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LONG TERM EVALUATION OF ETIOLOGICAL TREATMENT OF CHAGAS DISEASE WITH BENZNIDAZOLE

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SUMMARY

The aim of this article is to present an investigation of cure rate, after long follow up, of specific chemotherapy with benznidazole in patients with both acute and chronic Chagas disease, applying quantitative conventional serological tests as the base of the criterion of cure. Twenty one patients with the acute form and 113 with one or other of the various chronic clinical forms of the disease were evaluated, after a follow up period of 13 to 21 years, for the acute, and 6 to 18 years, for the chronic patients. The duration of the acute as well as the chronic disease, a condition which influences the results of the treatment, was determined. The therapeutic schedule was presented, with emphasis on the correlation between adverse reactions and the total dose of 18 grams, approximately, as well as taking into consideration precautions to assure the safety of the treatment. Quantitative serological reactions consisting of complement fixation, indirect immunofluorescence, indirect hemagglutination, and, occasionally, ELISA, were used. Cure was found in 76 per cent of the acute patients but only in 8 per cent of those with chronic forms of the disease. In the light of such contrasting results, fundamentals of the etiological therapy of Chagas disease were discussed, like the criterion of cure, the pathogenesis and the role of immunosuppression showing tissue parasitism in long standing chronic disease, in support of the concept that post-therapeutic consistently positive serological reactions mean the presence of the parasite in the patient's tissues. In relation to the life-cycle of *T. cruzi* in vertebrate host, there are still some obscure and controversial points, though there is no proof of the existence of resistant or latent forms. However, the finding over the last 15 years, that immunosuppression brings about the reappearance of acute disease in long stand chronic patients justifies a revision of the matter. Facts were quoted in favor of the treatment of chronic patients.

KEYWORDS: Chagas disease; Treatment; Cure; Benznidazole; Therapeutic Schedule; *Trypanosoma cruzi*; Side-effects

INTRODUCTION

Since 1962, we have examined, at the University Hospital and in private practice, in Belo Horizonte, MG, Brasil, 2,405 Chagas disease patients, 47 with the acute form and 2,358 with one of the various chronic clinical forms of the disease.

The data derived from this work, specially on etiological treatment, are included in several academic theses and controlled clinical trials, chapters of books as well as research articles, as cited elsewhere[8,15,16,17,18,19,20,21,37,38,39,49].

The objective of the present article is to evaluate, after a long follow up period, the results of specific chemotherapy with benznidazole of patients treated, both during the acute and chronic phase of the disease, using quantitative conventional serological (CS) tests as the base of the criterion of cure[19].

PATIENTS AND METHODS

PATIENTS. **Acute form.** Table 1 contains the details of 21 acute phase of Chagas disease patients, treated with benznidazole, from 1974 to 1982.

Eligible patients included 15 men and 6 women, ranging from 0.7 to 60 years old, who fulfilled two basic conditions:

1. Benznidazole as the only drug used for at least 32 days, consecutively or with short interval

2. Periodic post-therapeutic examinations availability over a period of at least 13 years.

All acute patients were admitted to the Hospital, treated and followed up by the author.

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Table 1
Long term evaluation of specific treatment with benznidazole of 21 patients of acute Chagas disease

No.	Name	Age (years)	Date of treatment	Duration of the disease (days)	Dosage mg/kg/d (x days)	Follow-up (years)	Results	
7	WRJ	18	1974	40	7 x 65	21	C	
8	AAS	18	1974	17	8 x 60			
			1985	10 y	6.6 x 51	21		F
9	MAB	39	1974	30	6.6 x 60	21	C	
13	CMC	16	1974	31	12 x 22			
			1975	10 m	5 x 60	21	C	
15	JBS	0.7	1974	30	30 x 25 c			
			1979	5 y	14 x 40	21	C	
25	RAA	2	1976	20	20 x 19			
			1979	3 y	5 x 60	19		F
26	ARB	14	1976	29	10 x 40	21	C	
27	BFF	38	1976	32	8.2 x 32	20	C	
28	SCPL	13	1977	40	8.3 x 40	19	C	
30	CMD	23	1978	6 m	5 x 23			
			1979	1 y 6 m	7.1 x 40	18	C	
32	NRT	9	1978	29	10 x 26			
			1979	11 m	10-20 x 32	17	C	
33	JP	0.5	1978	37	18-6 x 60			
			1986	8 y	6.3 x 70	19		F
34	MVC	60	1978	58	5.2 x 36	9*	C	
37	WB	27	1979	1 y 3 m	5.5 x 35			
			1980	2 y 4 m	8.6 x 30	16	C	
38	ZKS	35	1979	60	7.5 x 35	13	C	
39	IFR	29	1979	40	5.6 x 39			
			1985	6 y	8 x 33	18		F
40	COC	24	1980	30	8.3 x 40	15	C	
41	EFS	25	1980	32	8 x 33			
			1987	7 y	5.7 x 50	15		F
43	IAS	2	1981	56	20 x 40	14	C	
44	LFTS	13	1982	30	10 x 32			
			1983	1 y 5 m	8 x 35	13	C	
45	CNTN	7	1982	20	8 x 40	13	C	
			Treated:	*21*	*Cured: 16*	*(76%)*	16	5

C, cure; F, failure; y, years; m, months; c, combination. * Died from prostate cancer.

Chronic form. From among the many hundreds patients treated during the chronic phase, 113 were selected (tables 2 and 3), who fulfilled the two following requirements:

1. Benznidazole as the only drug used for at least 40 consecutive days
2. Periodic post-therapeutic examinations availability for 6 to 18 years.

The chronic patients were treated and followed up by the author in the Outpatient Clinic; 56 were male, 57, female; the youngest was 9 years old and the oldest, 69. The details of clinical forms are listed in Table 3.

Informed consent was obtained from adults and from the parents, in case of children.

Therapeutic schedule. A daily dose of benznidazole, varying from 5 to 10 mg/kg/day, was given in equal fractions with intervals of 6, 8 or 12 hours, consecutively or with a short pause. With 73 patients the treatment was repeated, once, sometimes twice or even three times. The duration of the treatment was around 40 days, limited by a total dose of 18 grams approximately, a limit beyond which interruption is mandatory, because of the appearance of sensitive peripheral polyneuritis, a known toxic side effect of this drug[17,18,20].

Adverse reactions. A safe clinical application of benznidazole demands attention to its various adverse reactions, which we have described in detail in previous publication[18]. Here we only mention the difficulties they raise for the treatment.

Table 2
Follow up of 113 patients of chronic Chagas disease treated with benznidazole

Follow up (years)	No. of patients	C	F	D
6	19	1	16	2
7 and 8	22	0	18	4
9 and 10	34	0	33	1
11 and 12	24	3	14	7
13 and 14	10	2	6	2
15 and 16	3	2	0	1
18	1	1	0	0
Total	113	9	87	17

C, cure; F, failure; D, doubtful.

Table 3
Clinical form of 113 patients of chronic Chagas disease treated with benznidazole

Clinical form	No. of patients	C	F	D
Recent	2	2	0	0
Indeterminate	41	1	30	10
Cardiac *				
Class I	32	5	24	3
Class II	21	1	17	3
Class III	4	0	4	0
Digestive	6	0	6	0
Cardio-digestive	7	0	6	1
Total	113	9	87	17

* NYHA functional classification. C, cure; F, failure; D, doubtful

Dermatitis from hypersensitivity. The most common side effect of benznidazole is a dermatitis from hypersensitivity, of the serum sickness type, characterized by cutaneous eruption, generalized edema, fever, lymphnode enlargement and articular and muscular pain. It appears around the fifth to the tenth day of treatment, most often in the ninth day, and is the most relevant adverse reaction to the drug, since it is common, present in around 20 percent of the patients who receive the drug, and very often it hinders the treatment. It is an allergic phenomenon, mediated by IgE, and therefore unpredictable and inevitable. The patients were advised of this possibility.

Polyneuritis. This is a serious toxic effect induced by benznidazole, with close connection with its therapeutic index. All patients are susceptible to it, when the treatment achieves the total dose around 18 grams.

For instance, a dose of 10 mg/kg/day for an adult patient of 60 kg of weight, i.e., a daily dose of 600 mg, cannot go beyond 30 consecutive days, when it reaches 18 grams, because symptoms of peripheral polyneuritis would then arise if not still present. On the other hand, the same dose of 10 mg/kg/day, given to a child of 20 kg of weight, i.e., a daily dose of 200 mg, would take 90 days to cause the same effect. That is why it is said that children tolerate benznidazole better than adults. This also explains some confusion prevailing in the literature, concerning the untoward reactions to the drug.

It is interesting to note that patients perceive the first symptoms of polyneuritis, saying that cutting the nails and washing the hands in cold water become somewhat painful. Different from the dermatitis, this is a toxic phenomenon. However, being dose dependent it is preventable.

Depression of bone marrow. Another significant side effect is depression of bone marrow (neutropenia, agranulocytosis and thrombocytopenic purpura). Fortunately, the latter two hematological diseases are extremely rare, according to our experience[17,18,20]. These untoward reactions are reversible and corrected safely with corticosteroid and antibiotic coverage, if infection is present. Since agranulocytosis can develop rapidly, periodic white-cell counts are of little help. Patients should be advised that in case of sore throat, and fever, which are the first symptoms of agranulocytosis, or petechias, specially hemorrhagic bubles in the oral mucosa, which usually herald the onset of thrombocytopenic purpura, the drug should be immediately stopped and the physician informed, who would institute the adequate therapy.

Lymphoma. We have already circumstancially examined the possible relation between benznidazole and lymphoma, concluding that there was no reason to stop the clinical use of the drug[18]. Clinical experience over the last 30 years in Latin America, where the drug has been extensively used, did not favor the view that benznidazole therapy is a risk factor for lymphoma. In the booklet on the etiologic treatment of Chagas disease, edited by the Brazilian Ministry of Health, with the contribution of several experts in the field[55], the hypothesis of this risk was discarded.

Patient compliance. For the reliable evaluation of the results of ambulatory treatment, it is imperative to check the full compliance of the patient to the physician prescription. Every one of our patients received a printed card where date, dose, time and any abnormal symptom were recorded and weekly controlled.

Duration of the chronic disease. The duration of the chronic disease at the beginning of the treatment was determined. This has been an estimate because the patient usually is unaware of when he was infected, as the acute phase frequently goes unnoticed. The estimates were based on the anamnesis and the time elapsed since the patient had moved away from the endemic area. The minimal duration of the disease could be determined in 88 of the 113 chronic patients. In 45 cases (52%), the duration was more than 20 years when treatment was started.

METHODS

Prior to treatment, the patient was subjected to a complete clinical examination, conventional quantitative serological tests, parasitological examination, i.e. xenodiagnosis (XD) or hemoculture (HC), electrocardiogram and x-rays of the thorax (postero-anterior and in profile with contrasted esophagus).

The conventional quantitative serological tests consisted of complement fixation (CF)[42,58], indirect immunofluorescence (IF)[32,48], indirect hemagglutination (HA)[9], and Enzyme-linked Immunosorbent Assay (ELISA)[77].

Not every patient was tested by all the above mentioned assays. For instance, in the first years of the study, serology consisted of quantitative CF only[58]. From 1972, quantitative IF and HA tests were added. The ELISA test was introduced lately.

Parasitological examination was by standardized XD,[26] until 1983, when it was replaced by HC[37]. The results of these tests were not used as base of the criterion of cure.

In order to study the dynamics of the serological reversion, in case of cure of the disease, 11 cured acute patients and 11 cured chronic patients were selected. The titres of quantitative IF test were chosen to disclose, by the method of Katan Meier Estimates,[47] the fall of the positivity of serology, following the cure. The results were plotted in figures 1 and 2, for acute and chronic disease, respectively.

All laboratory tests were done in research institutions (Instituto de Ciências Biológicas, UFMG, and Centro de Pesquisas René Rachou), in Belo Horizonte, MG, Brasil, using techniques adopted by their investigators. During part of the study serum was collected at the hospital and sent coded to the laboratory for testing.

In general, the drug was bought by the patient, in city drugstores.

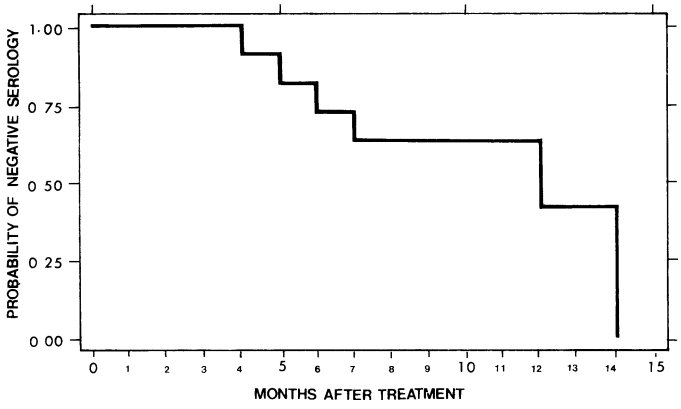

Fig. 1 - Katan Meier estimate[47] of the fall of the serological IF test positivity, in 11 cured patients with acute Chagas disease. The median time of cure (50%) occurs between 11 and 12 months of the follow up. At the end of 14 months all patients showed negative serology

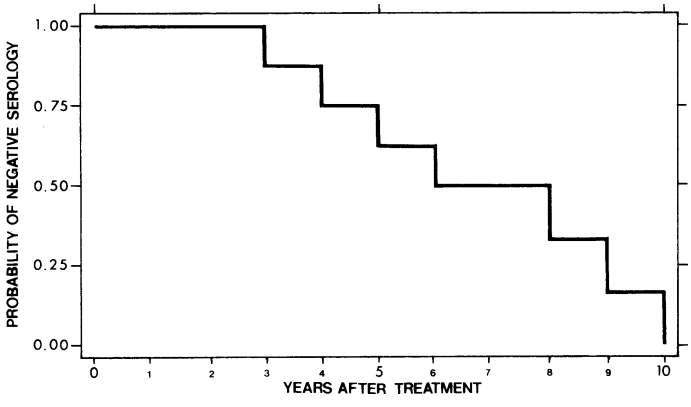

Fig. 2 - Katan Meier estimate[47] of the fall of the serological IF test positivity in 11 cured patients with chronic Chagas disease. The median time of cure (50%) occurs at 6 years of the follow up. At the end of 10 years all patients showed negative serology.

RESULTS

Acute disease. The results of the treatment of the 21 patients in the acute phase of Chagas disease, based in the post-therapeutic quantitative CF, IF, and HA are summarized in Table 1.

Of the 21 treated patients, 16 (76%) consistently presented negative serological tests for the follow up period of at least 13 years (patient no. 34 died from prostate cancer after 9 years of follow up), and were considered cured of the infection. For five patients the serological tests were persistently positive, indicating treatment failure.

Chronic disease. The results of the treatment of the 113 patients with different chronic forms of the disease are summarized in Table 4. For only 9 patients (8%), did post-therapeutic serological tests become completely and consistently negative, indicating cure.

Table 4
Results of treatment with benznidazole of 113 chronic patients after a follow up of six to 18 years

Efficacy	No. of patients - (%)
Cure	9 - 8%
Failure	87 - 77%
Doubtful	17 - 15%

With 17 patients (15%) the serological tests oscillated between negative and positive. So they were considered doubtful cases, because of a possible evolution over the years to persistent negativity.

The remainder 87 patients (77%) had consistently positive post-therapeutic serological tests, and were classified as treatment failure.

The marked difference between results with acute and chronic cases is discussed further on.

Recent disease. During the evaluation of the efficacy of the specific treatment of patients with acute disease (Table 1) we noticed that some patients (no. 13,15,30,32,37) were cured following the second treatment, administered up to 5 years after the acute phase. It was a demonstration that cure was also possible following chronic disease of short duration[17,18,20].

This finding leaded the members of the Symposium on Specific Treatment, in the II Meeting on Applied Research in Chagas Disease, in Araxá, MG, in November 1985, to recommend the treatment in recent chronic infections (in practice, every child with chagasic infection)[66].

Though we cannot infer, from our data, the percentage of cure in recent disease, it is high, close to that observed in acute disease.

Controlled clinical trials in Brazil[2], Argentina[68,69] and Chile[65] confirmed the high percentage of cure in children and adolescents, up to 14 years, a fact already observed by pediatricians.

The Brazilian Ministry of Health recommends the specific treatment in cases of recent infection, including all sero-positive children and adolescents[55].

In congenital disease, which is an acute form of the infection, efficacy is excellent, cure reaching 100 per cent in children younger than 1 year and 97% in those up to 3 years[29,35,36,56].

Recent disease may be assumed as an asymptomatic acute form. During how many years, after the infection, the disease may be judged as early is unknown.

These facts demonstrate that the duration of the infection influences the therapeutic results.

DISCUSSION

Criterion of cure. Parasitological tests (XD and HC) can be discarded as base of the criterion of cure of American trypanosomiasis in the chronic phase of the disease, because they are of low sensitivity and in the long standing disease they may yield negative results, even when repeated many times over a long period[17,18,19]. They cannot be used by themselves, without taking in account the results of serological tests, to indicate parasitological cure, as in chronic disease they may only reflect periods of non-detectable parasitemia[12,17]. As pointed out a long time ago, they are aleatory, casual methods[75].

On the other hand, serological tests, i.e., the detection of specific serum antibodies against components of *Trypanosoma cruzi*, have been accepted as reliable diagnostic standards, since their introduction in 1913, by GUERREIRO & MACHADO[42,50]. Continuous technological development has resulted in the current range of tests: FC, IF, HA and ELISA[25]. These tests use extracts of *T. cruzi* or the whole parasite as antigens. They permit screening of blood donors when satisfactorily standardized[14]. Besides being the most sensitive and specific method for the diagnosis of the disease, they are quick, inexpensive, and easy to execute. They have been widely employed and approved as trustworthy, since the discovery of the disease. In our experience, the sensitivity of CF, IF and HA is 91.5%, 99% and 100%, respectively[19]. Only CF requires a more refined technology and reagents[58], but the other tests in fact suffice for the purpose at hand. Positive results conclusively demonstrate *T. cruzi* infection, i.e., Chagas disease. Therefore, we take them as the base for evaluation of drug efficacy against *T. cruzi* infection in humans.

In the last years there have been intensive researches on more defined and purified antigens for the diagnosis of *T. cruzi* infection[1,62,67,71]. Due to the high complexity of the molecular constitution and antigenic composition of that parasite, it became clear that single antigens lack the required sensitivity when compared with conventional tests[71]. There have been attempts to increase sensitivity by the use of cocktails of recombinant antigens[67]. However, the use of any one of these products is only recommended, if performed in parallel with one of the conventional tests, mainly IF or ELISA. Up to now, tests with crude antigens remain indeed the gold standard for Chagas disease serological diagnosis.

An immunodiagnostic method based on antibody binding to a single epitope may be of limited usefulness, if the target epitope is not present in all natural parasite population[71].

Another base for the criterion of cure would be the detection of serum *T. cruzi* antigen instead of the antibody, a possibility raised today by the development of the polymerase chain reaction (PCR)[10,19].

Results. Concerning the treatment results, we found a high therapeutic efficacy of benznidazole for *acute* human Chagas disease, with the cure of 76 per cent of treated patients. This is in accordance with the experience of other authors. CERISOLA *et al.*[27] reported negative serology in 80 per cent of 76 treated children, one year after treatment. FERREIRA[30] cured seven of ten treated patients and RASSI *et al.*[59] reported 51.6 per cent of cure rate.

The five patients classified as treatment failures in Table 1 had uniformely positive CF, IF and HA throughout the follow up period, even after repetition of therapy. Two of them (no. 8 and 41), developed cardiomyopathy. The titres of the antibodies detected, though variable from time to time, remained similar to those prior to therapy.

The most probable cause of the treatment failure in these five patients is the natural resistance of the strains of *Trypanosoma cruzi*, a previously documented phenomenon[3,11,33].

In *chronic* patients cure rate was only 8% (Table 4). Possibly it may be higher, since some patients of the doubtful group may progress to persistent CS negativity.

Treatment failure in chronic disease was reported by other authors[34,44,54].

We do not have an incisive interpretation for the remarkable difference between cure rate in acute (76%) and chronic (8%) disease.

In our judgment, there must be a connection with the fact that, in long standing chronic Chagas disease, the perpetuation of the infection is due to the infectivity of the amastigote forms[53] in many tissues of the patient, a state in which complete *T. cruzi* erradication becomes more difficult.

Serological reversion. In patients cured during the acute phase of the disease, the median time for the reversion of the serology was between 11 and 12 months after the treatment (Fig. 1), whereas it was of six years in case of chronic disease (Fig. 2).

It should be noted also that all acute patients showed negative serology at the end of 14 months, while only after 10 years all chronic patients displayed negative serology.

In acute Chagas disease similar results have been observed in Argentina, where 80 percent of 232 acute patients, precociously treated with nifurtimox, showed serological reversion at the end of six months[25].

There is not an adequate explanation for such a long follow up of 10 years, in case of the chronic disease, to have a post-therapeutic serological reversion. Repetition of the treatment and immune response may be involved.

Positive CS demonstrates real parasitism. It has been proposed that conventional serology would not be a reliable method on which to base the criterion of cure, because it might not change following the cure of long standing chronic disease. Possible explanations for such a phenomenon include immunological memory[43,63], auto-immunity[45], sequestration of antigens of *T. cruzi* in cells of the spleen[4], presence of determinants of carbohydrates derived from intestinal and lung microflora[39], inespecific reactivity due to the use of crude antigens[1].

However, if any one of these phenomena prevailed, it would occur in only a few patients and the tests would show, all along the years, decreasing or low titres. A comparison in this regard has been invoked with syphilis[63]. In this disease the quantitative VDRL titre should return to normal within 12 months of therapy of primary syphilis or 24 months after therapy of secundary syphilis. Nevertheless, in small percentage of patients with early syphilis, the VDRL will remain reactive in low titre for long periods of time[43]. The situation with long standing Chagas disease is quite distinct. According to our experience, the post-therapy CS tests maintain, throughout the years, titres similar to those seen prior to treatment.

Clinical evidence. As we have pointed out previously[19], there are many clinical evidences that the parasite remains in the patient throughout the entire evolutive process of the disease. For instance, the reactivation of the infection following heart transplantation in cases of terminal chronic chagasic cardiomyopathy[7,24,72], where the immunosuppressive drugs used result in the reappearance of *T. cruzi* in blood and tissues. Patients exhibit a return to the acute phase of the disease, occasionally with myocarditis in the allograft. Similarly, non-chagasic patients submitted to immunosuppressive regimens following organ transplantation (kidney, heart, pancreas, bone marrow) from sero-positive donors acquired the infection from the transplanted organ[22,28,40].

A further demonstration of the presence of the *T. cruzi* in chronic patients is the reactivation of the disease in AIDS sufferers, with accompanying meningoencephalitis, myocarditis and other lesions, as well as high parasite burdens[31,61].

Another proof of the presence of the parasite in long standing Chagas disease patients is the finding, by polymerase chain reaction (PCR), of *T. cruzi* DNA in the peripheral blood of those patients[10], as we have shown[21].

Immunosuppression in chronic Chagas disease patients has revealed reservoirs of amastigotes in quite distinct organs and tissues, including the central nervous system, the heart, the skin and the subcutaneous cellular tissue, the esophagus, the colon, the liver, the bone marrow and the kidney[31]. A well-known reservoir of the parasite is the adipose tissue[5].

The parasite, which had been occult, disseminates when the strong and sustained immune response is suppressed. Therefore, it is reasonable to presume that cure of chronic Chagas disease depends on the concurrence of chemotherapy and immune response.

Human Chagas disease is a life-long infection[50,73]. In 45 of 88 treated chronic patients (52%) we estimated that the duration of the disease was in excess of 20 years. In the chronic disease, XD positivity may persist for life. Positive XD has already been documented, in the absence of reinfection, 35 years after the patients moved to an area where there is no transmission by the vector[64]. It is well known that a large proportion of chronic chagasic patients lives a normal life and are unaware of their long standing infection. In the absence of a specific serological test, they are taken as healthy, as evidenced by many cases of acute disease in nonendemic areas, such as Canada and United States, caused by transfusion of blood from Latin America immigrants who have lived there sometimes for more than 20 years[40,41,46,57].

There are still some obscure and controversial points concerning the life-cycle of *T. cruzi* in vertebrate host. For instance, there is evidence that trypomastigotes are programmed to develop into amastigotes whether or not they enter cells and that the differentiation can occur in the blood of the vertebrate host[6]. The fact that amastigotes circulate in the bloodstream contradicts conventional views regarding them as essentially intracellular. Whether these forms are destined to destruction or play a role in the parasite life cycle is not known[6]. There is also evidence that amastigotes are infective to mice, both *in vitro* and *in vivo*[23,53], having already been suggested that they play an important part in the maintenance of the infection *in vivo*[70]. It is not known the relative importance of the two stages (trypomastigotes and amastigotes) in perpetuating the infection leading to the chronic phase of the disease[53].

Though there is no evidence of resistant or latent forms, the finding, over the last 15 years, that immunosuppression results in the reappearance of the acute disease in long standing chronic patients justifies a revision regarding conventional views on the life cycle of *T. cruzi.*

Phenomena related to immunoprotection, immunopathogenesis and autoimmunity are the object of profuse and fascinating research in experimental models, particularly the mouse. They are also the subject of much controversy. In human disease these aspects are not yet well defined[13,45,52,60].

FINAL REMARKS

In general, clinical application of benznidazole is a safe procedure if the physician is aware of the adverse reactions to the drug. Our conclusion is that it may be used under close supervision, like other drugs with similar side effects, such as metronidazol[51] and the antithyroid propyltiuracil and metimazole[74], that even so are largely applied in clinical practice.

Considering the severity of Chagas disease, until a better drug is available, benznidazole should be used also in the treatment of chronic patients, due to its high efficacy against both the acute and recent disease, its proved activity in at least 8 per cent of chronic cases, its suppressive effect of the parasitemia in chronic patients, its possible favorable effect on the clinical evolution of the disease[76], and the fact that it is today one rational tool available to the physician for specific antichagasic therapy. Besides, its untoward reactions are well known and can be controlled.

RESUMO

Avaliação a longo prazo do tratamento etiológico da doença de Chagas com benznidazol

O objetivo deste artigo é verificar o resultado da terapêutica específica com o benznidazol na doença de Chagas aguda e crônica, após prazo

longo de seguimento dos pacientes, tomando como base do critério de cura a reversão pós-terapêutica definitiva à negatividade das reações sorológicas convencionais quantitativas.

Foram avaliados 21 pacientes agudos e 113 crônicos, em uma ou outra das diferentes formas clínicas, selecionados por terem sido tratados somente com o benznidazol e acompanhados por longo tempo, de 13 a 21 anos os agudos e de seis a 18 anos os crônicos.

Expôs-se o esquema terapêutico, dando ênfase à estreita correlação entre os efeitos colaterais e a dose total de 18 g, aproximadamente, limite obrigatório porque com essa dose surge a polineurite, se já não estiver presente. Foram relacionadas algumas precauções para a segurança do tratamento.

Anotou-se a duração da doença, tanto aguda como crônica, circunstância que influi no resultado do tratamento.

As reações sorológicas usadas foram a de fixação do complemento, a de imunofluorescência indireta, a de hemaglutinação indireta, e, ocasionalmente, a da ELISA.

Verificou-se a cura em 76 por cento dos pacientes agudos e de apenas 8 por cento dos crônicos. Tendo em mente esses resultados, discutiram-se pontos duvidosos da terapêutica etiológica da doença de Chagas, como critério de cura, o papel da imunossupressão para o conhecimento da patogenia da doença e as reações adversas ao medicamento. A hipótese do autor é que na doença crônica de longa duração o *T. cruzi* persiste nos tecidos, após o tratamento, na grande maioria dos doentes tratados, escapando à ação do medicamento e mantendo positivos os testes sorológicos.

Relacionam-se razões que justificam o tratamento na doença crônica.

Com relação ao ciclo vital do *Trypanosoma cruzi* no hospedeiro vertebrado, há ainda pontos obscuros e controvertidos. Embora não haja prova da existência de formas resistentes ou latentes, a descoberta, ao longo dos últimos 15 anos, de que a imunossupressão desencadeia a doença aguda nos pacientes crônicos de longa duração, justifica revisão do assunto.

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