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Does progressive introduction of benznidazole reduce the chance of adverse events in the treatment of Chagas disease?

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Complete List of Authors:	LOSADA GALVAN, IRENE; Hospital Clinic de Barcelona, Tropical Medicine & International Health; Hospital Universitario 12 de Octubre, Internal Medicine; Instituto de Salud Global Barcelona, Tropical Medicine and International Health MADRID PASCUAL, OLAYA; Hospital Universitario 12 de Octubre, Internal Medicine HERRERO-MARTÍNEZ, JUAN MARÍA; Hospital Universitario 12 de Octubre, Internal Medicine Perez-Ayala, Ana; Hospital Universitario 12 de Octubre, Microbiology LIZASOAIN HERNANDEZ, MANUEL; Hospital Universitario 12 de Octubre, Internal Medicine
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Irene Losada Galván* (1,3), Olaya Madrid Pascual (1), Juan María Herrero Martínez (1), Ana Pérez-Ayala (2), Manuel Lizasoain Hernández (1)

(1) Internal Medicine, Hospital Universitario 12 de Octubre, Madrid; (2) Microbiology, Hospital Universitario 12 de Octubre, Madrid; (3) Tropical Medicine and International Health, ISGlobal, Hospital Clínic - Universitat de Barcelona, Barcelona, Spain.

The toxicity of antiparasitic treatment for Chagas disease continues to be a limiting factor. In this work, we explored the use of staggered doses vs complete doses in benznidazole treatment and its effect on the number and severity of adverse effects as well as treatment discontinuations. To our knowledge, this is the first time these two strategies have been compared.

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Tables 1 and 2

Figure 1

* *Carrer Roselló, 132 2-2; 08036, Barcelona. Telf: 932 271 806. e-mail: irenelosada@gmail.com*

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Irene Losada Galván (1,3,4), Olaya Madrid Pascual (1), Juan María Herrero Martínez (1), Ana Pérez-Ayala (2), Manuel Lizasoain Hernández (1)

(1) Internal Medicine, Hospital Universitario 12 de Octubre, Madrid; (2) Microbiology, Hospital Universitario 12 de Octubre, Madrid; (3) Tropical Medicine and International Health, Hospital Clinic, Barcelona. (4) ISGlobal, Barcelona.

Abstract

In this retrospective cohort study we aimed to assess whether introducing benznidazole at escalating doses reduces the probability of adverse events or treatment discontinuation compared to a full dose scheme. We collected data from patients who had chronic *T.cruzi* infection and underwent treatment from July 2008 to January 2017 in a referral centre in Madrid. Dose was adjusted to body weight (5mg/kg/day), with treatment introduction with full dose or escalating dose according to local consensus and protocols.

Among the 62 patients treated, benznidazole was introduced at full dose in 28 patients and on escalating dose in the remaining 34. We found no statistical differences in the number of adverse events, treatment discontinuations, days of treatment or socio-demographic profiles. There is insufficient evidence to support escalating dose as a strategy for reducing adverse effects of benznidazole. Further research is needed in order to evaluate this strategy.

Introduction

Chagas disease is a zoonosis caused by the parasite *Trypanosoma cruzi*. The World Health Organization (WHO) estimates that there are 6-7 million people infected worldwide.[1] Most cases are in endemic regions of Latin America but an increasing number of cases are being diagnosed in other countries (mainly the United States and southern Europe) due to migration.[2-4] In endemic areas, the primary vector for transmission is the triatomine bug, whose presence in households has been related to substandard building construction. Other means of transmission in endemic and non-endemic countries are vertical (mother to child) and parenteral transmission through blood transfusion and organ transplantation. After a typically self-limited acute phase with unspecific symptoms (therefore difficult to diagnose), the disease enters a chronic phase in which organ complications (mostly cardiac and digestive) occur in approximately one-third of patients.[5]

The therapeutic options available for antiparasitic treatment of Chagas disease have remained unchanged for around 50 years. The only two available treatments are nifurtimox and benznidazole, which were introduced in 1965 and 1971 respectively.[6]

The efficacy of these treatments is highly variable, since it is affected by the drug dose, disease stage, and the age and area of origin of the patient, among other factors. Cure rates between 60% and 100% are reported when treatment with benznidazole is provided in the acute phase and in younger patients.[7-9] The antiparasitic effect of the treatment in the chronic phase is well documented.[10-14] However, clinical effectiveness (defined as reduction in clinical events) is still the subject of intense scientific debate.[15] Treatment with antitrypanosomal drugs is currently indicated in acute infection, congenital infection, reactivations and chronic infection in children under 18 years of age. Although in recent

years there seems to be some consensus regarding the absence of benefit of antiparasitic treatment in patients with advanced forms of cardiac or digestive involvement, most national and regional guidelines recommend offering treatment in the indeterminate chronic phase,[16,17] as well as in patients with mild to moderate determinate disease.

The biggest challenge associated with the available antitrypanosomal drugs is their safety profile. From 48% to 86% of patients experience adverse effects of benznidazole, with the result that treatment discontinuation occurs in 9% to 31% of cases.[18-21] This further limits global treatment coverage, which is already low given that only 4% to 6% of migrants with Chagas disease are aware of their condition[4] and that treatment reaches less than 1% of patients with Chagas disease.[22-25] The most frequently observed adverse events are dermatological, gastro-intestinal and neurological, usually mild and with acceptable response to symptomatic treatment or to benznidazole discontinuation.[18-21] Serious adverse events such as DRESS syndrome are rare, and life-threatening conditions such as severe neutropenia are extremely uncommon.[18-21,26]

Alongside the search for new and better tolerated drugs,[14,27-29] efforts are being made to increase the tolerability of existing antitrypanocidal drugs.[30] Studies aimed at identifying risk factors for adverse responses to benznidazole have found associations with female sex,[21] graduation from elementary school, and white and mulatto race.[31] Additionally, carrying HLA-B*3505 allele could be associated with moderate to severe cutaneous reaction.[32] Another study found that adverse events, female sex, drug dose and eosinophilia were the main predictors of treatment interruption.[33] A study attempting to find a measurable proxy for toxicity failed to correlate adverse events with serum concentrations of benznidazole.[34] Some researchers have proposed the use of corticosteroid therapy along with benznidazole[35] to prevent cutaneous reactions. However, this strategy failed to show a

clear advantage and raised concerns because of the high rate of *Strongyloides stercoralis* coinfection in patients with Chagas disease[36] and risk of hyperinfection syndrome. A clinical trial evaluating shorter regimes and lower dosing of benznidazole is expected to soon provide some insight on the feasibility of this strategy.[37] Moreover, some researchers have proposed the use of escalating doses of benznidazole during the first days of treatment in order to increase its tolerability.[38] However, this strategy has not been compared to standard treatment with full (adjusted to weight) doses from the beginning of treatment.

In this study we aim to ascertain whether introducing benznidazole at progressively higher dose until the target daily dose is reached reduces the probability of adverse events or treatment discontinuation.

Methods

In this retrospective cohort study we reviewed clinical records of patients referred to the Infectious Diseases department in Hospital 12 de Octubre (Madrid, Spain) from July 2008 to January 2017. Inclusion criteria were chronic infection with *T.cruzi* as defined by WHO criteria (two positive serological tests)[39], age 18 years or older and previous treatment with benznidazole in our center. (Those who were receiving it at the time of data collection were excluded.)

The usual evaluation of these patients includes a questionnaire about their country of origin and risk factors for Chagas disease. The patient's medical history is obtained and a physical examination aimed at detecting cardiac or digestive involvement is performed. Electrocardiogram and echocardiogram are routinely performed to rule out cardiac

involvement. Tests to rule out digestive tract involvement are carried out according to symptoms.

In the evaluated time frame, some patients began treatment with benznidazole at full doses and others at progressive doses according to local protocols or consensus when the former were lacking. Changes in schemes of benznidazole treatment took place over time, both before and after the first protocol was launched in 2011. Thus, we divided the patients into two groups, according to the method of introduction of benznidazole treatment. In all cases, the standard dose of 5 mg per kilogram of body weight was calculated, and then the treatment was started according to the physicians' criteria. The maximum daily dose was 300mg in the majority of patients, although some received 250mg and others 400mg. In the full-dose group, the previously calculated dose was divided into two daily doses for 60 days. In the progressive dose group, treatment was started with 50mg per day (half a tablet), then increased by 50mg every day until the correct dosage according to weight was reached.

Statistical analysis: categorical variables were described by frequencies and percentages. Quantitative variables were described as means and standard deviations or medians and interquartile ranges. A chi-square test or Fisher's exact test was used to compare qualitative variables. Student's *t* test was used to compare normally distributed continuous variables, and Mann-Whitney U test was used to compare non-normally distributed variables with qualitative variables. Statistical significance was set at $P< 0.05$. Data analysis was performed using Stata15 (Stata Corp., College Station, TX).

This work was submitted and approved under number 17/051 by the Research Ethics Committee of Hospital 12 de Octubre, Madrid, Spain.

Results

In this study a total of 62 patients were treated with benznidazole adjusted to body weight either on a full dose from the start or with an escalating dose regime. As shown in Table 1, the two groups did not differ in baseline characteristics, comorbidities or clinical stage of Chagas disease. A large majority of patients were from Bolivia (97%). One patient in the full-dose group was from Honduras, and one patient who received escalating dose treatment was from Brazil.

The median maximum daily dose was approximately 300mg, without differences between groups.

There were no significant differences between groups regarding the occurrence of adverse events (Table 2). At least one adverse event was observed in 88.7% of patients, with no differences between groups. The most frequent disturbances were cutaneous (61.3%). The second most frequent adverse reactions were neuromuscular (50%) which included headache, vertigo, insomnia, polyneuropathy, paresthesia, arthralgia and myalgia. Other disturbances (hematologic, liver, digestive and renal) occurred in smaller percentages of patients on both groups.

Treatment interruption due to adverse events occurred in 33.9% of all patients. Mean number of treatment days was 50.5 (sd 18.9), with no differences between groups (Figure 1). Adverse events leading to early interruption (when established at 50% or 80% of total dose), occurred in 3 to 5 of 25 patients on the full dose group, and in 7 to 11 of 29 patients of the escalating dose group. That is to say that 18.5 to 29.6% of adverse events (depending on the 'early interruption' threshold used) led to early interruption of treatment that would need further antiparasitic treatment. Patients were referred to a specialist because of an

adverse event in 43.5% of cases, with dermatology (85%), neurology (11%) and allergy (4%) being the most frequent. Specific treatment for an adverse event was prescribed in 42% of patients, with oral corticosteroids (50%) and antihistaminics (30.8%) as the most frequent prescriptions.

Discussion

To our knowledge, this is the first study to compare how the strategy of progressively introducing benznidazole compares to initiating treatment at a full dose. We could not find any significant differences in the rate of adverse effects, treatment discontinuations or number of treatment days completed, although the results showed numerically fewer hematologic, liver, and digestive disturbances in the escalating dose group. Although adverse events were not systematically rated for severity, it is possible to ascertain through indirect data such as need for specific treatment and need for treatment discontinuation that they were mostly mild. We found an unusually high referral rate to a specialist for adverse events (43.55%), which is not related to severity but to a local agreement of multidisciplinary evaluation of all benznidazole adverse events.

The global adverse event rate for benznidazole is in agreement with previous work, although we found a slightly higher rate of discontinuation than previous studies.[18-21] With such a high rate of adverse events, an intervention such as the progressive introduction of the same drug is unlikely to yield mayor advantages. Hence, a larger sample size would be needed to detect whether these two treatment strategies yield different outcomes.

There is currently no consensus regarding the ideal treatment schedule with benznidazole in terms of length, especially after it has been necessary to discontinue treatment. Some groups consider it sufficient to have received 30 days and others 80% of the dose calculated

for 60 days[10,40]. In our study, the median duration of treatment in both groups exceeds even the most ambitious threshold of 48 days (80%). This means that although suspension is necessary in a high percentage of patients, treatment with a second drug would not be indicated in most of them due to having met the minimum dose requirement. As shown in Figure 1, most treatment discontinuations occurred after previously mentioned thresholds of 30 and 48 days. This is because clinicians would be more prone to discontinue treatment when a mild adverse event occurs after a sufficient duration of antiparasitic treatment has been reached, taking into account the risk/benefit balance.

The retrospective nature of this study and the fact that these two different strategies were put in place by different physicians may have introduced some measurement bias. Given that the patients were assigned to each doctor according to availability (without choice by the doctor or the patient), and treatments assigned according to local protocols (or consensus) at each point in time, we think that this would not constitute a source of selection bias. Nonetheless, data were collected using electronic medical records by different physicians than the ones who treated the patients, in order to increase objectivity.

Each time a benznidazole treatment is started, it constitutes both an opportunity and a challenge. Any doctor faced with this situation longs for alternatives that improve the safety of antiparasitic treatment, either with new drugs, dosing changes in existing drugs, or the use of adjuvant drugs. With currently available data, it cannot be asserted that a strategy of progressive doses is better than the use of full doses from the beginning. However, prospective randomized studies are needed to improve knowledge about this issue, given the possibility that different benznidazole treatment introduction strategies might improve tolerability and therefore might improve patient health outcomes.

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Transparency

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Irene Losada Galván*

International Health Department

ISGlobal, Hospital Clínic - Universitat de Barcelona, Barcelona, Spain.

Carrer Roselló, 132 2-2; 08036, Barcelona

Telf: 932 271 806

e-mail: irenelosada@gmail.com

Olaya Madrid Pascual

Internal Medicine Department

Hospital Universitario 12 de Octubre

Avda de Córdoba s/n; 28016, Madrid

Telf: 91-3908247

e-mail: olayamadrid@gmail.com

Juan María Herrero-Martínez

Internal Medicine Department

Hospital Universitario 12 de Octubre

Avda de Córdoba s/n; 28016, Madrid

Telf: 91-3908247

e-mail: juanmariaherrero@yahoo.es

Ana Pérez-Ayala

Microbiology Department

Hospital Universitario 12 de Octubre

Avda de Córdoba s/n; 28016, Madrid

Telf: 91-3908247

e-mail: anpayala@hotmail.com

Manuel Lizasoain Hernández

Internal Medicine Department

Hospital Universitario 12 de Octubre

Avda de Córdoba s/n; 28016, Madrid

Telf: 91-3908247

e-mail: manuel.lizasoain@salud.madrid.org

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256 Table 1. Baseline characteristics

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CHARACTERISTICS	**FULL DOSE (N=28)**	**ESCALATING DOSE (N= 34)**	**p**
Age - mean years (sd)	40.7 (8.9)	39.7 (8.2)	0.68
Male sex - no. (%)	7 (25%)	12 (35.3%)	0.38
Habits			
Smoker- no. (%)	3/18 (16.7%)	6/22 (27.3%)	0.42
Alcohol consumption - no. (%)	2/19 (10.5%)	6/22 (27.3)	0.18
Comorbidities			
Hypertension - no. (%)	1 (3.6%)	1 (2.9%)	0.89
Diabetes - no. (%)	1 (3.6%)	0 (0%)	0.27
Obesity - no. (%)	3/26 (11.5%)	2/33 (6.1%)	0.45
Cerebrovascular disease - no. (%)	1 (3.6%)	1 (2.9%)	0.89
Liver disease - no. (%)	0	1 (2.9%)	0.36
Renal disease, coronary heart disease, HIV, transplantation	0	0	
CLINICAL STAGE			
Indeterminate form	22 (78.6%)	25 (73.5%)	0.64
Cardiac form - no. (%)	6 (21.4%)	9 (26.4%)	0.64
Gastrointestinal form -no. (%)	0	0	
no: number, sd: standard deviation			
Data are No./number tested (%) of patients, unless otherwise indicated.			

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263 Table 2. Adverse events

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ADVERSE EVENTS	**FULL DOSE (N=28)**	**ESCALATING DOSE (N= 34)**	**p value**
At least one adverse event - no. (%)	25 (89.29)	29 (85.29)	0.64
Skin disturbances - no. (%)	17 (60.71)	21 (61.76)	0.93
Neuromuscular side effects - no. (%)	15 (53.57)	16 (47.06)	0.61
Hematologic toxicity - no. (%)	7 (25)	5 (14.71)	0.24
Liver toxicity - no. (%)	7 (25)	5 (14.71)	0.24
Digestive disturbances - no. (%)	7 (25)	3 (8.82)	0.08
Kidney injury - no. (%)	0	1 (2.94)	1
MANAGEMENT			
Need of specific treatment - no. (%)	12 (42.86)	14 (41.18)	0.89
Referral to a specialist - no. (%)	12 (42.86)	15 (44.12)	0.92
Hospital admission - no. (%)	1 (3.57)	2 (5.88)	0.67
Treatment interruption - no. (%)	7 (25)	14 (41.18)	0.18
Treatment duration, days (sd)	51.75 (15.4)	49.4 (21.5)	0.26
Completed at least 80% of total dose - no. (%)	21 (75)	23 (67.65)	0.53
Completed at least 30 days- no. (%)	25 (89.29)	27 (79.41)	0.29
Maximum dose per day, median grams (sd)	316.1 (38.7)	304.5 (26.1)	0.14
no: number, sd: standard deviation			

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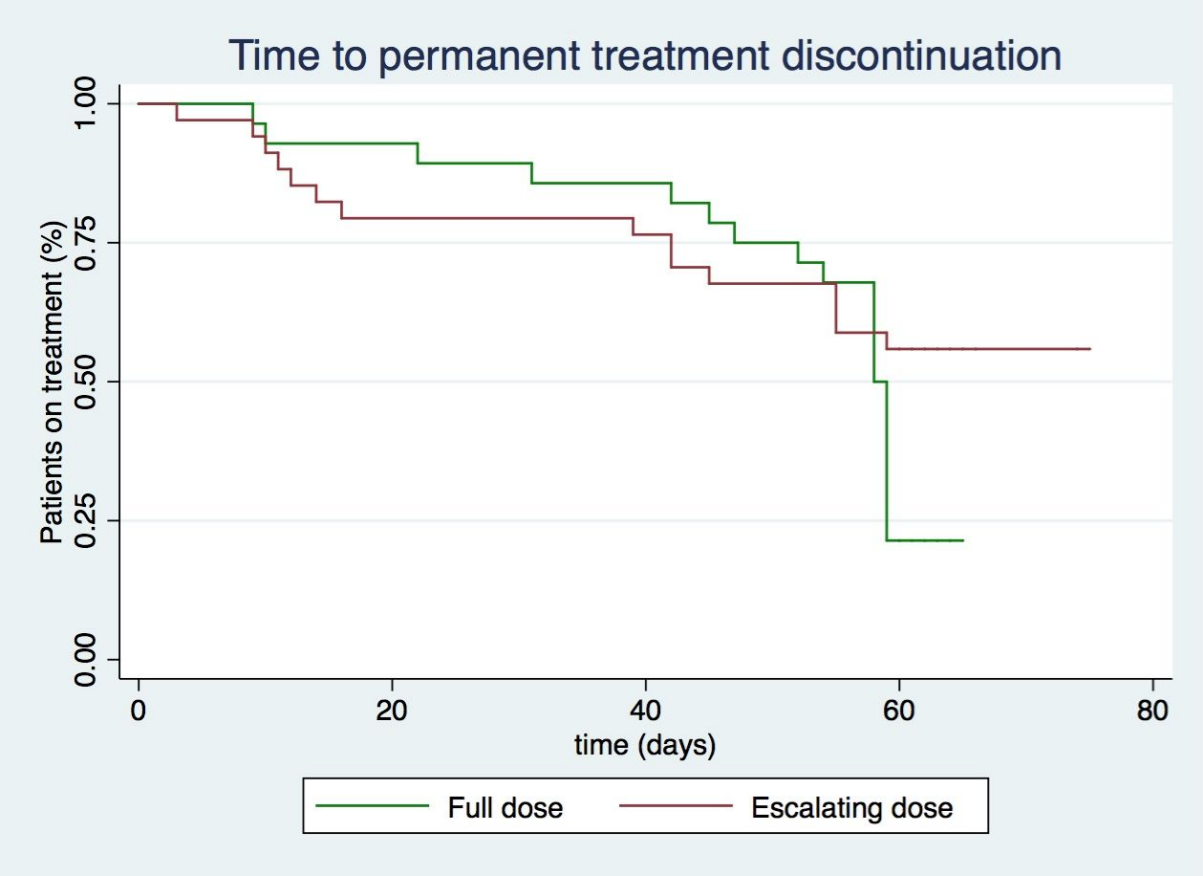
Figure 1. Time to permanent treatment discontinuation



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Title: Does progressive introduction of benznidazole reduce the chance of adverse events in the treatment of Chagas disease?

Irene Losada Galván* (1,3~~,4~~), Olaya Madrid Pascual (1), Juan María Herrero Martínez (1), Ana Pérez-Ayala (2), Manuel Lizasoain Hernández (1)

(1) Internal Medicine, Hospital Universitario 12 de Octubre, Madrid; (2) Microbiology, Hospital Universitario 12 de Octubre, Madrid; (3) Tropical Medicine and International Health, ISGlobal, Hospital Clínic - Universitat de Barcelona, Barcelona, Spain~~Hospital Clinic, Barcelona. (4) ISGlobal, Barcelona~~.

The toxicity of antiparasitic treatment for Chagas disease continues to be a limiting factor. In this work, we explored the use of staggered doses vs complete doses in benznidazole treatment and its effect on the number and severity of adverse effects as well as treatment discontinuations. To our knowledge, this is the first time these two strategies have been compared.

This material is original, has not already been published, and has not and will not be submitted for publication elsewhere as long as it is under consideration by the AJTMH.

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Tables 1 and 2

Figure 1

* *Carrer Roselló, 132 2-2; 08036, Barcelona. Telf: 932 271 806. e-mail: irenelosada@gmail.com*

Does progressive introduction of benznidazole reduce the chance of adverse events in the treatment of Chagas disease?

Irene Losada Galván (1,3,4), Olaya Madrid Pascual (1), Juan María Herrero Martínez (1), Ana Pérez-Ayala (2), Manuel Lizasoain Hernández (1)

(1) Internal Medicine, Hospital Universitario 12 de Octubre, Madrid; (2) Microbiology, Hospital Universitario 12 de Octubre, Madrid; (3) Tropical Medicine and International Health, Hospital Clinic, Barcelona. (4) ISGlobal, Barcelona.

Abstract

In this retrospective cohort study we aimed ~~at assessing~~to assess whether introducing benznidazole at escalating doses reduces the probability of adverse events or treatment discontinuation compared to a full dose scheme. We collected data ~~of~~ from patients ~~with~~ who had chronic *T.cruzi* infection ~~with~~ and underwent treatment ~~*T.cruzi* treated with~~ ~~benznidazole~~ from July 2008 to January 2017 in a referral centre in Madrid. Dose ~~were~~ was adjusted to body weight (5mg/kg/day), with treatment introduction with full dose or escalating dose according to local consensus and protocols.

~~Of~~ Among the 62 patients treated ~~in this period~~, benznidazole was introduced at full dose in 28 patients and on escalating dose in the remaining 34. We found no statistical differences in the number of adverse events, treatment discontinuations, days of treatment or socio-demographic profiles. There is ~~not enough~~insufficient evidence ~~supporting~~ to support escalating dose as a strategy ~~to reduce~~ for reducing adverse ~~events~~ effects of benznidazole. Further research is needed in order to evaluate this strategy.

Introduction

Chagas' disease (CD) is a zoonosis caused by the parasite *Trypanosoma cruzi*. WHO (The World Health Organization (WHO)) estimates that there are 6-7 million people infected worldwide.[1] Most cases are in endemic regions of Latin America but an increasing number of cases are being diagnosed in other countries (mainly USA the United States and southern Europe) due to migratory flowsmigration.[2-4] In endemic areas, the primary vector for transmission occurs primarily throughis the triatomine bug vector, whose presence in the households has been related to substandard building constructionpoor housing. Other means of transmission present in endemic and non-endemic countries are vertical (mother to child) and parenteral transmission through blood transfusions and organ transplantation. After a usually typically self-limited acute phase with unspecific symptoms (therefore difficult to suspect and diagnose), the disease evolves tonters a chronic phase that can lead toin which organ complications (mostly cardiac and digestive) on occur in approximately one-third of the patients.[5]

The therapeutic options available for antiparasitic treatment of Chagas disease have remained unchanged for around 50 years. The only two available therapeutic alternatives reatments are nifurtimox and benznidazole, which were released introduced in 1965 and 1971 respectively.[6]

The reported efficacy of these treatments is very highly variable, since it is affected by the drug dose, the stage of the diseasedisease stage, and the age and area of origin of the patient, among other factorss. Cure rates between 60% and 100% are reported when treatment with benznidazole is provided in the acute phase and in younger patients.[7-9] The antiparasitic effect of the treatment in the chronic phase is well documented.[10-14]

However, clinical effectiveness (defined as reduction in clinical events) is still the subject of intense scientific debate.[15] Treatment with antitrypanosomal drugs is currently indicated in acute infection, congenital infections, reactivationss and chronic infection in children under 18 years of age. Although in recent years there seems to be some consensus in regarding the absence of benefit of antiparasitic treatment in patients with advanced forms of cardiac or digestive involvement, most national and regional guidelines recommend offering treatment in the indeterminate chronic phase,[16,17] and as well as in patients with mild to moderate determinate disease.

The biggest challenge associated with the available antitrypanosomal drugs is their safety profile. A rate of adverse effects of benznidazole ranging fFrom 48% to 86% of patients experience adverse effects of benznidazole, with the result that leads to treatment discontinuation occurss in 9% to 31% of cases.[18-21] This further jeopardizes limits the already slim global antiparasitic treatment coverage of patients with CD,, which is already low given that only 4% to 6% of migrants with ChagasD disease are aware of their condition[4] and the that CD treatment coverage rate reaches less than 1% of patients with Chagas diseaseD.[22-25] The most frequently observed adverse events are dermatological, gastro-intestinal and neurological, usually mild and with acceptable response to symptomatic treatment or to benznidazole discontinuation.[18-21] Serious adverse events such as DRESS syndrome are rare, and life-threatening conditions such as severe neutropenia are extremely uncommon.[18-21,26]

Along withside the search for new and better tolerated drugs,[14,27-29] efforts are been being made in order to increase the tolerability of existing antitrypanocidal drugs.[30] Some sStudies aimed at finding identifying risk factors for adverse responses to benznidazole found an association of adverse eventshave found associations with female sex,[21] graduation from

elementary school, and white and mulatto race.[31] Additionally, carrying HLA-B*3505 allele could be associated with moderate to severe cutaneous reaction.[32] Another study found that adverse events, female sex, drug dose and eosinophilia where the main predictors for of treatment interruption.[33] Likewise, an attemptA study attempting to find a measurable proxy for toxicity failed to correlate adverse events with serum concentrations of benznidazole.[34] Some groups researchers have proposed the use of corticosteroid therapy along with benznidazole[35] to prevent cutaneous reactions. However, this strategy failed to show a clear advantage and raised some concerns because of the high rate of *Strongyloides stercoralis* coinfection in patients with CD[36] Chagas disease[36] and risk of hyperinfection syndrome. A clinical trial where evaluating shorter regimes and lower dosing of benznidazole are been evaluated willis expected to soon provide some insight on the feasibility of this strategy.[37] Moreover, some groups researchers have proposed the use of escalating doses of benznidazole during the first days of treatment in order to increase its tolerability.[38] However, this strategy has not been compared to standard treatment with full (adjusted to weight) doses from the beginning of treatment.

In this study we aim to ascertain whether introducing benznidazole at progressively higher dose until the target daily dose is reached reduces the probability of adverse events or treatment discontinuation.

Methods

In this retrospective cohort study we reviewed clinical records of patients referred to the Infectious Diseases department who fulfilled WHO criteria of *T.cruzi* infection (two positive serological tests)[39] in Hospital 12 de Octubre (Madrid, Spain) from July 2008 to January

2017. Inclusion criteria were: chronic infection by with *T.cruzi* as defined by WHO criteria (two positive serological tests)[39], age over 18 years or older and having receivedprevious treatment with benznidazole in our center. (excluding tThose who were receiving it at the time of data collection were excluded.).

The usual evaluation of these patients includes a questionnaire about their country of origin and risk factors for Chagas disease. The patient's medical history is obtained Anamnesis and a physical examination aimed at detecting cardiac or digestive involvement are is performed. Electrocardiogram and echocardiogram are routinely performed to rule out cardiac involvement. Tests to rule out digestive tract involvement are carried out according to symptoms.

In the evaluated time frame, some of the patients began treatment with benznidazole at full doses and others at progressive doses according to local protocols or consensus when the former were lacking. Changes in schemes of benznidazole treatment took place over time, both before and after the first protocol was launched in 2011. Thus, we divided the patients into two groups, according to the method of introduction of benznidazole treatment. In all cases, the standard dose of 5 mg per kilogram of body weight was calculated, and then the treatment was started according to the physicians' criteria. The maximum daily dose was 300mg in the majority of patients, although some received 250mg and others 400mg. In the full--dose group, the previously calculated dose was divided into two daily doses for 60 days. In the progressive dose group, treatment was started with 50mg per day (half a tablet), then increased by 50mg every day until the correct dosage according to weight was reached.

Statistical analysis: categorical variables were described by frequencies and percentages. Quantitative variables were described as means and standard deviations or medians and

interquartile ranges. A chi-square test or ~~a~~ Fisher's exact test ~~were~~ was used to compare qualitative variables. S~~A s~~tudent's *t* test was used ~~when comparing~~to compare normally distributed continuous variables, and Mann-Whitney U test ~~to compare~~was used to compare non-normally distributed variables with qualitative variables. Statistical significance was set at P< 0.05. Data analysis was performed using Stata15 (Stata Corp., College Station, TX).

This work was submitted and approved under number 17/051 by the Research Ethics Committee of Hospital 12 de Octubre, Madrid, Spain.

Results

In this study a total of 62 patients were treated with benznidazole adjusted to body weight either on a full dose from the start or with an escalating dose regime. As shown in Table 1, ~~both~~ the two groups did not differ in baseline characteristics, comorbidities or ~~CD~~ clinical stage of Chagas disease. A large majority of patients were from Bolivia (97%)~~, one~~. One patient in the full-dose group was from Honduras ~~and was allocated in the full dose group,~~ and one ~~and the remaining~~ patient ~~was from Brazil and~~who received escalating dose treatment was from Brazil.

The median maximum daily dose was ~~around~~ approximately 300mg, without differences between groups.

There were no significant differences between groups regarding the occurrence of adverse events (Table 2). At least one adverse event was observed in 88.7% of ~~the~~ patients, with no differences between groups. The most frequent disturbances were cutaneous (61.3%). The second most frequent adverse reactions were neuromuscular (50%) which included

headache, vertigo, insomnia, polyneuropathy, paresthesia, arthralgia and myalgia. ~~The~~ ~~rest~~Other ~~of the~~ disturbances (hematologic, liver, digestive and renal) occurred in ~~a~~ ~~similar~~smaller percentages of patients~~, maintaining the absence of differences between~~ on both groups.

Treatment interruption due to adverse events occurred in 33.9% of all patients ~~and m~~. Mean number of treatment days was 50.5 (sd 18.9), with no differences between groups (Figure 1). Adverse events leading to early interruption (when established at 50% or~~/~~ 80% of total dose), ~~where~~ occurred in 3 to ~~/~~5 of 25 patients on the full dose group, and in 7 to ~~/~~11 of 29 patients of the escalating dose group.~~;~~ T~~t~~hat is to say that 18.5 to ~~/~~29.6% of adverse events (depending on the 'early interruption' threshold used) ~~of adverse events~~ led to early interruption of treatment that would need further antiparasitic treatment. Patients were referred to a specialist because of an adverse event in 43.5% of ~~the~~ cases, with ~~Dermatology~~ dermatology (85%), ~~Neurology~~ neurology (11%) and ~~Allergy~~ allergy (4%) being the most frequent. Specific treatment for an adverse event was prescribed in 42% of ~~subjects~~patients, with oral corticosteroids (50%) and antihistaminics (30.8%) as the most frequent prescriptions.

Discussion

To our knowledge, this is the first ~~comparative~~ study ~~between strategies~~to compare how the strategy of ~~progressive introduction of~~progressively introducing benznidazole ~~and~~ compares to initiating treatment at a full dose~~full doses~~. We could not find any significant differences in the rate of adverse effects, treatment discontinuations or number of treatment days completed, although the results showed numerically fewer hematologic, liver, and digestive disturbances in the escalating dose group. Although adverse events were

not systematically rated for severity, it is possible to ascertain through indirect data such as need for specific treatment and need for treatment discontinuation that they were mostly mild. We found an unusually high referral rate to a specialist for adverse events (43.55%), which is not related to severity but to a local agreement of multidisciplinary evaluation of all benznidazole adverse events.

The global adverse event rate ~~to~~ for benznidazole is in agreement with previous work, although we found a slightly higher rate of discontinuation than previous studies.[18-21] With such a high rate of adverse events, an intervention such as the~~like a~~ progressive introduction of the same drug is unlikely to yield mayor advantages. Hence, a ~~bigger~~ larger sample size would be needed to ~~observe a difference between these two strategies, if any~~detect whether these two treatment strategies yield different outcomes.

There is currently no consensus regarding the ideal treatment schedule with benznidazole in terms of length, especially ~~when~~ after it has been necessary to discontinue treatment. Some groups consider it sufficient to have received 30 days and others 80% of the dose calculated for 60 days[10,40]. In our study, the median duration of treatment in both groups exceeds even the most ambitious threshold of 48 days (80%). This means that~~,~~ although suspension is necessary in a high percentage of patients~~,~~; treatment with a second drug would not be indicated in most of them due to having met the minimum dose requirement. As shown in F~~f~~igure 1, most treatment discontinuations occurred after previously mentioned thresholds of 30 and 48 days. This is because clinicians would be more prone to discontinue treatment when a mild adverse event occurs after a sufficient ~~length~~ duration of antiparasitic treatment has been reached, taking into account the risk/benefit balance.

The retrospective nature of this study and the fact that these two different strategies were put in place by different physicians may have introduced some ~~measuring~~ measurement

bias. Given that the patients were assigned to each doctor according to availability (without choice by the doctor or the patient), and treatments assigned according to local protocols (or consensus) at each point in time, we think that this would not constitute a source of selection bias. Nonetheless, data were collected using electronic medical records by different physicians than the ones who treated the patients, in order to ~~improve~~ increase objectivity.

Each time a benznidazole treatment is started, it constitutes both an opportunity and a challenge. Any doctor faced with this situation longs for~~to find~~ alternatives that improve the safety of antiparasitic treatment, either with new drugs, ~~changing the posology of existing ones~~dosing changes in existing drugs, or ~~through~~ the use of adjuvant drugs. ~~In spite of that,~~ W~~w~~ith currently available data, it cannot be asserted that a strategy of progressive doses is better than the use of full doses from the beginning. However, prospective randomized studies are needed to improve ~~the~~ knowledge ~~on this field~~about this issue, given the possibility that different ~~strategies of~~ benznidazole treatment introduction strategies might improve tolerability and therefore might improve patient health outcomes.~~.~~

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Transparency

None of the authors declares having conflicts of interest.

Irene Losada Galván*

International Health Department

ISGlobal, Hospital Clínic - Universitat de Barcelona, Barcelona, Spain

~~*Hospital Clínic Barcelona, ISGlobal.*~~

Carrer Roselló, 132 2-2; 08036, Barcelona

Telf: 932 271 806

e-mail: irenelosada@gmail.com

Olaya Madrid Pascual

Internal Medicine Department

Hospital Universitario 12 de Octubre

Avda de Córdoba s/n; 28016, Madrid

Telf: 91-3908247

e-mail: olayamadrid@gmail.com

Juan María Herrero-Martínez

Internal Medicine Department

Hospital Universitario 12 de Octubre

Avda de Córdoba s/n; 28016, Madrid

Telf: 91-3908247

e-mail: juanmariaherrero@yahoo.es

Ana Pérez-Ayala

Microbiology Department

Hospital Universitario 12 de Octubre

Avda de Córdoba s/n; 28016, Madrid

Telf: 91-3908247

e-mail: anpayala@hotmail.com

Manuel Lizasoain Hernández

Internal Medicine Department

Hospital Universitario 12 de Octubre

Avda de Córdoba s/n; 28016, Madrid

Telf: 91-3908247

e-mail: manuel.lizasoain@salud.madrid.org

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276 Table 1. Baseline characteristics

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CHARACTERISTICS	FULL DOSE (N=28)	ESCALATING DOSE (N= 34)	p
Age - mean years (sd)	40.7 (8.9)	39.7 (8.2)	0.68
Male sex - no. (%)	7 (25%)	12 (35.3%)	0.38
Habits			
Smoker- no. (%)	3/18 (16.7%)	6/22 (27.3%)	0.42
Alcohol consumption - no. (%)	2/19 (10.5%)	6/22 (27.3)	0.18
Comorbidities			
Hypertension - no. (%)	1 (3.6%)	1 (2.9%)	0.89
Diabetes - no. (%)	1 (3.6%)	0 (0%)	0.27
Obesity - no. (%)	3/26 (11.5%)	2/33 (6.1%)	0.45
Cerebrovascular disease - no. (%)	1 (3.6%)	1 (2.9%)	0.89
Liver disease - no. (%)	0	1 (2.9%)	0.36
Renal disease, coronary heart disease, HIV, transplantation	0	0	
CLINICAL STAGE			
Indeterminate form	22 (78.6%)	25 (73.5%)	0.64
Cardiac form - no. (%)	6 (21.4%)	9 (26.4%)	0.64
Gastrointestinal form -no. (%)	0	0	
no: number, sd: standard deviation			
Data are No./number tested (%) of patients, unless otherwise indicated.			

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283 Table 2. Adverse events

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ADVERSE EVENTS	**FULL DOSE (N=28)**	**ESCALATING DOSE (N= 34)**	**p value**
At least one adverse event - no. (%)	25 (89.29)	29 (85.29)	0.64
Skin disturbances - no. (%)	17 (60.71)	21 (61.76)	0.93
Neuromuscular side effects - no. (%)	15 (53.57)	16 (47.06)	0.61
Hematologic toxicity - no. (%)	7 (25)	5 (14.71)	0.24
Liver toxicity - no. (%)	7 (25)	5 (14.71)	0.24
Digestive disturbances - no. (%)	7 (25)	3 (8.82)	0.08
Kidney injury - no. (%)	0	1 (2.94)	1
MANAGEMENT			
Need of specific treatment - no. (%)	12 (42.86)	14 (41.18)	0.89
Referral to a specialist - no. (%)	12 (42.86)	15 (44.12)	0.92
Hospital admission - no. (%)	1 (3.57)	2 (5.88)	0.67
Treatment interruption - no. (%)	7 (25)	14 (41.18)	0.18
Treatment duration, days (sd)	51.75 (15.4)	49.4 (21.5)	0.26
Completed at least 80% of total dose - no. (%)	21 (75)	23 (67.65)	0.53
Completed at least 30 days- no. (%)	25 (89.29)	27 (79.41)	0.29
Maximum dose per day, median grams (sd)	316.1 (38.7)	304.5 (26.1)	0.14
no: number, sd: standard deviation			

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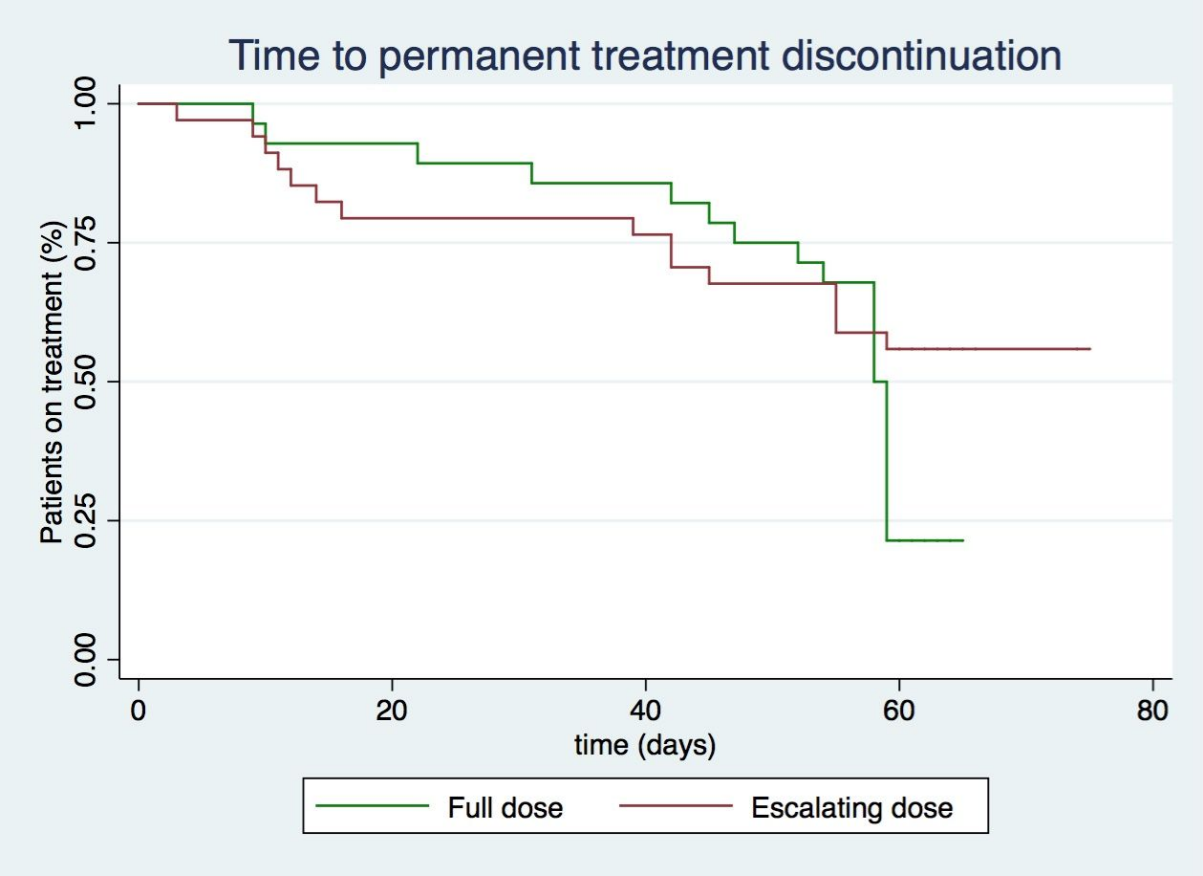
289 Figure 1. Time to permanent treatment discontinuation



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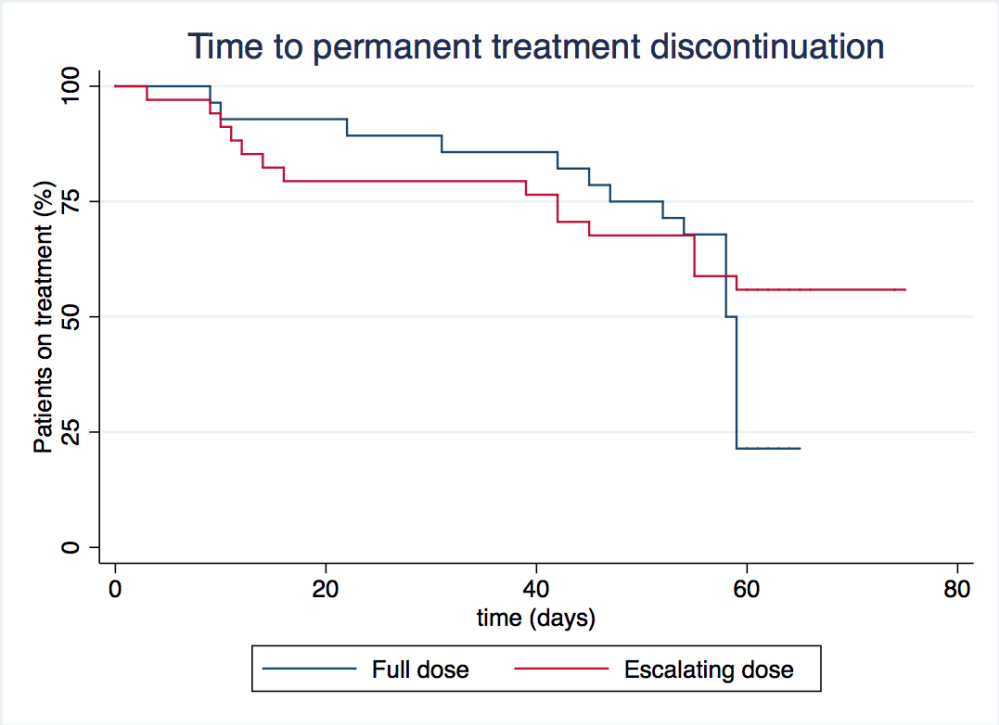

Figure 1. Time to permanent treatment discontinuation

190x138mm (144 x 144 DPI)