ORIGINAL ARTICLE

Randomized Trial of Posaconazole and Benznidazole for Chronic Chagas' Disease

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ABSTRACT

BACKGROUND

Current therapeutic options for Chagas' disease are limited to benznidazole and nifurtimox, which have been associated with low cure rates in the chronic stage of the disease and which have considerable toxicity. Posaconazole has shown trypanocidal activity in murine models.

METHODS

We performed a prospective, randomized clinical trial to assess the efficacy and safety of posaconazole as compared with the efficacy and safety of benznidazole in adults with chronic *Trypanosoma cruzi* infection. We randomly assigned patients to receive posaconazole at a dose of 400 mg twice daily (high-dose posaconazole), posaconazole at a dose of 100 mg twice daily (low-dose posaconazole), or benznidazole at a dose of 150 mg twice daily; all the study drugs were administered for 60 days. We assessed antiparasitic activity by testing for the presence of *T. cruzi* DNA, using real-time polymerase-chain-reaction (rt-PCR) assays, during the treatment period and 10 months after the end of treatment. Posaconazole absorption was assessed on day 14.

RESULTS

The intention-to-treat population included 78 patients. During the treatment period, all the patients tested negative for *T. cruzi* DNA on rt-PCR assay beyond day 14, except for 2 patients in the low-dose posaconazole group who tested positive on day 60. During the follow-up period, in the intention-to-treat analysis, 92% of the patients receiving low-dose posaconazole and 81% receiving high-dose posaconazole, as compared with 38% receiving benznidazole, tested positive for *T. cruzi* DNA on rt-PCR assay ($P<0.01$ for the comparison of the benznidazole group with either posaconazole group); in the per-protocol analysis, 90% of the patients receiving low-dose posaconazole and 80% of those receiving high-dose posaconazole, as compared with 6% receiving benznidazole, tested positive on rt-PCR assay ($P<0.001$ for the comparison of the benznidazole group with either posaconazole group). In the benznidazole group, treatment was discontinued in 5 patients because of severe cutaneous reactions; in the posaconazole groups, 4 patients had aminotransferase levels that were more than 3 times the upper limit of the normal range, but there were no discontinuations of treatment.

CONCLUSIONS

Posaconazole showed antitrypanosomal activity in patients with chronic Chagas' disease. However, significantly more patients in the posaconazole groups than in the benznidazole group had treatment failure during follow-up. (Funded by the Ministry of Health, Spain; CHAGASAZOL ClinicalTrials.gov number, NCT01162967.)

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Chagas' disease, a chronic parasitic infection caused by the protozoan *Trypanosoma cruzi*, is considered to be one of the neglected tropical diseases.[1] Although Chagas' disease was identified more than 100 years ago, current therapeutic options for this condition are limited mainly to benznidazole and nifurtimox. The phase of the disease is one of the factors that determine the success of treatment. Cure rates of 65 to 80% have been documented when treatment is administered in the acute phase of the disease, with rates reaching almost 100% in cases of congenitally acquired infection that is treated during the first years of life.[2] Whereas the therapeutic response is as high as 60% among children at an early chronic stage of the disease,[3,4] cure rates among adults when the disease is in the chronic phase range from 15 to 35%.[5,6] In addition to the low efficacy of current drugs in patients with chronic disease, another major drawback to these drugs is their toxicity profiles, which lead to definitive withdrawal of treatment in 15 to 30% of patients.[2,7]

In light of these problems, safer and more effective therapeutic options for patients with Chagas' disease are clearly needed. Many candidate drugs are currently being tested, but inhibitors of ergosterol synthesis are particularly promising because of their antiprotozoal activity, the stage of development reached, and their safety profile in humans.[8] Posaconazole is an antifungal agent of the triazole class that has been approved for the treatment of invasive fungal infection in humans.[9] Its trypanocidal activity has been assessed in both in vitro and in vivo models. In a murine model of acute Chagas' disease, posaconazole cured up to 90% of animals infected with susceptible and partially susceptible *T. cruzi* strains, whereas only 76% were cured with benznidazole. In the model of chronic Chagas' disease, the differences were even greater: posaconazole was associated with cure rates of up to 60% in animals infected with susceptible and partially susceptible *T. cruzi* strains, whereas none of the animals treated with benznidazole were cured.[10,11]

Given the toxicity and poor therapeutic effectiveness of current treatment options for chronic Chagas' disease, the clinical and microbiologic efficacy of posaconazole as a trypanocidal agent in animal models, and the safety and side-effect profile of posaconazole in persons who received the drug for the treatment of fungal infections, we designed the CHAGASAZOL trial to evaluate the efficacy, safety, and side-effect profile of posaconazole in patients with chronic Chagas' disease.

Methods

Study Design

We conducted the CHAGASAZOL trial, a randomized, open-label clinical trial, at three centers that were participating in the International Health Program of the Catalan Institute of Health (PROSICS), which is the main public health provider in our setting. Patients who met the enrollment criteria were randomly assigned, in a 1:1:1 ratio, to receive oral benznidazole at a dose of 150 mg twice daily, oral posaconazole at a dose of 100 mg twice daily (low-dose posaconazole group), or oral posaconazole at a dose of 400 mg twice daily (high-dose posaconazole group) for 60 days.

Study Oversight

The study protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board at Vall d'Hebron Teaching Hospital, Barcelona. There was no commercial sponsorship of the study. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol. Written informed consent for participation was obtained from all the patients.

Patients

Patients were eligible for participation in the study if they met the following inclusion criteria: an age of 18 years or older, detection of *T. cruzi* on two different serologic tests, and a positive result of a real-time polymerase-chain-reaction (rt-PCR) assay for *T. cruzi* DNA. Exclusion criteria were previous treatment for Chagas' disease, current liver disease, plans for travel during the follow-up period to a country where the disease is endemic (because the patient could be at risk for reinfection), pregnancy, immunosuppression, prolonged QT interval on electrocardiography, and receipt of drugs that could affect the QT interval or interfere with metabolism

For serologic tests, we used two enzyme-linked immunosorbent assays (ELISAs) — one that used recombinant antigen (Bioelisa Chagas, Biokit) and another that used a crude antigen

(*T. cruzi* ELISA, Ortho-Clinical Diagnostics). The QT interval was assessed as the corrected QT interval and as QT dispersion (an approximate measure of a general abnormality of repolarization, calculated as the maximum QT interval minus the minimum QT interval). In all cases, cardiac involvement and gastrointestinal involvement were evaluated with the use of 12-lead electrocardiography, chest radiography, echocardiography, barium enema examination, and esophagography. Cardiac involvement was classified according to the criteria of Kuschnir et al.,[12] and esophagographic findings were assessed according to the classification of de Rezende et al.[13] An abnormal barium enema examination was defined by the presence of a dolichocolon or a sigmoid colon with a diameter of more than 6 cm.[14] Patients who had chronic *T. cruzi* infection but had no clinical, radiologic, or electrocardiographic evidence of visceral involvement were categorized as having an indeterminate form of Chagas' disease.

STUDY INTERVENTIONS

Treatment was started after the patients underwent randomization. Study visits were scheduled at 7, 14, 28, 45, and 60 days after the initiation of treatment. Patients were weighed and measured at each visit, and electrocardiography, blood tests for cell counts and general biochemical values, and rt-PCR testing for detection of *T. cruzi* DNA were performed. *T. cruzi* serologic testing was performed at baseline, 6 months after the completion of treatment, and at the end of the follow-up period. Adherence to treatment and adverse events were evaluated at each visit. Patients receiving posaconazole were asked whether they had eaten fatty meals with the drug, as instructed, to improve absorption.

Patients were followed for 40 weeks after the end of the treatment period. An rt-PCR assay for *T. cruzi* DNA was performed at 8, 16, 24, and 40 weeks after the end of the treatment period. Additional details regarding the methods are provided in the Supplementary Appendix (available at NEJM.org).

A pharmacokinetic analysis of posaconazole was performed in all patients on day 14 of treatment (when the steady-state level of the drug is reached) and in 10 randomly selected patients at the end of the treatment period to determine drug exposure and to confirm adherence. Serum posaconazole concentrations were measured with the use of a validated high-performance liquid chromatography method.[15]

PCR PROCEDURE

With the use of a commercial kit (NucliSENS easyMAG, bioMérieux), DNA was extracted from 200 μl of blood diluted at a 1:1 ratio with 6 M guanidine hydrochloride (Sigma Aldrich) and eluted in 50 μl. Amplification was performed in duplicate, according to a method described previously.[16] A sample was considered to be positive when the cycle threshold of both amplifications was less than 40 and negative when the cycle threshold of both amplifications was higher than 45. If the results of amplifications were discordant or cycle thresholds were between 40 and 45, amplifications were repeated and were considered to be positive when at least one cycle threshold result was less than 40. Four panels were prepared at an external reference laboratory (INGEBI [Instituto de Investigaciones en Ingeniería Genética y Biología Molecular]-CONICET [Consejo Nacional de Investigaciones Científicas y Técnicas]) in Argentina to validate the rt-PCR results.

END POINTS

The primary end point of the study was consistently negative results for detection of *T. cruzi* DNA on rt-PCR assays over the entire follow-up period. Secondary end points were the percentage of patients who discontinued treatment because of adverse events and the incidence of serologic conversion from positive to negative or any variation in the absorption index (the amount of light that is absorbed by the serum, as compared with a standard control) on serologic ELISA, indicating some treatment activity at the end of the follow-up period.

The intention-to-treat analysis included all patients who underwent randomization. Patients who were lost to follow-up, those who dropped out owing to adverse events, and those who had positive results on an rt-PCR assay at any time after the completion of treatment were considered to have had treatment failure. The per-protocol analysis included patients who completed treatment and follow-up (patients lost to follow-up were excluded unless rt-PCR testing after treatment was positive). Patients were considered to have had treatment failure if even one result on an rt-PCR assay was positive at any time during the follow-up period.

STATISTICAL ANALYSIS

Descriptive results are presented as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. Differences between groups in baseline values were analyzed with the use of Fisher's exact test for categorical variables and analysis of variance for continuous variables. P values for the between-group differences in the proportion of patients meeting the criteria for the primary end point were adjusted with the use of the Holm method to account for multiple testing. Two-tailed P values of less than 0.05 were considered to indicate statistical significance. We analyzed the time to a positive test result using methods that were suitable for interval-censored data.[17] Analyses were performed with the use of SAS software, version 9.2 (SAS Institute), and the R statistical package.[18]

Owing to the lack of information on the efficacy of benznidazole as measured by rt-PCR, we estimated that the rate of negative results on *T. cruzi* DNA testing at the end of follow-up would be the same (60%) in each treatment group. On the basis of this estimate, we calculated that we would have to enroll 26 patients in each treatment group for the study to have 80% power, at an alpha-error level of 0.10, assuming a dropout rate of 10%.

RESULTS

PATIENTS

From September 2010 through August 2011, a total of 79 patients underwent randomization (Fig. 1). A randomization error occurred in the case of 1 patient, who was withdrawn from the trial. Of the remaining 78 patients, 47 were women and 31 were men; the country of origin of 75 of the 78 patients was Bolivia. The mean (±SD) age of the patients was 39±9 years. A total of 51 of the patients (65%) were classified as having an indeterminate form of Chagas' disease, 17 (22%) as having cardiac involvement, 5 (6%) as having gastrointestinal involvement, and 5 (6%) as having involvement of more than one organ system

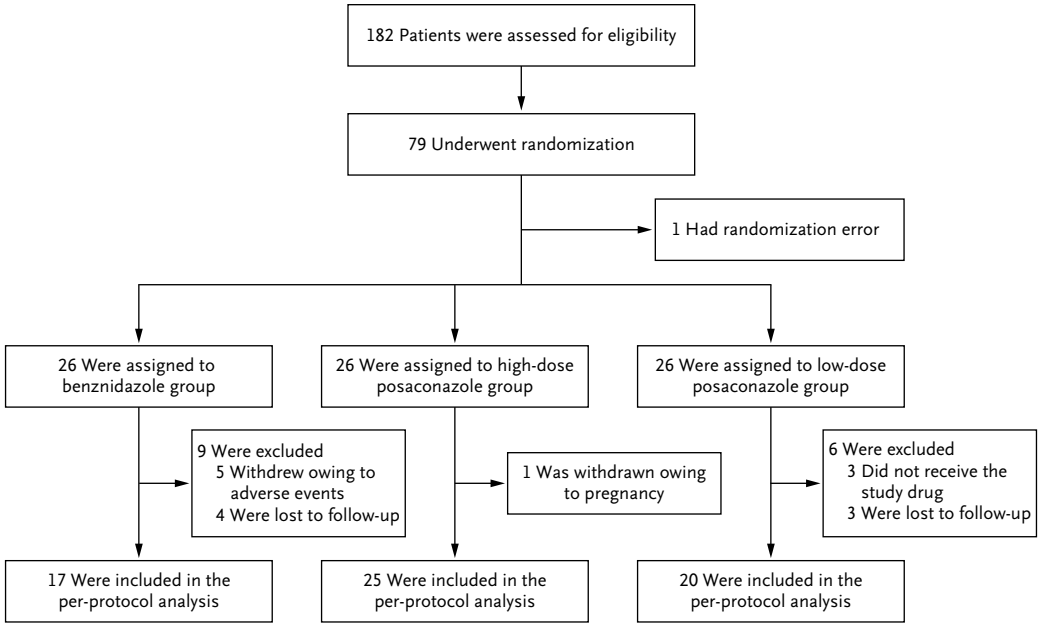

Figure 1. Screening, Randomization, and Follow-up.

The single patient for whom a randomization error occurred had a negative result of a real-time polymerase-chain-reaction (rt-PCR) assay for *Trypanosoma cruzi* DNA; this patient was excluded from the study. The pregnant patient had a positive result on an rt-PCR assay at the time the investigators became aware of her pregnancy; she was excluded from the per-protocol analysis.

(mixed form). The baseline clinical characteristics were well balanced among the treatment groups (Table 1). Three patients who were randomly assigned to the low-dose posaconazole group did not receive any dose of the drug; 5 patients in the benznidazole group did not complete treatment owing to adverse events. A total of 7 patients were lost to follow-up (3 in the low-dose posaconazole group and 4 in the benznidazole group). One patient in the high-dose posaconazole group became pregnant during the treatment period. Once the investigators became aware of the pregnancy, the patient was withdrawn from the study; she was considered in the intention-to-treat analysis as having had treatment failure. The patient gave birth to a healthy girl.

Table 1. Baseline Demographic and Clinical Characteristics.*

Characteristic	Benznidazole (N=26)	High-Dose Posaconazole (N=26)	Low-Dose Posaconazole (N=26)
Female sex — no. (%)	15 (58)	16 (62)	16 (62)
Country — no. (%)			
Bolivia	24 (92)	25 (96)	26 (100)
Brazil	1 (4)	0	0
Paraguay	1 (4)	1 (4)	0
Age — yr	40±9	37±9	39±10
Abnormal electrocardiogram — no. (%)†	9 (35)	3 (12)	8 (31)
Cardiothoracic index >0.5 on chest radiography — no. (%)‡	0	2 (8)	1 (4)
Score on Kuschnir scale — no. (%)§			
0	17 (65)	22 (85)	18 (69)
1	9 (35)	2 (8)	7 (27)
2	0	2 (8)	1 (4)
Results of barium enema examination — no. (%)¶			
Normal	23 (88)	24 (92)	21 (81)
Megacolon or abnormally wide sigmoid colon	0	0	1 (4)
Dolichocolon or abnormally long sigmoid colon	3 (12)	2 (8)	4 (15)
Normal esophagogram — no. (%)	26 (100)	26 (100)	26 (100)
Clinical involvement — no. (%)			
Indeterminate	15 (58)	21 (81)	15 (58)
Cardiac	8 (31)	3 (12)	6 (23)
Gastrointestinal	1 (4)	1 (4)	3 (12)
Mixed	2 (8)	1 (4)	2 (8)

* Plus–minus values are means ±SD. There were no significant between-group differences in any of the baseline characteristics ($P>0.05$).

† All the abnormalities that were found, except for one, were considered to be clinically nonrelevant or unrelated to Chagas' disease. The most common abnormalities were complete right bundle-branch block, left anterior fascicular block, sinus bradycardia, and first-degree atrioventricular block. One patient had undergone pacemaker implantation 7 years previously owing to a complete atrioventricular block.

‡ The cardiothoracic index is calculated according to the following formula: (MRD + MLD) ÷ ID, where MRD denotes the greatest perpendicular diameter from midline to the right heart border, MLD denotes the greatest perpendicular diameter from midline to the left heart border, and ID denotes the internal diameter of the chest at the level of the right hemidiaphragm. The normal range is 0.05 or less.

§ The Kuschnir scale measures clinical cardiac involvement in Chagas' disease. A score of 0 indicates reactive serum and a normal electrocardiogram and chest radiograph; a score of 1, reactive serum, an abnormal electrocardiogram, and a normal chest radiograph; a score of 2, reactive serum, a chest radiograph showing cardiac enlargement, and no radiologic or clinical signs of heart failure; and a score of 3, heart failure.

¶ Findings on the barium enema examination were assessed according to the classification of Ximenes.[14]

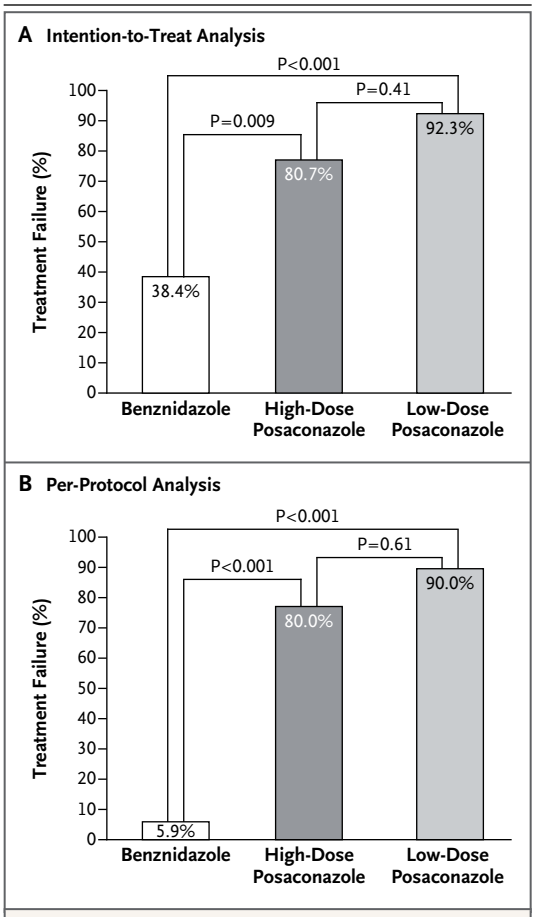

Figure 2. Efficacy End Points.

The intention-to-treat analysis included all patients who underwent randomization; the per-protocol analysis included patients who completed treatment and follow-up. Patients who were lost to follow-up were excluded from the per-protocol analysis unless rt-PCR testing after the end of the treatment period was positive.

PRIMARY END POINT

From the end of the treatment period to the end of the follow-up period, consistently negative rt-PCR results were documented in 16 patients in the benznidazole group, 2 in the low-dose posaconazole group, and 5 in the high-dose posaconazole group. One patient in the benznidazole group had a single positive rt-PCR result during the follow-up period (cycle threshold, 39.9, with a threshold of 40 for a positive result). There was no significant difference between the two posaconazole groups in the percentage of patients who were positive for *T. cruzi* DNA on rt-PCR testing. In the intention-to-treat analysis, 92% of the patients in the low-dose posaconazole group and 81% in the high-dose posaconazole group, as compared with 38% in the benznidazole group, tested positive on rt-PCR during the follow-up period. Differences between the groups were more marked in the per-protocol analysis (Fig. 2).

During the treatment period, rt-PCR assays for *T. cruzi* were negative in all the patients after day 14. Detection of parasite DNA began again at the end of the treatment period, on day 60, with positive rt-PCR results in two patients, both of whom were in the low-dose posaconazole group. The time to treatment failure is shown in Figure 3.

SECONDARY END POINTS

There were no significant differences in the absorption indexes on serologic tests performed at the end of the follow-up period as compared with those performed at the beginning of the study. The most common treatment-related adverse events are shown in Table 2. Treatment had to be withdrawn in five patients — all in the benznidazole group — because of serious adverse events. Five of these patients had severe allergic dermatitis, one of whom had anaphylaxis with angioedema. As was expected, dysgeusia and leukopenia (clinically nonrelevant) were recorded only in the benznidazole group, and cutaneous reactions (rash and pruritus) occurred more frequently with benznidazole than with posaconazole. No serious adverse events were reported in the posaconazole groups.

Elevated aminotransferase and alkaline phosphatase levels were recorded in both the benznidazole group and the two posaconazole groups, but the greatest increases were documented in the high-dose posaconazole group. Nevertheless, the increases were not large enough to require an interruption in treatment.

In the pharmacokinetic study, the mean posaconazole serum concentration was 0.909±0.384 μg per milliliter in the low-dose posaconazole group, with an average area under the concentration–time curve from 0 to 24 hours ($AUC_{0\text{-}24}$) of 20.656±8.809 μg per milliliter per hour, and 1.666±0.935 μg per milliliter in the high-dose posaconazole group, with an average $AUC_{0\text{-}24}$ of 42.202±22.840 μg per milliliter per hour. Patients' age, weight, sex, body-mass index, and body-surface area had no significant effect on posaconazole exposure. Neither posaconazole nor benznidazole had a significant effect on the QT interval.

DISCUSSION

A safe, effective treatment for Chagas' disease in the chronic phase has been elusive. The currently available options for treating *T. cruzi* infection, benznidazole and nifurtimox, have shown limited efficacy in the treatment of late stages of the disease and have an unfavorable side-effect profile. Several clinical trials, mainly observational studies, have been conducted to assess the efficacy of these treatments in the chronic phase of Chagas' disease, which is the phase in which most patients with this condition receive the diagnosis.[3-6,19-26] Although the results seem to point to a beneficial effect, a meta-analysis of studies focused on benznidazole concluded that the efficacy of this drug in the late chronic stage of infection is doubtful.[27] However, because of the potential clinical benefit in preventing cardiomyopathy associated with Chagas' disease, these treatments are typically offered to patients younger than 50 years of age who do not have advanced myocardial involvement.[28-30] Nonetheless, there is an unquestionable need for new treatments for *T. cruzi* infection.

In this clinical trial, we tested a new drug, posaconazole, for the treatment of chronic Chagas' disease. Unfortunately, posaconazole did not show efficacy for this purpose, as evidenced by the finding that most of the patients treated with the drug tested positive for *T. cruzi* DNA on follow-up rt-PCR assays. One of the limitations of clinical trials that attempt to evaluate the efficacy of trypanocidal drugs in chronic Chagas' disease is that there is no definitive test to determine cure. For this reason, surrogate markers such as detection of *T. cruzi* DNA are used. Taking into account the kinetic characteristics of the parasite, a PCR assay appears to be the most sensitive and feasible technique for this purpose, despite the constraints inherent in the assay. In our study, we did not use the PCR results as a measure of efficacy or cure but used them only as a marker of treatment failure. A negative PCR result may be indicative only of the absence of circulating DNA at the moment when blood is drawn for testing.

Posaconazole has shown considerable activity in murine models of acute and chronic Chagas' disease,[10,11] and this effect was expected to be reproducible in humans; unfortunately, however, only suppressive activity was shown. There is only one reported case of Chagas' disease successfully treated with posaconazole, but this case was a reactivation of chronic disease.[31]

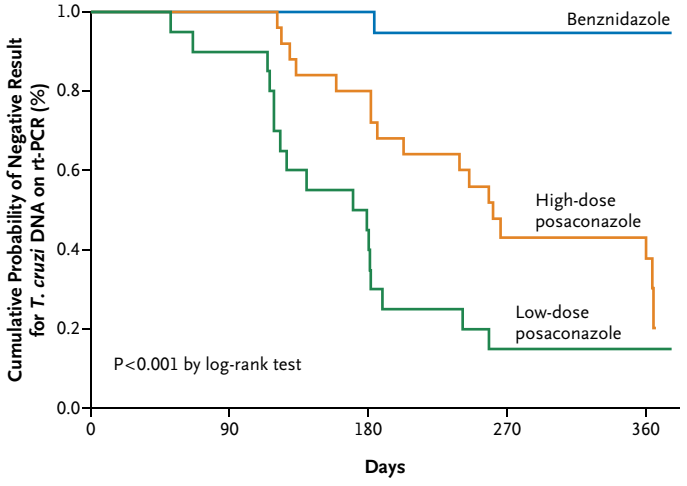

Figure 3. Time to Treatment Failure.

During the 60-day treatment period, all the patients in the three study groups had negative results for *T. cruzi* DNA on rt-PCR testing beyond day 14 of therapy. Two patients in the low-dose posaconazole group had positive results on day 60. Treatment failure occurred at a significantly earlier time in patients treated with low-dose posaconazole than in those receiving the higher dose.

Beyond the second week of treatment, *T. cruzi* DNA was undetectable in the blood of all the patients, even those who were receiving the lower posaconazole dose, thus indicating the suppressive activity of this drug. This effect was sustained until the end of the treatment period, except in two patients who were receiving low doses. Therefore, despite the unfavorable final outcome of this treatment in our study, it is possible that ergosterol inhibitors could be useful as a partner drug in future combination therapies.

In murine models, the dose of posaconazole was directly related to the efficacy of the drug. The high-dose posaconazole regimen in our study was chosen to provide the highest exposure approved in humans.[32] Since the cost of the drug might be an important restriction to its use, we included another group that received a lower dose of the drug. It is known that the effective dose in rodents is at least 10 times as high as that required in humans.[33] Hence, we included a low-dose posaconazole group that received an experimental, reduced dose. Although the dose might have had an effect on the re-

Table 2. Adverse Events and QT Interval According to Treatment Group.*

Adverse Event or QT Interval	Benznidazole (N=26)	High-Dose Posaconazole (N=26)	Low-Dose Posaconazole (N=26)
Cutaneous reaction — no. (%)	16 (62)	5 (19)	4 (15)
Gastrointestinal symptom — no. (%)	7 (27)	4 (15)	3 (12)
Dysgeusia — no. (%)	2 (8)	0	0
Mucosal dryness — no. (%)	0	3 (12)	2 (8)
General symptom — no. (%)			
Headache	10 (38)	2 (8)	1 (4)
Asthenia	2 (8)	0	1 (4)
Sleepiness	4 (15)	0	2 (8)
Arthralgia	4 (15)	0	0
Dizziness	3 (12)	0	0
Laboratory abnormality — no. (%)†			
Leukopenia	3 (12)	0	0
Increase in alanine aminotransferase			
>1.5–3× ULN	2 (8)	8 (31)	6 (23)
>3–5× ULN	3 (12)	2 (8)	0
>5× ULN	0	2 (8)‡	0
Increase in aspartate aminotransferase			
>1.5–3× ULN	3 (12)	7 (27)	4 (15)
>3–5× ULN	0	1 (4)	0
>5× ULN	0	1 (4)‡	0
Increase in alkaline phosphatase >1–2.5× ULN	13 (50)	19 (73)	11 (42)
Increase in γ-glutamyltransferase >1–2.5× ULN	0	3 (12)	1 (4)
QT interval — msec			
Maximum	3.5±9.46	5.23±6.54	2.26±4.75
Change in dispersion§	−0.73±10.15	1.85±4.85	−0.13±7.07

* Plus–minus values are means ±SD. Adverse events were coded according to the Common Terminology Criteria for Adverse Events, version 4.03.
† Results were interpreted according to local standards. All variables returned to normal limits once the treatment period was over.
‡ The increase in the aminotransferase level was detected at the end of the treatment period and normalized thereafter.
§ The change was calculated as the QT dispersion on the last treatment day minus the baseline QT dispersion.

sponse to the drug, there were no significant differences in efficacy between the two posaconazole groups.

Posaconazole exposure may be greatly altered by fat intake.[34] Therefore, a pharmacokinetic study was included to ensure that the drug was taken and absorbed properly. Serum concentrations on day 14 and at the end of the treatment period in all the patients who were receiving posaconazole were in a range similar to the reported therapeutic range for the treatment of fungal infections in humans.[32] Nonetheless, posaconazole did not meet our expectations, even with the maximum dose approved in humans and proper adherence to the regimen. One possible explanation for this difference in response may be related to the murine model in which the drug has been evaluated and to the characteristics of the parasite. It is likely that the murine model represents the early chronic stage of the disease, when the response of the drugs could be overestimated. It has been suggested

that in the late chronic stage of Chagas' disease, *T. cruzi* may have a quiescent amastigote form, against which ergosterol inhibitors could be less effective.[35]

In contrast to posaconazole, benznidazole showed sustained trypanocidal activity; among the 17 patients included in the per-protocol analysis, all patients except one had rt-PCR findings that were consistently negative until the end of follow-up. The single patient with a non-negative finding had one positive result out of four at month 6 (cycle threshold, 39.9, with a threshold of 40 for a positive result). All the results of rt-PCR testing before and after that were negative, but the patient was considered to have had treatment failure according to the study protocol.

There were several differences between the posaconazole and benznidazole groups with respect to the side-effect and toxicity profile of the drug. Five patients had to discontinue benznidazole because of adverse events (allergic dermatitis), whereas no serious adverse events were reported in the posaconazole groups. Nonetheless, patients receiving posaconazole had a greater likelihood of a relevant increase in aminotransferase and alkaline phosphatase levels, although treatment interruption was not required in any case.

In conclusion, in patients with chronic Chagas' disease, treatment with low-dose or high-dose posaconazole resulted in a significantly larger percentage of treatment failures than did treatment with benznidazole, which is the current standard of care.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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