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Long-Term Cardiac Outcomes of Treating Chronic Chagas Disease with Benznidazole versus No Treatment

A Nonrandomized Trial

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Background: Benznidazole is effective for treating acute-stage Chagas disease, but its effectiveness for treating indeterminate and chronic stages remains uncertain.

Objective: To compare long-term outcomes of patients with nonacute Chagas disease treated with benznidazole versus outcomes of those who did not receive treatment.

Design: Clinical trial with unblinded, nonrandom assignment of patients to intervention or control groups.

Setting: Chagas disease center in Buenos Aires, Argentina.

Patients: 566 patients 30 to 50 years of age with 3 positive results on serologic tests and without heart failure.

Measurements: The primary outcome was disease progression, defined as a change to a more advanced Kuschnir group or death. Secondary outcomes included new abnormalities on electrocardiography and serologic reactivity.

Intervention: Oral benznidazole, 5 mg/kg of body weight per day for 30 days (283 patients), or no treatment (283 patients).

Results: Fewer treated patients had progression of disease (12 of 283 [4%] vs. 40 of 283 [14%]; adjusted hazard ratio, 0.24 [95% CI, 0.10 to 0.59]; $P = 0.002$) or developed abnormalities on electrocardiography (15 of 283 [5%] vs. 45 of 283 [16%]; adjusted hazard ratio, 0.27 [CI, 0.13 to 0.57]; $P = 0.001$) compared with untreated patients. Left ventricular ejection fraction (hazard ratio, 0.97 [CI, 0.94 to 0.99]; $P < 0.002$) and left ventricular diastolic diameter (hazard ratio, 2.45 [CI, 1.53 to 3.95]; $P < 0.001$) were also associated with disease progression. Conversion to negative results on serologic testing was more frequent in treated patients than in untreated patients (32 of 218 [15%] vs. 12 of 212 [6%]; adjusted hazard ratio, 2.1 [CI, 1.06 to 4.06]; $P = 0.034$).

Limitations: Nonrandom, unblinded treatment assignment was used, and follow-up data were missing for 20% of patients. Loss to follow-up was more common among patients who were less sick. Two uncontrolled interim analyses were conducted.

Conclusions: Compared with no treatment, benznidazole treatment was associated with reduced progression of Chagas disease and increased negative seroconversion for patients presenting with nonacute disease and no heart failure. These observations indicate that a randomized, controlled trial should now be conducted.

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Chagas disease is the leading cause of infectious myocarditis (1). Currently, there are 18 to 20 million persons infected with the protozoan parasite *Trypanosoma cruzi* and 40 million additional persons at risk for the disease (2). Chagas disease includes a 30- to 60-day acute stage, with few symptoms and a low mortality rate, and a chronic symptomatic stage, which leads to irreversible lesions in the gastrointestinal tract and in the heart in 30% to 40% of patients (3). A subclinical stage of variable duration (indeterminate phase) separates the acute and chronic stages.

Cardiac manifestations of Chagas disease include abnormalities of the intraventricular conduction system, ventricular arrhythmias, sinus node dysfunction, heart failure, left ventricular aneurysms, and enlargement and dysfunction of the heart (4). Heart failure (70%) and sudden death (30%) are the most common causes of death in patients with Chagas disease (5).

The pathogenesis of chronic Chagas heart disease is not completely understood. Parasite persistence and inflammation (6–9) and alteration of the host's immune system have been implicated in progressive heart damage caused by infection (10, 11). Chemotherapy against *T. cruzi* infection during the acute stage of the infection leads to regression of clinical symptoms and a parasitologic cure (12), but its effectiveness during the indeterminate and chronic stages remains unclear. The main limitations in evaluating treatment for chronic Chagas disease arise from the need for long-term follow-up, which usually lasts several decades, and the lack of reliable tests to ensure elimination of the parasite (12, 13). Previous observational studies found that benznidazole treatment for patients with chronic Chagas disease delayed or prevented clinical progression of heart damage (14–16). Benznidazole may induce seronegative conversion during the chronic (14–17) and indeterminate stages of the disease (18, 19). We compare long-term outcomes of patients with nonacute Chagas

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disease treated with benznidazole versus the outcomes of those who did not receive treatment.

METHODS

Study Sample and Recruitment

A total of 1968 patients with chronic Chagas disease were evaluated in the Chagas Disease Section at Hospital Eva Perón, Buenos Aires, Argentina, between 1984 and 2001. Patients were screened within 30 days of their first hospital visit to determine their eligibility for inclusion in the study. During this period, we obtained the patients' medical history and performed a physical examination and clinical tests, including baseline serologic testing, electrocardiography, chest radiography, and echocardiography. A diagnosis of *T. cruzi* infection was made by serologic testing, including complement fixation, indirect hemagglutination, immunofluorescence, or enzyme-linked immunosorbent assay, performed at the reference center, Instituto Nacional de Parasitología Dr. Mario Fatala Chaben.

Patients were stratified as follows according to the clinical classification of Kuschnir and colleagues (20): group 0, positive results of serologic testing, normal results on electrocardiography and chest radiography and no cardiac enlargement; group I, positive results on serologic testing, abnormal results on electrocardiography, normal results on chest radiography, and no cardiac enlargement; group II, positive results on serologic testing, abnormal results of electrocardiography and chest radiography with cardiac enlargement but no clinical signs of heart failure; group III, positive results of serologic testing, abnormal results on electrocardiography and chest radiography with cardiac enlargement, and clinical signs of heart failure.

Thirty- to 50-year-old patients with 3 positive results on serologic tests for *T. cruzi* infection and no clinical signs of heart failure (Kuschnir groups 0, I, or II) at admission were considered for inclusion in the study. Patients older than 50 years of age were excluded to avoid misinterpretation of electrocardiographic changes; patients younger than 30 years of age were excluded because patients in this age group rarely present to our center. A total of 772 patients did not fulfill the age inclusion criteria and thus were excluded from the study. Sixty-nine patients with overt heart failure (Kuschnir group III, considered to have irreversible end-stage disease), 81 patients with a history of previous treatment for *T. cruzi* infection (complete, incomplete, or unknown), and 113 patients with only 2 positive results on serologic tests were excluded from the study. A total of 297 patients with concomitant disorders, such as chronic obstructive pulmonary disease, hypothyroidism and hyperthyroidism, cancer, valvular heart disease, arterial hypertension, congenital heart disease, coronary artery disease, alcoholism, diabetes mellitus, morbid obesity, or other severe systemic diseases, were also excluded. The recruitment period ended in 2001.

Context

The effect of antitrypanosomal drug therapy on progression of heart involvement in patients with chronic Chagas disease is uncertain.

Contribution

The authors assigned alternating patients with 3 positive results on serologic tests for *Trypanosoma cruzi* and no evidence of heart failure to receive benznidazole for 30 consecutive days ($n = 283$) or no treatment ($n = 283$). After a median follow-up of 9.8 years, 14.1% of untreated patients and 4.2% of treated patients ($P = 0.002$) had progression of heart disease.

Cautions

Assignment of patients was not randomized. Twenty percent of patients from both groups were lost to follow-up.

Implications

Treatment during the chronic phase of Chagas disease may reduce the risk for progression of heart disease.

—The Editors

Treatment Intervention

Eligible patients were assigned to receive either oral, self-administered benznidazole twice per day, at a maximum dosage of 5 mg/kg of body weight per day for 30 consecutive days, or no treatment. Patients were assigned by using an alternating sequence wherein every other individual enrolled (for example, patients 1, 3, and 5) was assigned to treatment and the alternate individuals (for example, patients 2, 4, and 6) were assigned to the control group. We also included 34 patients from a previous study (17 patients assigned to receive treatment and 17 patients assigned to remain untreated) who met the inclusion and exclusion criteria of the current trial.

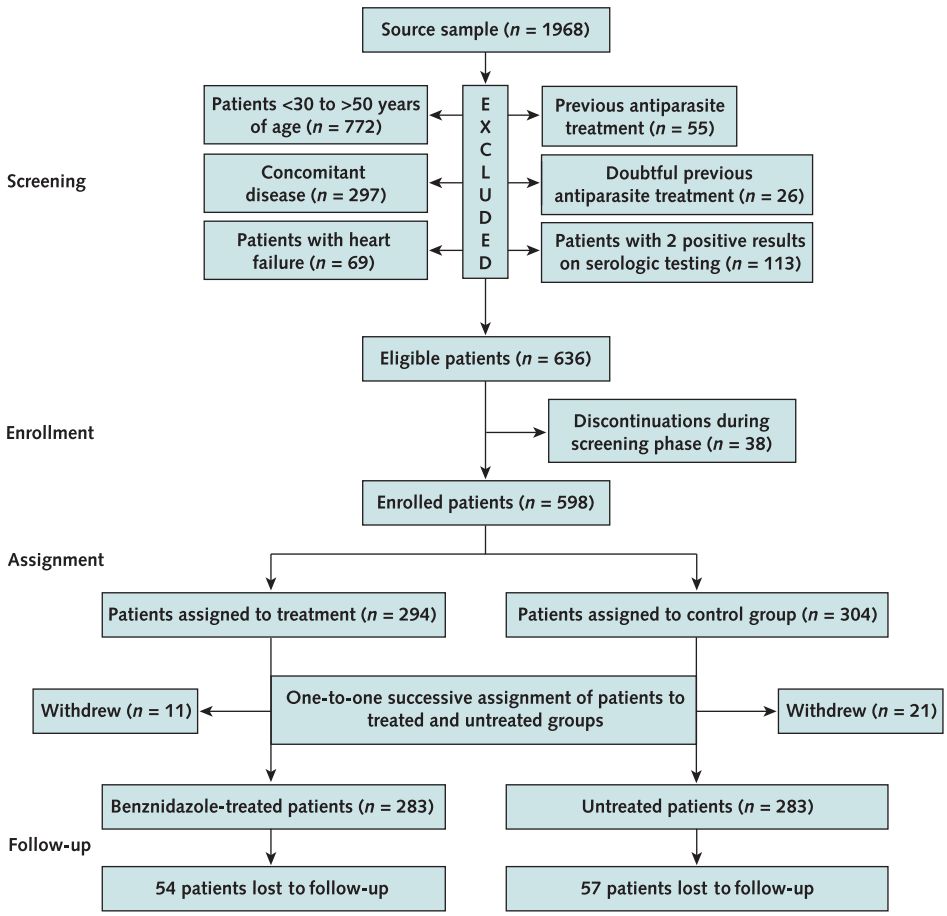
A pathologist who was not involved in the clinical evaluation assigned patients to treatment and control groups. If a patient withdrew from the study or declined to participate, the same physician maintained the 1:1 ratio by assigning the next eligible patient to the respective group. Physical examination was performed by 3 participating cardiologists who were not aware of their patients' assignments.

Data Collection and Follow-up

The clinical status of enrolled patients was evaluated by serial electrocardiography, chest radiography, and serologic testing for *T. cruzi* infection. Follow-up visits and results of electrocardiography were recorded every 6, 4, and 3 months in patients in Kuschnir groups 0, I, and II, respectively.

Complete left and right bundle-branch block, left anterior fascicular block, sinus bradycardia less than 50 beats/min, electric inactivation areas, types 2 and 3 atrio-

Figure 1. **Flow diagram of the screening process, reasons for nonenrollment, and follow-up.**



ventricular block, sustained supraventricular arrhythmias, nonsustained and sustained ventricular tachycardia, and pacemaker implantation were all considered electrocardiographic abnormalities related to Chagas heart disease (14), whereas other abnormalities were considered nonspecific (21).

Chest radiographs were obtained annually for all patients to evaluate heart size and signs of heart failure. A cardiothoracic ratio greater than 0.50 indicated cardiac enlargement. Bidimensional echocardiography was performed according to the guidelines from the American Society of Echocardiography (22) on all patients with cardiac enlargement on chest radiographs. A left ventricular end-diastolic diameter of 57 mm or greater was considered to be left ventricle dilation. The 57-mm limit was determined from the values obtained from healthy adults at the echocardiographic department at our hospital.

Two cardiologists who had access to patient information but were blinded to treatment assignment and to the results of the interim analysis reviewed the electrocardiogram tracings, chest radiographs, and echocardiograms; disagreements were resolved by discussion. Standard criteria were used for electrocardiographic diagnosis of Chagas disease (23). The cardiothoracic ratio was obtained by using the relation between the transverse diameter of the heart and the transverse diameter of the thorax at the level of the right diaphragmatic cupula (24). Three serologic tests for *T. cruzi* infection, enzyme-linked immunosorbent assay, indirect hemagglutination, and immunofluorescence tests (25, 26) were used for follow-up, which was done at 3-year intervals.

Patients were informed about possible side effects of benznidazole therapy and were advised to consult the study physician immediately if a symptom occurred. Information on adverse events was obtained on days 10 and 30 after treatment initiation. No data regarding adverse events were collected from control patients. Patients who discontinued treatment because of side effects were included in the intention-to-treat analysis. Follow-up stopped in December 2004.

Outcomes Evaluated

The primary outcome was a change from a lower to a more advanced Kuschnir group or cardiac death (change of

clinical group). We also examined factors associated with this outcome. Secondary outcomes were the appearance of new abnormalities on electrocardiography, persistence of 3 positive results on serologic evaluation, or complete negative seroconversion on the last serologic test done for each patient.

Statistical Analyses

Continuous variables are presented as means (SDs) or medians (25% to 75% interquartile ranges), and categorical variables are presented as percentages of all patients. The *t*-test and the chi-square test were used to compare continuous and categorical baseline variables, respectively. The Mann–Whitney test was used to compare baseline variables that were not normally distributed. Survival curves for change of clinical group were generated by using the Kaplan–Meier method and were compared by using the log-rank test.

Multivariate Cox proportional hazards regression analyses were used to calculate the hazard ratios with 95% CIs for treatment with benznidazole versus no treatment, adjusted for age, sex, clinical group at admission, left ventricular ejection fraction, and left ventricular diastolic diameter

Table 1. **Baseline Characteristics of Study Participants***

Characteristic	All Patients (n = 566)	Treated Patients (n = 283)	Untreated Patients (n = 283)	*P* Value
Mean age (SD), *y*	39.40 (5.59)	39.39 (5.35)	39.42 (5.83)	0.93
Men, *n (%)*	261 (46.1)	134 (47.3)	127 (44.9)	0.55
Endemic area in South America, *n (%)*				
Latitude 16° S to 24° S	23 (4.1)	8 (2.8)	15 (5.3)	0.136
Latitude 24° S to 28° S	227 (40.1)	115 (40.6)	112 (39.6)	0.80
Latitude 28° S to 32° S	248 (43.8)	125 (44.2)	123 (43.5)	0.86
Latitude 32° S to 36° S	68 (12.0)	35 (12.4)	33 (11.7)	0.80
Inhabitants born in rural areas, *n (%)*	490 (86.6)	246 (86.9)	244 (86.2)	0.80
Mean years living in endemic areas (SD)	16.33 (7.65)	16.56 (7.32)	15.91 (8.13)	0.34
Socioeconomic indicators				
Mean inhabitants per home/number of bedrooms (SD)	1.84 (1.03)	1.77 (0.86)	1.91 (1.19)	0.148
Mean individuals with employment/inhabitants per home (SD)	0.42 (0.26)	0.42 (0.26)	0.43 (0.26)	0.77
Mean school enrollment (SD), *y*	5.63 (2.76)	5.84 (2.78)	5.43 (2.72)	0.194
Clinical group at admission, *n (%)*				
0	360 (63.6)	180 (63.6)	180 (63.6)	1.00
I	148 (26.1)	73 (25.8)	75 (26.5)	0.85
II	58 (10.2)	30 (10.6)	28 (9.9)	0.78
Presenting symptoms, *n (%)*				
Asymptomatic	249 (44.0)	121 (42.8)	128 (45.2)	0.55
Palpitations	153 (27.0)	72 (25.4)	81 (28.6)	0.39
Atypical chest pain	143 (25.3)	78 (27.6)	65 (23.0)	0.21
Dizziness	42 (7.4)	19 (6.7)	23 (8.1)	0.52
Syncope	13 (2.3)	5 (1.8)	8 (2.8)	0.40
New York Heart Association class I or II	27 (4.8)	14 (4.9)	13 (4.6)	0.84
Mean heart rate (SD), *beats/min*	70.62 (13.7)	71.50 (12.4)	69.74 (14.9)	0.171
Mean systolic blood pressure (SD), *mm Hg*	119.36 (13.6)	119.35 (13.1)	119.38 (14.3)	0.98
Mean diastolic blood pressure (SD), *mm Hg*	80.07 (9.3)	80.21 (8.8)	79.92 (9.7)	0.72
Electrocardiographic findings, *n (%)*				
Normal	283 (50.0)	136 (48.1)	147 (51.9)	0.36
Not relevant to Chagas disease	92 (16.3)	54 (19.1)	38 (13.4)	0.068
Conduction abnormalities	129 (22.8)	66 (23.3)	63 (22.3)	0.76
Ventricular premature contractions ≥ Lown III†	18 (3.2)	9 (3.2)	9 (3.2)	1.00
Atrial fibrillation	3 (0.5)	2 (0.7)	1 (0.4)	1.00
Sinus bradycardia <50 beats/min	14 (2.5)	4 (1.4)	10 (3.5)	0.174
Electric inactivation area	5 (0.9)	2 (0.7)	3 (1.1)	1.00
Permanent pacemaker	6 (1.1)	4 (1.4)	2 (0.7)	0.69
Echocardiographic characteristics‡				
Mean Teichholtz left ventricular ejection fraction (SD)§	66.65 (11.2)	67.28 (10.8)	65.97 (11.5)	0.24
Aneurysms, *n (%)*	26 (6.1)	14 (6.3)	12 (5.8)	1.00
Mean left ventricular end-diastolic diameter (SD), *mm*	49.29 (5.3)	49.0 (5.2)	49.6 (5.4)	0.22
Mean left ventricular end-systolic diameter (SD), *mm*	30.98 (6.2)	30.60 (5.8)	31.39 (6.5)	0.187
Mean left atrial systolic diameter (SD), *mm*	33.45 (4.9)	33.59 (4.8)	33.30 (5.1)	0.56
Medication on admission, *n (%)*				
Antiarrhythmic agents	46 (8.1)	21 (7.4)	25 (8.8)	0.54
Angiotensin-converting enzyme inhibitors	10 (1.8)	5 (1.8)	5 (1.8)	1.00

* S = south.
† Polymorphics, coupling, and ventricular tachycardia.
‡ Data were available for 429 patients, 221 in the treated group and 208 in the untreated group.
§ The Teichholtz formula was used to calculate left ventricular ejection fraction.

Table 2. **Baseline Characteristics of Patients Lost and Not Lost to Follow-up**

Characteristic	Treated Patients		Untreated Patients	
	Lost to Follow-up (n = 54)	Not Lost to Follow-up (n = 229)	Lost to Follow-up (n = 57)	Not Lost to Follow-up (n = 226)
Mean age (SD), *y*	39.13 (5.57)	39.45 (5.3)	37.21 (5.34)*	39.98 (5.83)*
Men, *n (%)*	33 (61.1)†	101 (44.1)†	25 (43.9)	102 (45.1)
Median follow-up (25%–75% interquartile range), *y*	4.84 (1.93–7.84)‡	11.86 (7.5–17.6)	3.0 (1.78–8.58)‡	11.3 (7.6–14.4)
Mean inhabitants per home/number of bedrooms (SD)	2.08 (1.02)§	1.72 (0.82)§	2.05 (1.08)	1.89 (1.21)
Clinical group on admission, *n (%)*				
0	35 (64.8)	145 (63.3)	43 (75.4)‖	137 (60.6)‖
I	12 (22.2)	61 (26.6)	10 (17.5)	65 (28.8)
II	7 (13.0)	23 (10)	4 (7.0)	24 (10.6)
Changes of clinical group, *n (%)*	1 (2)	11 (4.8)	4 (7)	36 (13)
Abnormal electrocardiogram, *n (%)*	27 (50)	120 (52.4)	21 (36.8)	115 (50.9)
Mean Teichholtz left ventricular ejection fraction (SD)¶	68.01 (10.0)	67.22 (10.02)	65.84 (9.6)	65.68 (11.8)
Mean left ventricular end-diastolic diameter (SD), *mm*	48.0 (4.7)	49.05 (5.26)	47.8 (4.8)	49.91 (5.5)

* $P = 0.001$.
† $P = 0.024$.
‡ $P < 0.001$ versus patients who were not lost to follow-up.
§ $P = 0.032$.
‖ $P = 0.054$.
¶ The Teichholtz formula was used to calculate left ventricular ejection fraction.

(primary outcome, change of clinical group; secondary outcome, new electrocardiographic abnormalities) and for age, sex, and clinical group at admission (secondary outcome, serologic evaluation). Death was adjusted for left ventricular ejection fraction. We tested assumptions of the proportional hazards models and interactions (27) and observed no violation.

The primary analysis was intention-to-treat and included all patients as assigned to treated and untreated groups, including those who discontinued treatment because of side effects. The sample size was calculated on the basis of a previous study with 8 years of follow-up, in which untreated patients had a rate of 17% for change of clinical group (14). An expected reduction of 40% was established for benznidazole-treated patients. For an α value of 0.05 and $1-\beta$ value of 0.9, the sample size was calculated to be 319 patients per group.

Physicians participating in the study performed 2 interim analyses every 5 years of follow-up. The study was stopped once the sample size was achieved or once a statistically significant difference in the primary outcome of time to change of clinical group was found. No formal rules were applied for stopping the study, and no adjustment was made for multiple testing.

Sensitivity Analysis

An observed association between treatment and outcome in nonrandomized studies may reflect the effect of unknown or unmeasured confounders (covariates that are associated with treatment and outcome). Thus, we investigated the effects of an unmeasured binary confounder on the hazard ratio for benznidazole treatment, varying the prevalence of the unknown confounder (in treatment and control groups) and the relative hazard of changes of clinical group associated with the unmeasured confounder (28).

Worst-Case Sensitivity Analysis

A worst-case sensitivity analysis was applied to address differential withdrawal between treated and untreated groups. For this analysis, we assumed that no patients in the untreated lost to follow-up group and 20% to 40% of patients in the treated lost to follow-up group changed clinical group. We used SPSS, version 6.1 (SPSS Inc., Chicago, Illinois) for all analyses. The institutional review committee at our hospital approved the study protocol, and all patients provided informed consent before enrollment.

Role of the Funding Source

All materials, equipment, and drugs were provided by Ministerio de Salud, Provincia de Buenos Aires, Argentina. The design, conduct, analysis, and submission of the paper for publication were the sole responsibility of the authors.

RESULTS

A flow diagram describing the phases of screening, enrollment, assignment, and follow-up of the participants is shown in **Figure 1**. The baseline characteristics of the 566 study participants (283 treated patients and 283 untreated patients) are summarized in **Table 1**. Median time to follow-up was 9.8 years (interquartile range, 5.24 to 14.2 years).

In the first interim analysis, statistical differences between intervention groups were observed for the secondary outcome of new abnormalities on electrocardiography, but not for change of clinical group. In the second interim analysis, statistical differences were also observed for the

primary outcome of change of clinical group in patients in group I at admission and for the secondary outcome of serologic evaluation. Thus, the study was continued until the final analysis, in which statistically significant differences in primary outcomes were attained for all Kuschnir groups.

The data on the comparison between treated and untreated patients lost to follow-up and those not lost to follow-up are shown in **Table 2**. Approximately 20% of patients from both intervention groups were lost to follow-up during the study. Treated patients who were lost to follow-up were more likely to be male and had a higher number of inhabitants per home and number of bedrooms per home than treated patients who were not lost to follow-up. Untreated patients who were lost to follow-up were younger and were more likely to be in Kuschnir group 0 at admission than untreated patients who were not lost to follow-up. Follow-up data on 49 patients, 24 who were treated (mean age, 38.5 years [SD, 5.1]; median follow-up, 10.7 years [25% to 75% interquartile range, 9.3 to 14.7 years]) and 25 who were not treated (mean age, 40.8 years [SD, 6.3]; median follow-up, 9.75 years [25% to 75% interquartile range, 6.5 to 12.7 years]), were missed intermittently; statistically significant differences were not observed between groups (**Table 3**).

Primary Outcomes

Change of Clinical Group

The cumulative percentage of patients with a change to a more severe Kuschnir group was statistically significantly lower in treated than in untreated patients ($P < 0.001$) (**Figure 2**). Fewer patients in the treated group progressed to a more severe clinical Kuschnir group (12 of 283 patients [4.2%]) compared with those in the untreated group (40 of 283 patients [14.1%]; adjusted hazard ratio, 0.24 [95% CI, 0.10 to 0.59]; $P = 0.002$). The results of the Cox regression model for change of clinical group showed that a lower left ventricular ejection fraction (adjusted hazard ratio, 0.96 [CI, 0.93 to 0.99]; $P = 0.005$) and a higher left ventricular end-diastolic diameter (adjusted hazard ratio, 2.88 [CI, 1.27 to 6.54]; $P = 0.012$) were independent predictors of change of clinical group.

The comparison of follow-up data according to clinical group at admission (Kuschnir groups 0, I, and II) showed that treated patients were less likely than untreated patients to change clinical group. Clinical group changed in 6 of 180 treated patients (3.3%) and 13 of 180 untreated patients (7.2%) in Kuschnir group 0 ($P = 0.005$), 3 of 73 treated patients (4.1%) and 14 of 75 untreated patients (18.7%) in Kuschnir group I ($P = 0.002$), and 3 of 30 treated patients (10%) and 13 of 28 untreated patients (46.4%) in Kuschnir group II ($P < 0.001$).

Worst-Case Sensitivity Analysis

To address the differences between treated and untreated patients who were lost to follow-up, a worst-case sensitivity analysis was performed (**Table 4**). We considered scenarios in which the rate of change of clinical group was higher in the treated patients who were lost to follow-up, because untreated patients who were lost to follow-up seemed to have less severe disease (lower Kuschnir group at admission) than untreated patients who were not lost to follow-up. According to the results of this analysis, the observed relationship between change of clinical group and benznidazole treatment would lose statistical significance only if 40% or more of the treated patients lost to follow-up changed clinical group and none of the untreated patients lost to follow-up changed clinical group.

Mortality

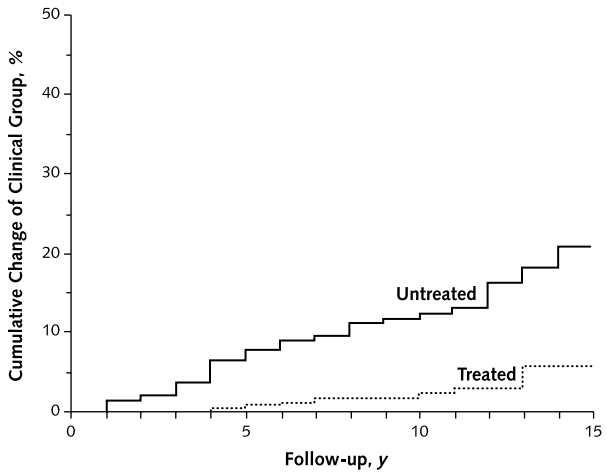
The mortality rate during the follow-up period was lower in the treated group (3 of 283 patients [1.1%]) than in the untreated group (12 of 283 patients [4.2%]); causes of death were sudden death and heart failure (**Appendix Table 1**, available at www.annals.org). However, no differences between the 2 intervention groups were found when data for mortality were adjusted for left ventricular ejection fraction (adjusted hazard ratio, 0.2 [CI, 0.03 to 1.2]; $P =$

Table 3. **Patients Remaining at Risk at the Beginning of Each Year and Those Who Were Lost to Follow-up**

Variable	Year																
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	>15
Patients at risk, *n*																	
Treated	283	279	271	266	255	236	217	198	182	169	153	139	125	110	93	82	–
Untreated	283	278	265	253	237	220	205	187	175	158	141	122	105	88	68	50	–
Lost to follow-up, *n*																	
Treated	–	9	5	4	6	4	3	7	4	2	1	2	1	3	1	1	1
Untreated	–	9	6	13	6	2	1	5	0	2	3	3	0	1	1	2	3
Lost to follow-up (intermittent), *n**																	
Treated	–	0	0	0	1	0	0	2	1	1	5	3	0	4	0	2	5
Untreated	–	0	0	0	2	1	2	4	0	3	2	3	1	1	1	2	3

*Patients for whom some follow-up data were not available.

Figure 2. **Kaplan–Meier curves of cumulative percentage of patients who changed clinical group.**



0.085). At the time of their deaths, 2 patients (13.3%) were in Kuschnir group I, 5 patients (33.3%) were in group II, and 8 patients (53.3%) were in group III.

Secondary Outcomes

New Electrocardiographic Abnormalities

Fewer patients in the treated group developed electrocardiographic abnormalities (15 of 283 patients [5%]) compared with those in the untreated group (45 of 283 patients [16%]; adjusted hazard ratio, 0.27 [CI, 0.13 to 0.57]; $P = 0.001$) (**Appendix Table 2**, available at www.annals.org). The results of the Cox regression model showed that older age at admission (adjusted hazard ratio, 1.11 [CI, 1.03 to 1.19]; $P = 0.006$), a lower left ventricular ejection fraction (adjusted hazard ratio, 0.96 [CI, 0.94 to 0.99]; $P = 0.003$), and a higher left ventricular end-diastolic diameter (adjusted hazard ratio, 2.47 [CI, 1.2 to 5.1]; $P = 0.014$) were independent predictors of new electrocardiographic abnormalities.

The comparison of follow-up data according to clinical group at admission (Kuschnir groups 0, I, and II) showed that treated patients were less likely than untreated patients to develop new electrocardiographic abnormalities: 5 of 180 treated patients (2.7%) and 11 of 180 untreated patients (6.1%) in Kuschnir group 0 ($P = 0.009$), 4 of 73 treated patients (5.5%) and 19 of 75 untreated patients (25.3%) in Kuschnir group I ($P = 0.001$), and 6 of 30 treated patients (20%) and 15 of 28 untreated patients (53.6%) in Kuschnir group II ($P < 0.001$). Electrocardiographic changes consisted of specific conduction abnormalities (9 treated patients vs. 16 untreated patients), atrial arrhythmias (3 treated patients vs. 8 untreated patients), implantation of a pacemaker (3 treated patients vs. 10 untreated patients; $P = 0.050$), nonsustained ventricular tachycardia (2 untreated patients), sustained ventricular tachycardia (10 untreated patients; $P = 0.001$), electric inactivation areas (2 untreated patients), and sinus bradycardia less than 50 beats/min (2 untreated patients).

Serologic Evaluation

Serologic follow-up included data from 430 patients (218 treated patients and 212 untreated patients). Sixty patients were lost to serologic follow-up, 23 patients did not complete the serologic protocol, and 53 patients did not remain in the study for the 3-year period required for repetition of serologic tests. Thus, serologic data for 136 patients—65 treated patients (mean age, 39.1 years [SD, 5.5]) with a median follow-up of 6.1 years (25% to 75% interquartile range, 3.4 to 11.6 years) and 71 untreated patients (mean age, 38.5 years [SD, 6.1] with a median follow-up of 5.2 years (25% to 75% interquartile range, 3.0 to 11.4 years)—were not available. These patients did not differ statistically significantly in clinical group at admission, left ventricular ejection fraction, and left ventricular end-diastolic diameter.

The proportion of patients with 3 positive results on serologic tests at the end of the study was statistically significantly lower in the treated group than in the untreated group (130 of 218 patients [60%] vs. 177 of 212 patients [83%]; adjusted hazard ratio, 0.55 [CI, 0.44 to 0.70]; $P < 0.001$). Complete seronegative conversion was more frequent in treated patients than in untreated patients (32 of 218 patients [15%] vs. 12 of 212 patients [6%]; adjusted hazard ratio, 2.1 [CI, 1.06 to 4.06]; $P = 0.034$). Complete seronegative status was achieved in a median of 11.7 years (25% to 75% interquartile range, 5.9 to 15.7 years).

Table 4. **Worst-Case Sensitivity Analysis for Patients Lost to Follow-up***

Assumption	Treated Patients with Change of Clinical Group, *n/n*	Untreated Patients with Change of Clinical Group, *n/n*	Adjusted Hazard Ratio for Change of Clinical Group (95% CI)
Observed data	12/283	40/283	0.24 (0.10–0.59)
20% of treated patients lost to follow-up with assumed change of clinical group	23/283	40/283	0.45 (0.26–0.75)
30% of treated patients lost to follow-up with assumed change of clinical group	28/283	40/283	0.54 (0.33–0.89)
40% of treated patients lost to follow-up with assumed change of clinical group	33/283	40/283	0.65 (0.40–1.03)

*This analysis assumes that no untreated patients who were lost to follow-up had change of clinical group and that 20%, 30%, and 40% of treated patients who were lost to follow-up had change of clinical group. In the analysis, where noninformative censoring was assumed, the hazard ratio was 0.24 (95% CI, 0.10 to 0.59).

Table 5. **Sensitivity of the Hazard Ratio for Change of Clinical Group to an Unmeasured Binary Confounder**

Prevalence of Unmeasured Binary Confounder in Untreated Group, %	Prevalence of Unmeasured Binary Confounder in Treated Group, %	Unmeasured Binary Confounder Hazard Ratio	Benznidazole Hazard Ratio Adjusted for Unmeasured Binary Confounder (95% CI)
90	10	6.0	0.51 (0.20–1.31)
90	50	6.0	0.28 (0.14–0.56)
90	10	5.5	0.44 (0.17–1.18)
90	50	5.5	0.26 (0.13–0.53)
90	10	5.0	0.39 (0.13–1.14)
90	50	5.0	0.26 (0.13–0.53)
90	10	4.5	0.31 (0.10–0.93)
90	50	4.5	0.25 (0.12–0.52)
90	10	4.0	0.26 (0.10–0.70)
90	50	4.0	0.25 (0.12–0.52)

Changes of Clinical Group according to Serologic Evaluation

Changes of clinical group were observed more frequently in patients with 3 persistent positive results on serologic tests than in those with other serologic evaluation (33 of 307 patients [10.7%] vs. 3 of 123 patients [2.4%]; hazard ratio, 4.88 [CI, 1.48 to 16.05]; $P = 0.009$). None of the patients who achieved complete negative results on serologic testing changed clinical group during the follow-up, regardless of treatment.

Sensitivity Analysis

A sensitivity analysis (**Table 5**) showed that an unmeasured confounder would account for the observed association of benznidazole treatment and change of clinical group only if it were extremely unequally distributed between the treated and untreated groups and increased change of clinical group by at least 5-fold. For example, to account for the reduction in change of clinical group, a confounder would have to be 9 times more prevalent in the untreated group and have a hazard ratio of 5 or greater.

Side Effects of Benznidazole Treatment

The side effects of benznidazole that required discontinuation of treatment (37 of 283 patients [13%]) were severe allergic dermatitis in 33 patients, 30 who required antihistamine treatment and 3 who required corticosteroids, and gastrointestinal disorders in 4 patients. These patients continued to be followed within the treated group, and only 6 patients (16%) were lost to follow-up. Side effects of benznidazole in the group of patients who completed the treatment program (55 of 246 patients [22%]) were mild allergic dermatitis (36 patients [14.6%]), moderate allergic dermatitis (2 patients [0.8%]), headache (3 patients [1.2%]), gastrointestinal intolerance (11 patients [4.5%]), fever (1 patient [0.4%]), and pruritus (2 patients [0.8%]).

DISCUSSION

Our results suggest that benznidazole treatment for patients with indeterminate- and chronic-stage Chagas disease may decrease the risk for disease progression. The analysis of clinical, electrocardiographic, and echocardiographic predictor variables showed that a lower left ventricular ejection fraction and a higher left ventricular end-diastolic diameter were associated with disease progression.

Although improvement in prognosis after parasiticidal treatment has been reported in other observational studies, this is, to our knowledge, the first systematic prospective study showing a benefit of etiologic treatment to prevent clinical progression in patients with indeterminate and chronic Chagas disease. The results of our trial are similar to those of previous studies, which reported the development of new electrocardiographic abnormalities or progression of heart disease in 2.2% to 5.9% of patients after etiologic treatment compared with 13% to 25% of untreated patients (14–16, 29). Other authors could not identify beneficial effects of specific treatment on the clinical evolution of Chagas disease, but small sample sizes may explain these findings (30). Left ventricular end-diastolic diameter and left ventricular ejection fraction were associated with progression of heart disease and death, as reported in other studies of Chagas disease (31–34).

The rate of disease progression recorded in the group of untreated patients with indeterminate-stage disease (Kuschnir group 0) during our 10-year study period was much lower than the 2% to 4% annual rate of progression reported previously (35). However, the incidence of electrocardiographic changes in our sample of untreated patients was lower than that reported by other authors (36). It is possible that these differences are related to the diverse origin and characteristics of the patients in each study.

There is little information in the literature regarding progression to more advanced disease in patients with electrocardiographic abnormalities but no radiologic signs of cardiac enlargement. A progression rate of 20% was observed in a group of 115 patients with these characteristics who were followed for more than 5 years (37), a proportion similar to that of the untreated patients in group I in our series.

We chose changes in clinical group, electrocardio-

graphic abnormalities, and serologic evaluation of conventional *T. cruzi*–specific tests as end points so that we could determine the impact of treatment with benznidazole on the evolution of the disease. The Kuschnir classification of patients with chronic Chagas heart disease has been useful in differentiating the main disease stages (20) and assessing the progression of cardiomyopathy (14). Electrocardiography is essential for staging patients early during development of Chagas heart disease, and its correlation with anatomopathologic lesions has been well established (38, 39).

Diagnosis of active infection is based mainly on the immunologic recognition of the parasite, and seronegative conversion is the major criterion used to define parasitologic cure. Thus, it can be assumed that patients who became seronegative had eradication of the infection. In our study, we confirmed previous observations that etiologic treatment of patients with chronic Chagas disease is associated with seronegative conversion on conventional serologic tests (14–17), but conversion was achieved several years after treatment. Seronegative conversion rates of 43% to 75% were reported in children up to 14 years of age who were treated with benznidazole; conversion rates decreased according to their ages at treatment (18, 19, 40). The lower rates of seronegative conversion in treated adult patients with chronic Chagas disease in our series (>30 years of infection) suggest that effectiveness in eradicating the infection depends on the length of time between infection and treatment initiation. The more favorable clinical course of patients who became seronegative supports the role of parasite persistence in the development of cardiac lesions (41, 42). On the other hand, clinical and serologic data from untreated patients confirm previous reports of a spontaneous cure in patients with chronic Chagas disease (14, 43).

The main limitations of our study were the nonrandomized design, the number of patients lost to follow-up, incomplete blinding, and absence of a placebo control group. The problems in designing a long-term study of a slowly evolving illness, such as chronic Chagas disease, are the need for long-term follow-up and for reliable methods to confirm the persistence or elimination of the parasite. Also, the socioeconomic characteristics of the sample can affect adherence to the protocol, as we observed in the group of patients who were lost to follow-up. To avoid bias in our nonrandomized approach, we took extensive precautions, including one-to-one placement of incoming patients in either group, sensitivity analysis, lost to follow-up analysis, worst-case sensitivity analysis, and standardized approaches for diagnosis of the disease and reporting of the data (44). Results of the worst-case sensitivity analysis and the sensitivity analysis to address unmeasured confounding indicate that the current results would be diminished only under extreme assumptions. Potential bias could have been introduced in the interim analyses because no formal rules for stopping the study were prespecified. To avoid bias from this source, the physicians were not informed of the results of the interim analysis that determined the primary outcome; they remained blinded to treatment assignment throughout the study.

The efficacy of currently available drugs (nifurtimox and benznidazole) against *T. cruzi* infection was proven to be limited for patients with chronic-stage infection (45). Experimental studies done on mice infected with *T. cruzi* have shown that the therapeutic efficacy of nifurtimox and benznidazole depends on the source of the parasite strain (46). Thus, our results should be generalized with caution because the susceptibility of *T. cruzi* strains to benznidazole may differ in other populations. Other chemotherapeutic agents, such as allopurinol and itraconazole (29), are being evaluated for the treatment of chronic Chagas disease, but their advantages over benznidazole have not been determined.

In conclusion, benznidazole treatment was associated with a reduced risk for progression of Chagas heart disease and an increased rate of negative seroconversion without serious side effects (47). These observations indicate that a randomized, controlled trial should be performed.

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Congratulations to Jeffrey Levine, MD, winner of the 2005 *Annals* Personae prize. Dr. Levine's photograph was published on the cover of the 5 April 2005 issue (vol. 143, no. 7) and is reprinted below.

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Appendix Table 1. Characteristics of Patients Whose Heart Condition Worsened

Group	Age, y	Sex	New Abnormalities on Electrocardiography	Clinical Group at Admission	Change of Clinical Group	Cause of Death*
Treated						
	30	Female	Left anterior fascicular block	0	I	
	37	Male	Left anterior fascicular block and right bundle-branch block	0	I	
	37	Male	–	0	II	
	42	Male	Left anterior fascicular block	0	I	
	45	Male	Right bundle-branch block	0	I	
	48	Female	Right bundle-branch block	0	I	
	41	Female	–	I	I	Sudden death
	44	Male	–	I	II	
	49	Male	–	I	II	
	40	Male	Atrial fibrillation	II	III	Heart failure
	42	Female	Atrial fibrillation	II	III	
	45	Female	Left anterior fascicular block and right bundle-branch block	II	III	Heart failure
Untreated						
	32	Male	Areas of electric inactivation	0	I	
	33	Female	Atrial flutter	0	I	
	38	Female	Left anterior fascicular block	0	I	
	38	Male	–	0	II	
	39	Female	Sinus bradycardia <50 beats/min	0	I	
	39	Female	Permanent pacemaker	0	II	
	41	Female	Left anterior fascicular block	0	I	
	41	Male	Left anterior fascicular block	0	I	
	44	Male	Sustained ventricular tachycardia	0	I	
	44	Female	Atrial fibrillation	0	I	
	46	Male	Areas of electric inactivation	0	I	
	47	Male	Nonsustained ventricular tachycardia	0	I	
	49	Female	Left anterior fascicular block	0	I	
	31	Female	Left anterior fascicular block	I	III	Heart failure
	35	Male	–	I	II	
	35	Female	Right bundle-branch block	I	II	
	35	Female	Right bundle-branch block	I	I	Sudden death
	36	Male	Sustained ventricular tachycardia	I	II	
	38	Female	–	I	III	Sudden death
	39	Male	–	I	II	
	40	Male	Permanent pacemaker	I	III	Sudden death
	42	Female	–	I	II	
	43	Female	–	I	III	
	44	Male	–	I	II	
	47	Female	Permanent pacemaker	I	III	
	48	Male	–	I	II	
	49	Female	–	I	III	
	33	Male	–	II	III	
	37	Female	–	II	II	Sudden death
	38	Female	Right bundle-branch block and sustained ventricular tachycardia	II	II	Sudden death
	40	Female	Permanent pacemaker	II	II	Sudden death
	41	Male	–	II	II	Sudden death
	42	Female	Sustained ventricular tachycardia	II	III	
	45	Female	Left anterior fascicular block and right bundle-branch block	II	III	
	45	Male	Atrial flutter and sustained ventricular tachycardia	II	II	Sudden death
	46	Female	–	II	III	
	48	Male	–	II	III	
	48	Male	Atrial flutter	II	III	Sudden death
	49	Female	Permanent pacemaker	II	III	Heart failure
	49	Female	Sustained ventricular tachycardia	II	III	Heart failure

* Where applicable.

Appendix Table 2. **Summary of Primary and Secondary Outcomes in Patients without Acute Chagas Disease after 10 Years of Follow-up**

Outcome	Treated Patients, *n/n (%)*	Untreated Patients, *n/n (%)*	Adjusted Hazard Ratio (95% CI)	*P* Value
Change of clinical group	12/283 (4)	40/283 (14)	0.24 (0.10–0.59)	0.002
New electrocardiographic abnormalities*	15/283 (5)	45/283 (16)	0.27 (0.13–0.57)	0.001
3+	130/218 (60)	177/212 (83)	0.55 (0.44–0.70)	<0.001
3−	32/218 (15)	12/212 (6)	2.1 (1.06–4.06)	0.034

* 3+ = persistence of positive results on 3 tests; 3− = negative seroconversion of 3 serologic tests.