and obtaining the cure of the infection in the first decade of life (Cichero et al. 1969, de Andrade et al. 1996, Cançado 1997). The cure of infection will also eliminate the risk of developing visceral alterations due to Chagas disease (Viotti et al. 1994) and will contribute to the interruption of *T. cruzi* transmission in areas under vector surveillance. Moreover, our study provided a new serological marker of cure after treatment, implemented as a quick and simple serological procedure. In a preliminary observation in this same population, we also found that at the end of treatment, the plasmatic concentration of p-Selectin (molecule of adhesion) was significantly lower in patients treated with benznidazol compared with the controls, evaluated through an enzymatic immune assay (Laucella et al. manusc. in prep.). These studies are being completed. Other clinical trials that reproduce the results previously mentioned have been documented in the last years in Argentina, although they were not performed under controlled conditions (del Barco et al. 1993, Blanco et al. 1997, Fabro et al. 1997).

SIDE EFFECTS

Different authors refer that side effects appear among 4% and 30% of cases (Barclay et al. 1978, Lugones 1978, Castro & Diaz de Toanzo 1988, Blanco et al. 1997, Sosa Estani et al. 1998). These could include dermal (cutaneous maculopapular rush), or gastrointestinal (colic, nausea, vomits) manifestations, central neurotoxicity (nervous irritability, insomnia, headache, anorexia), and peripheral neurotoxicity (paresthesia, hiperesthesia), mioartralgias. Laboratory tests showed normal bilirrubin values, while elevation of transaminases could sometimes be observed (Lugones et al. 1969, Castro & Diaz de Toanzo 1988); leucopenia or plaquetopenias are exceptionally observed (Cançado 1997). Side effects are directly related with the dose and the patient's age, being more tolerated in children and babies than in adolescents and adults (Bocca Tourres 1969, Cerisola 1977, Moya et al. 1985). In our experience, in all cases, side effects disappear when the dose is diminished or the treatment suspended. The treatment always demands direct medical supervision (Coura 1996).

EVALUATION OF TREATMENT

To evaluate the response to specific chemotherapy, it is advisable to use clinical, immunoserological and parasitological methods. For the last years in Argentina and other countries like Brazil, the response to specific treatment has also been performed using new tools, such as recombinants Ags, tripomastigote Ags, the polimerase chain reaction or adhesion molecules, that complete those already in existence. Presently, to evaluate the effectiveness of treatment, it is necessary to consider the absence of parasites and a significant decrease of Ab concentration, or until negativization of serology.

CURRENT SITUATION

Since 1994, the Control Program of Chagas in Argentina included the subprogram "Detection and treatment in children between 0 to 14 years old infected by *T. cruzi*", detecting children inhabiting the households under surveillance for triatomine populations. This is a necessary condition for the administration of specific treatment (OPAS 1998). In 1997, the guidelines for treatment of the chagasic patient in Argentina were revised and the current criteria has been elaborated based on results obtained through scientific investigations on medical care, and health system support. At the moment, treatment is recommended for (a) all patients undergoing the acute phase of Chagas disease; (b) children and young people undergoing the undetermined phase of Chagas disease; (c) adults undergoing the undetermined phase or with incipient heart lesions; and (d) transplant recipients or donors.

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