



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

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

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8

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

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

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20 Tables 1 and 2

21 Figure 1

22

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32

33 **Abstract**

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

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

46

47 **Introduction**

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

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

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

70 years there seems to be some consensus regarding the absence of benefit of antiparasitic
71 treatment in patients with advanced forms of cardiac or digestive involvement, most
72 national and regional guidelines recommend offering treatment in the indeterminate
73 chronic phase,^{16,17} as well as in patients with mild to moderate determinate disease.
74 The biggest challenge associated with the available antitrypanosomal drugs is their safety
75 profile. From 48% to 86% of patients experience adverse effects of benznidazole, with the
76 result that treatment discontinuation occurs in 9% to 31% of cases.¹⁸⁻²¹ This further limits
77 global treatment coverage, which is already low given that only 4% to 6% of migrants with
78 Chagas disease are aware of their condition⁴ and that treatment reaches less than 1% of
79 patients with Chagas disease.²²⁻²⁵ The most frequently observed adverse events are
80 dermatological, gastro-intestinal and neurological, usually mild and with acceptable
81 response to symptomatic treatment or to benznidazole discontinuation.¹⁸⁻²¹ Serious adverse
82 events such as DRESS syndrome are rare, and life-threatening conditions such as severe
83 neutropenia are extremely uncommon.^{18-21,26}

84 Alongside the search for new and better tolerated drugs,^{14,27-29} efforts are being made to
85 increase the tolerability of existing antitrypanocidal drugs.³⁰ Studies aimed at identifying risk
86 factors for adverse responses to benznidazole have found associations with female sex,²¹
87 graduation from elementary school, and white and mulatto race.³¹ Additionally, carrying
88 HLA-B*3505 allele could be associated with moderate to severe cutaneous
89 reaction.³² Another study found that adverse events, female sex, drug dose and eosinophilia
90 were the main predictors of treatment interruption.³³ A study attempting to find a
91 measurable proxy for toxicity failed to correlate adverse events with serum concentrations
92 of benznidazole.³⁴ Some researchers have proposed the use of corticosteroid therapy along
93 with benznidazole³⁵ to prevent cutaneous reactions. However, this strategy failed to show a

94 clear advantage and raised concerns because of the high rate of *Strongyloides stercoralis*
95 coinfection in patients with Chagas disease³⁶ and risk of hyperinfection syndrome. A clinical
96 trial evaluating shorter regimes and lower dosing of benznidazole is expected to soon
97 provide some insight on the feasibility of this strategy.³⁷ Moreover, some researchers have
98 proposed the use of escalating doses of benznidazole during the first days of treatment in
99 order to increase its tolerability.³⁸ However, this strategy has not been compared to
100 standard treatment with full (adjusted to weight) doses from the beginning of treatment.

101

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

105

106 **Methods**

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

113 The usual evaluation of these patients includes a questionnaire about their country of origin
114 and risk factors for Chagas disease. The patient's medical history is obtained and a physical
115 examination aimed at detecting cardiac or digestive involvement is performed.

116 Electrocardiogram and echocardiogram are routinely performed to rule out cardiac

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

119 In the evaluated time frame, some patients began treatment with benznidazole at full doses
120 and others at progressive doses according to local protocols or consensus when the former
121 were lacking. Changes in schemes of benznidazole treatment took place over time, both
122 before and after the first protocol was launched in 2011. Thus, we divided the patients into
123 two groups, according to the method of introduction of benznidazole treatment. In all cases,
124 the standard dose of 5 mg per kilogram of body weight was calculated, and then the
125 treatment was started according to the physicians' criteria. The maximum daily dose was
126 300mg in the majority of patients, although some received 250mg and others 400mg. In the
127 full-dose group, the previously calculated dose was divided into two daily doses for 60 days.
128 In the progressive dose group, treatment was started with 50mg per day (half a tablet), then
129 increased by 50mg every day until the correct dosage according to weight was reached.

130

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

138

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

141

142 **Results**

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

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

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

158 Treatment interruption due to adverse events occurred in 33.9% of all patients. Mean
159 number of treatment days was 50.5 (sd 18.9), with no differences between groups ([Figure](#)
160 [1](#)). Adverse events leading to early interruption (when established at 50% or 80% of total
161 dose), occurred in 3 to 5 of 25 patients on the full dose group, and in 7 to 11 of 29 patients
162 of the escalating dose group. That is to say that 18.5 to 29.6% of adverse events (depending
163 on the 'early interruption' threshold used) led to early interruption of treatment that would
164 need further antiparasitic treatment. Patients were referred to a specialist because of an

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

169

170 Discussion

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

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

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

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

197 The retrospective nature of this study and the fact that these two different strategies were
198 put in place by different physicians may have introduced some measurement bias. Given
199 that the patients were assigned to each doctor according to availability (without choice by
200 the doctor or the patient), and treatments assigned according to local protocols (or
201 consensus) at each point in time, we think that this would not constitute a source of
202 selection bias. Nonetheless, data were collected using electronic medical records by
203 different physicians than the ones who treated the patients, in order to increase objectivity.
204 Each time a benznidazole treatment is started, it constitutes both an opportunity and a
205 challenge. Any doctor faced with this situation longs for alternatives that improve the safety
206 of antiparasitic treatment, either with new drugs, dosing changes in existing drugs, or the
207 use of adjuvant drugs. With currently available data, it cannot be asserted that a strategy of
208 progressive doses is better than the use of full doses from the beginning. However,
209 prospective randomized studies are needed to improve knowledge about this issue, given
210 the possibility that different benznidazole treatment introduction strategies might improve
211 tolerability and therefore might improve patient health outcomes.

212

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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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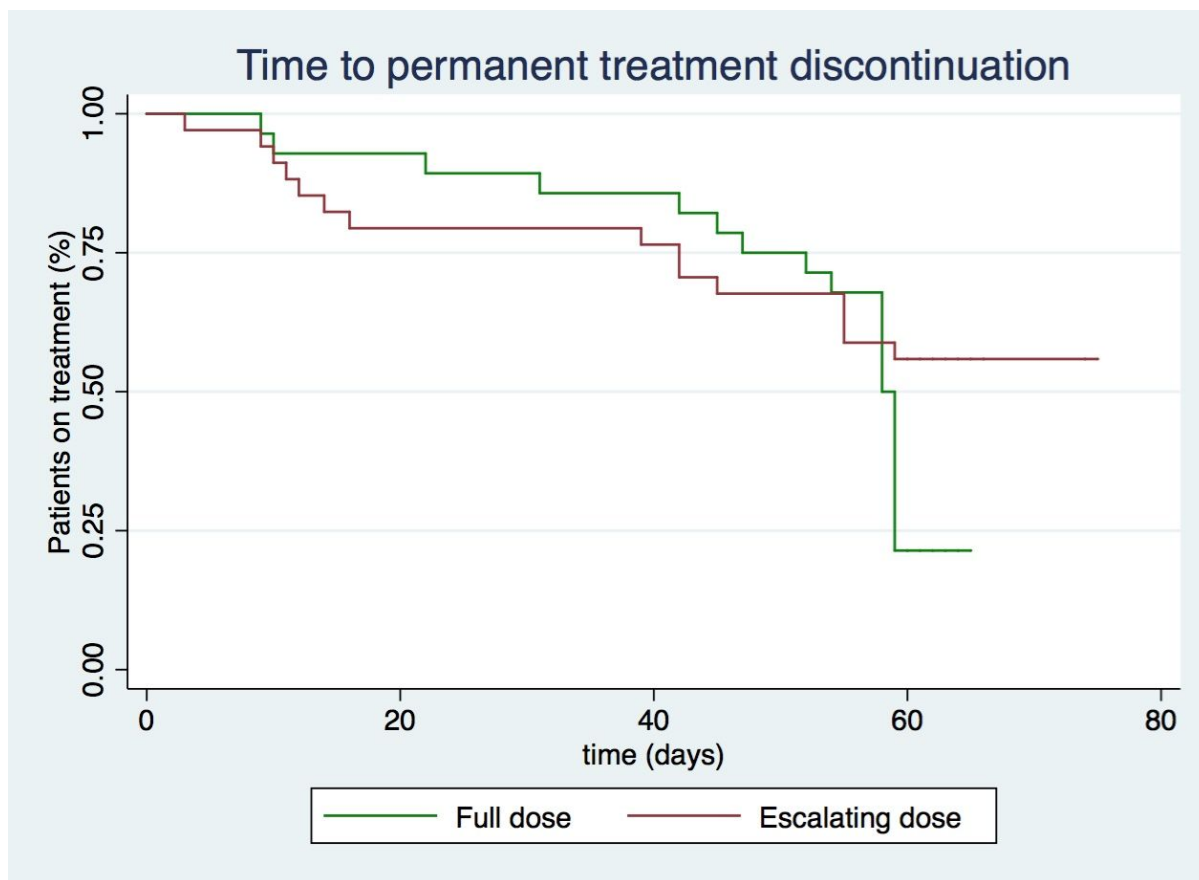
ADVERSE EVENTS	FULL DOSE (N=28)	ESCALATING DOSE (N= 34)	p value
At least one adverse event - no. (%)	25 (89.29)	29 (85.29)	0.64
Skin disturbances - no. (%)	17 (60.71)	21 (61.76)	0.93
Neuromuscular side effects - no. (%)	15 (53.57)	16 (47.06)	0.61
Hematologic toxicity - no. (%)	7 (25)	5 (14.71)	0.24
Liver 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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269 Figure 1. Time to permanent treatment discontinuation



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

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

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

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22 Figure 1

23

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

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33

34 **Abstract**

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

42 ~~Of Among~~ the 62 patients treated ~~in this period~~, benznidazole was introduced at full dose in
43 28 patients and on escalating dose in the remaining 34. We found no statistical differences
44 in ~~the~~ number of adverse events, treatment discontinuations, days of treatment or socio-
45 demographic profiles. There is ~~not enough~~insufficient evidence ~~supporting to support~~
46 escalating dose as a strategy ~~to reduce for reducing~~ adverse ~~events effects~~ of benznidazole.
47 Further research is needed in order to evaluate this strategy.

48

49

Introduction

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

63 The therapeutic options available for antiparasitic treatment of Chagas disease have
64 remained unchanged for around 50 years. The only two available ~~therapeutic alternatives~~
65 reatments are nifurtimox and benznidazole, which were released-introduced in 1965 and
66 1971 respectively.⁶

67 The ~~reported~~ efficacy of these treatments is very-highly variable, since it is affected by the
68 drug dose, the-stage-of-the-disease/disease stage, and the age and area of origin of the
69 patient, among other factors. Cure rates between 60% and 100% are reported when
70 treatment with benznidazole is provided in the acute phase and in younger patients.⁷⁻⁹ The
71 antiparasitic effect of the treatment in the chronic phase is well documented.¹⁰⁻¹⁴

72 However, clinical effectiveness (defined as reduction in clinical events) is still the subject of
73 intense scientific debate.¹⁵ Treatment with antitrypanosomal drugs is currently indicated in
74 acute infection, congenital infections, reactivations and chronic infection in children under
75 18 years of age. Although in recent years there seems to be some consensus in-regarding
76 the absence of benefit of antiparasitic treatment in patients with advanced forms of cardiac
77 or digestive involvement, most national and regional guidelines recommend offering
78 treatment in the indeterminate chronic phase,^{16,17} and-as well as in patients with mild to -
79 moderate determinate disease.

80 The biggest challenge associated with the available antitrypanosomal drugs is their safety
81 profile. A-rate-of adverse effects of benznidazole ranging from 48% to 86% of patients
82 experience adverse effects of benznidazole, with the result that-leads-to treatment
83 discontinuation occurss in 9% to -31% of cases.¹⁸⁻²¹ This further jeopardizes-limits the
84 already-slim global antiparasitic treatment coverage of patients with CD, which is already
85 low given that only 4% to -6% of migrants with ChagasD disease are aware of their
86 condition⁴ and the-that CD-treatment coverage-rate reaches less than 1% of patients with
87 Chagas diseaseD.²²⁻²⁵ The most frequently observed adverse events are dermatological,
88 gastro-intestinal and neurological, usually mild and with acceptable response to
89 symptomatic treatment or to benznidazole discontinuation.¹⁸⁻²¹ Serious adverse events such
90 as DRESS syndrome are rare, and life-threatening conditions such as severe neutropenia are
91 extremely uncommon.^{18-21,26}

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

96 elementary school, and white and mulatto race.³¹ Additionally, carrying HLA-B*3505 allele
97 could be associated with moderate to-severe cutaneous
98 reaction.³² Another study found that adverse events, female sex, drug dose and eosinophilia
99 were the main predictors ~~for of~~ treatment interruption.³³ ~~Likewise, an attempt~~ A study
100 attempting to find a measurable proxy for toxicity failed to correlate adverse events with
101 serum concentrations of benznidazole.³⁴ Some ~~groups-researchers have~~ proposed the use of
102 corticosteroid therapy along with benznidazole³⁵ to prevent cutaneous reactions. However,
103 this strategy failed to show a clear advantage and raised ~~some~~ concerns because of the high
104 rate of *Strongyloides stercoralis* coinfection in patients with ~~CD~~³⁶-Chagas disease³⁶ and risk
105 of hyperinfection syndrome. A clinical trial ~~where evaluating~~ shorter regimes and lower
106 dosing of benznidazole ~~are been evaluated willis expected to~~ soon provide some insight on
107 the feasibility of this strategy.³⁷ Moreover, some ~~groups-researchers~~ have proposed the use
108 of escalating doses of benznidazole during the first days of treatment in order to increase its
109 tolerability.³⁸ However, this strategy has not been compared to standard treatment with full
110 (adjusted to weight) doses from the beginning of treatment.

111

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

115

116 **Methods**

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

120 2017. Inclusion criteria ~~were:~~ chronic infection ~~by with~~ *T. cruzi* as defined by WHO criteria
121 (two positive serological tests)³⁹, age ~~over~~ 18 years or older and ~~having received previous~~
122 treatment with benznidazole in our center. ~~(excluding t~~ Those who were receiving it at the
123 time of data collection were excluded.)~~:-~~

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

130 In the evaluated time frame, some ~~of the~~ patients began treatment with benznidazole at full
131 doses and others at progressive doses according to local protocols or consensus when the
132 former were lacking. Changes in schemes of benznidazole treatment took place over time,
133 both before and after the first protocol was launched in 2011. Thus, we divided the patients
134 into two groups, according to the method of introduction of benznidazole treatment. In all
135 cases, the standard dose of 5 mg per kilogram of body weight was calculated, and then the
136 treatment was started according to the physicians' criteria. The maximum daily dose was
137 300mg in the majority of patients, although some received 250mg and others 400mg. In the
138 full-dose group, the previously calculated dose was divided into two daily doses for 60 days.
139 In the progressive dose group, treatment was started with 50mg per day (half a tablet), then
140 increased by 50mg every day until the correct dosage according to weight was reached.

141

142 Statistical analysis: categorical variables were described by frequencies and percentages.

143 Quantitative variables were described as means and standard deviations or medians and

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

150

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

153

154 Results

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

162 The median maximum daily dose was ~~around~~ [approximately](#) 300mg, without differences
163 between groups.

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

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

172 Treatment interruption due to adverse events occurred in 33.9% of all patients ~~and m.~~
173 ~~Mean~~ number of treatment days was 50.5 (sd 18.9), with no differences between groups
174 ([Figure 1](#)). Adverse events leading to early interruption (when ~~established~~ at 50% ~~or~~ 80% of
175 total dose), ~~where occurred in~~ 3 ~~to~~ 5 of 25 patients on the full dose group, and ~~in~~ 7 ~~to~~ 11
176 of 29 patients of the escalating dose group. ~~That is to say that~~ 18.5 ~~to~~ 29.6% ~~of adverse~~
177 ~~events (depending on the 'early interruption' threshold used) of adverse events~~ led to early
178 interruption of treatment that would need further antiparasitic treatment. Patients were
179 referred to a specialist because of an adverse event in 43.5% of ~~the~~ cases, with [Dermatology](#)
180 [dermatology](#) (85%), [Neurology](#) ~~neurology~~ (11%) and [Allergy](#) ~~allergy~~ (4%) being the most
181 frequent. Specific treatment for an adverse event was prescribed in 42% of ~~subject~~~~patients~~,
182 with oral corticosteroids (50%) and antihistaminics (30.8%) as the most frequent
183 prescriptions.

184

185 Discussion

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

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

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

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

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

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

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

231

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234

235 Transparency

236 None of the authors declares having conflicts of interest.

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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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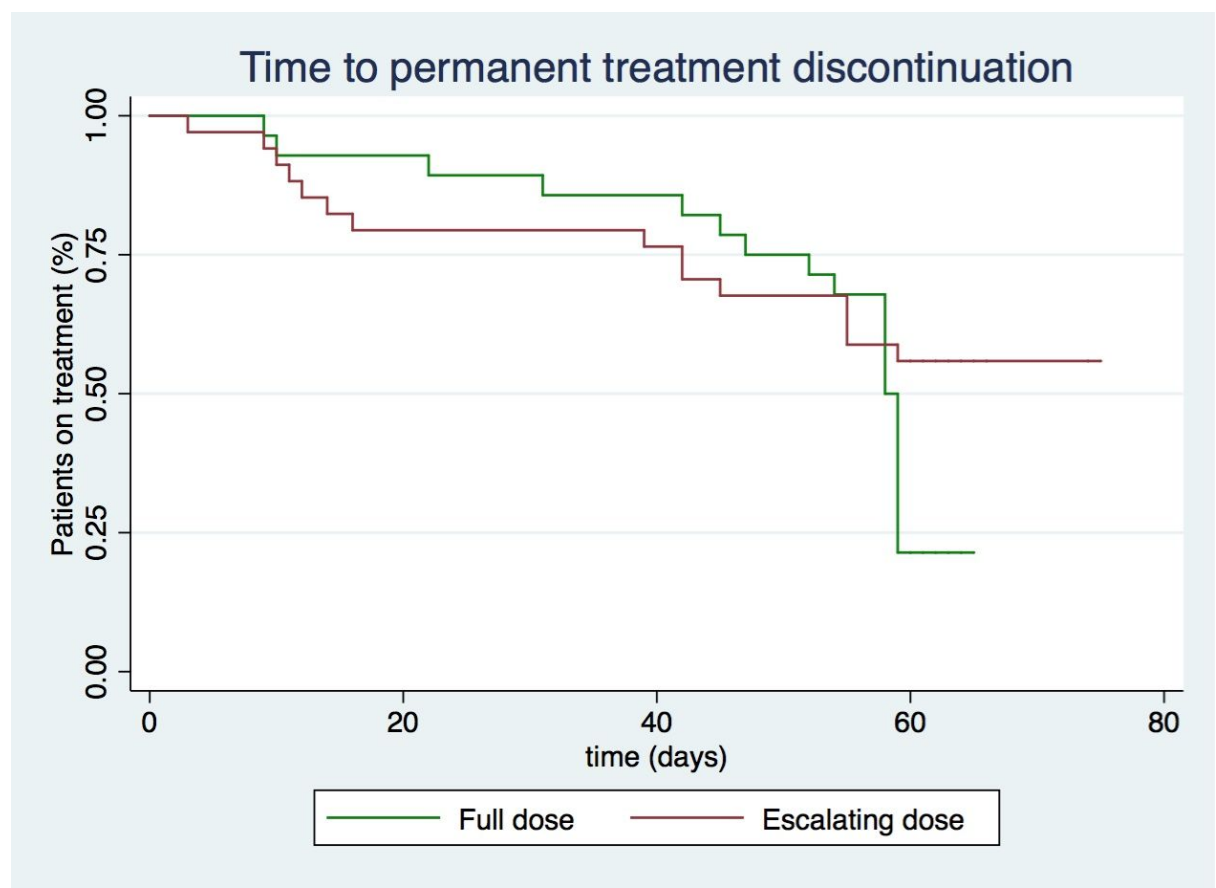
ADVERSE EVENTS	FULL DOSE (N=28)	ESCALATING DOSE (N= 34)	p value
At least one adverse event - no. (%)	25 (89.29)	29 (85.29)	0.64
Skin disturbances - no. (%)	17 (60.71)	21 (61.76)	0.93
Neuromuscular side effects - no. (%)	15 (53.57)	16 (47.06)	0.61
Hematologic toxicity - no. (%)	7 (25)	5 (14.71)	0.24
Liver 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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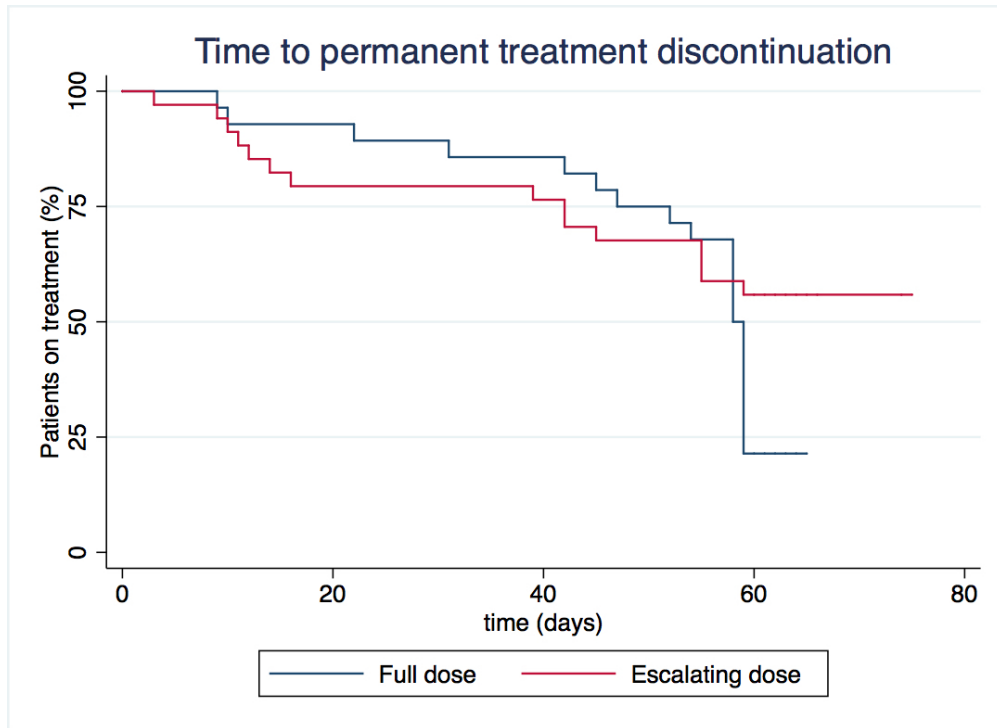


Figure 1. Time to permanent treatment discontinuation

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