MAJOR ARTICLE

Tolerance and Safety of Nifurtimox in Patients with Chronic Chagas Disease

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Background. Nifurtimox has been used to treat Chagas disease for 40 years, but tolerance and safety data in adults are scarce. We aimed to evaluate nifurtimox tolerance and safety in a cohort of *Trypanosoma cruzi*–infected adult patients in a country of nonendemicity.

Methods. This observational study included all consecutive adults patients who were given a diagnosis of *T. cruzi* infection from June through December 2008. Eligible patients received nifurtimox at 10 mg/kg/day for 60 days, with regular medical and biological follow-up. Adverse events (AEs) were recorded according to Common Terminology Criteria for Adverse Events, version 3.0.

Results. Eighty-one patients received nifurtimox. Eight were lost to follow-up during treatment, and 41 (56.2%) completed the 60-day course. All premature treatment terminations were caused by AEs; 97.5% of patients suffered from AEs, mostly expected (90.5%) and not severe. Gastrointestinal symptoms predominated. Six (7.4%) patients presented with a suspected unexpected serious adverse reaction: drug reaction with eosinophilia and systemic symptoms ($n = 3$), Quincke edema ($n = 1$), acute myocarditis ($n = 1$), and anaphylaxis ($n = 1$). Patients with 3 or more AEs had an increased risk of premature treatment termination (hazard ratio, 8.42; 95% confidence interval, 1.6–45.5).

Conclusion. Nifurtimox is poorly tolerated among adults with chronic Chagas disease, resulting in a low treatment completion rate. Considering the significant risk of serious AEs, close monitoring is required, which may be difficult to implement in poor rural areas of countries of endemicity. The safety and efficacy of nifurtimox and benznidazole should be compared to improve current therapeutic recommendations, and pharmacovigilance systems should be enhanced.

Chagas disease, a protozoan zoonosis caused by *Trypanosoma cruzi*, is endemic in 21 North, Central, and South American countries, where it affects 8–10 million persons [1]. Its distribution is rapidly changing, as millions of person at risk have recently moved to areas of nonendemicity in Europe, North America, Japan, and the West Pacific region [2]. Most affected persons outside areas of endemicity are adults in the indeterminate phase of the chronic stage [3]. A substantial proportion of them are at risk of developing cardomyopathy, digestive megasyndromes, or both, with a potentially severe outcome [4].

Until recently, treatment indications were restricted to acute (including reactivation) and early latent infections, with cure rates reaching 60%–90%, as assessed by parasitological and immunological responses [4, 5]. Two recent studies of chronically infected adults showed a reduction in the rate of progression toward advanced cardiopathy in patients treated with antiparasitic drugs, compared with untreated patients [6, 7]. The renewed interest in parasite persistence as a pivotal mechanism of chronic myocardial damage has also reinforced the importance of eliminating *T. cruzi* [8, 9]. Recent consensus treatment recommendations have therefore proposed treatment for adults at the chronic stage, even in the case of mild to moderate organ damage [10]. The expected benefits of antiparasitic treatment include a reduction in the incidence of chronic complications and a decrease in *T. cruzi* transmission, both congenital and by blood or organ donation.

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Currently, 2 antiparasitic drugs are recommended for treating *T. cruzi* infection: nifurtimox and benznidazole. Nifurtimox, a 5-nitrofuran derivative, is also used in combination with eflornithine to treat human African trypanosomiasis [11]. Because of the absence of strong scientific evidence, nifurtimox treatment regimens vary among countries and authors. Today, a 60-day course of 10 mg/kg/day is most frequently used, but some recommendations propose a course of up to 120 days [12]. Presently, nifurtimox efficacy data among different groups of patients with different *T. cruzi* strains remain scarce [13, 14]. In addition, data on safety and tolerance profiles in adults are still lacunar [13, 14]. Therefore, given that the evaluation of the risk-benefit ratio cannot be based on sufficient evidence, clinicians face difficulties in deciding whether to treat individual patients [13]. This is preoccupying, because a high proportion of *T. cruzi*–infected patients are eligible to receive treatment according to recent recommendations [8, 10]. To provide evidence and help strengthen guidelines, we aimed to describe the tolerance and safety of nifurtimox in a cohort of adult patients with chronic Chagas disease.

METHODS

Setting. This observational study was nested in a cohort study of Chagas disease conducted among Latin American migrants living in Geneva, Switzerland. It was conducted at the Geneva University Hospitals from June 2008 through July 2009 [15].

Participants and procedures. Participants were >16 years old and had been given a diagnosis of Chagas disease on the basis of 2 positive serological test results (ELISA Cruzi [bioMérieux] and Bioelisa Chagas [Biokit]). All patients were contacted by phone and invited to undergo medical evaluation to determine the stage of disease, in accordance with a procedure described elsewhere [15], and potential contraindications to treatment. Patients eligible for treatment received extensive information and, on acceptance, were treated with nifurtimox (Lampit; Corporación Bonima, Bayer) at 10 mg/kg/day divided into 3 doses for 60 days. Individual packages (100 tablets) were given one by one at the initial and during follow-up visits. Drugs were donated by the World Health Organization. Patients received a document in Spanish or Portuguese describing the daily dosage of nifurtimox, the dates of follow-up visits, and the phone numbers of the physician in charge.

Absolute contraindications to nifurtimox were previous anti–*T. cruzi* treatment, clinically significant psychiatric disorder (eg, moderate to severe depression, severe anxiety, and psychosis), peripheral neuropathy, epilepsy, pregnancy, hepatic or renal failure, and inability to attend follow-up visits. Age >50 years was a relative contraindication subject to case-by-case evaluation. Follow-up visits included clinical and biological evaluations (complete blood count, liver function tests, and determination of serum creatinine level) on days 7, 21, and 60. In the case of suboptimal adherence, duration of treatment was extended to make up for the missed pills. In the case of absence at a follow-up visit, patients were contacted on their mobile phones or by mail. Patients were encouraged to contact the investigators in the case of a medical problem at any time during the treatment course. When necessary, decisions regarding temporary or definitive treatment interruption were made jointly with the investigators. The study was approved by the Ethics Committee of the Geneva University Hospitals in January 2008.

Data collection. At each visit, patients were questioned on the occurrence of expected adverse reactions to nifurtimox (by checklist). The investigators also recorded other (unexpected) events spontaneously reported by the patients. Both expected and unexpected adverse events (AEs) were recorded on a case report form and graded according to Common Terminology Criteria for Adverse Events, version 3 (2006). The timing of occurrence and the duration of the event were also recorded on the case report form. Suspected unexpected serious adverse reactions (SUSARs) and serious AEs were reported to the national pharmacovigilance system. In the case of persistant symptoms reported at the end-of-treatment visit, follow-up was extended until the disappearance of symptoms. During the end-of-treatment visit, adherence to treatment was assessed by counting the remaining pills from the original packages given to the patient. In the case of premature treatment interruption, counting was compared with the expected pill consumption until the day of interruption.

Statistical methods. Results were presented with means and confidence intervals (CIs) or standard deviations for normally distributed variables or medians and interquartile ranges for skewed variables. Continuous variables were compared with the Student t test. Categorical variables were compared with χ^2 test or the Fisher exact test, as appropriate.

The risk of premature treatment termination with the number of days of treatment was analyzed by the Kaplan-Meier method. Patients without an identified date of treatment termination ($n = 8$) were not included in the logistic and survival analyses. The number of AEs as a risk factor for premature treatment termination was also analyzed using a time-dependent Cox model. The significance level was $P < .05$.

RESULTS

Of 130 patients with Chagas disease eligible to participate in the study, 124 completed medical evaluation. Their sociodemographic and clinical characteristics are presented in Table 1. All but one patient resided in Switzerland without a residency permit or health insurance (undocumented). After medical evaluation, 81 (65.3%) of 124 patients were deemed to be eligible for nifurtimox treatment (Table 1 and Figure 1).

AEs. A total of 535 AEs were recorded for 79 of the 81

Table 1. Demographic and Clinical Characteristics of *Trypanosoma cruzi*–Infected Patients and Patients Treated with Nifurtimox in Geneva, Switzerland

Characteristic	Patients with *T. cruzi* infection (n = 124)	Patients treated with nifurtimox (n = 81)
Female	107 (86.3)	66 (81.5)
Age, median years (range)	41 (17–70)	39 (17–58)
Bolivian	120 (96.8)	79 (97.5)
Disease stage		
Indeterminate form	109 (87.9)	68 (84)
Cardiopathy	14 (11.3)	12 (14.8)
Digestive tract involvement	1 (0.8)	1 (1.2)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

patients. The 2 patients without AEs were lost to follow-up early during the treatment course. Most AEs (n = 484; 90.5%) were expected, occurred early during the treatment course, and were mild or moderate (Table 2). The majority of expected AEs were digestive (n = 170; 35.1%), neurological (n = 133; 27.5%), constitutional (n = 100; 20.7%), musculoskeletal (n = 51; 10.5%), or dermatological (n = 33; 6.8%). Unexpected nonsevere AEs included fever (n = 13), loss of short-term memory (n = 11), dyspnea or tachypnea (n = 7), and edema (n = 6). SUSARs occurred in 6 patients (7.4%): drug reaction with eosinophilia and systemic symptoms (DRESS) (n = 3), acute myocarditis (n = 1), Quincke edema (n = 1), and grade 3 anaphylaxis reaction (n = 1) (Table 3). Nifurtimox was interrupted or terminated in the 6 patients with SUSARs, and they recovered without sequelae.

Weight loss. Weight measurements were available before and at completion of treatment in 62 patients. Fifty-two (83.9%) patients lost weight during treatment; the mean loss was 2.1 kg (95% CI, 1.6–2.6 kg).

Biological analysis. Hematological, liver, and renal function test results remained within normal ranges on days 7, 21, and 60 of treatment in all patients, except in the 6 with SUSARs.

Adherence to treatment. Pill counting was possible in 48 (59.3%) of 81 patients. Full adherence to prescribed treatment was found in 44 (92.1%) patients. Adherence was significantly higher in patients who completed the 60-day treatment course (97.6%) than in patients who terminated treatment before day 60 (78.6%) (P = .03).

Treatment duration and causes of interruption. Among the 81 patients who started treatment, 8 (9.9%) were lost to follow-up. The date of treatment termination was not available for these 8 patients, whose demographic and clinical characteristics did not statistically differ from those of the 73 patients with known treatment duration (data not shown). Thirty-two (43.8%) of the 73 patients did not complete the full 60-day treatment course (Table 4). On average, premature treatment termination occurred on day 14 (95% CI, 10.2–17.8 days) (Figure 2) and was caused by AEs in all cases. The following AEs were found to be associated with the risk of premature treatment termination in the univariate analysis (P < .10): pruritus, asthenia, neuropathy, dyspnoea, headache, myalgia, and rash. The risk significantly increased in the presence of 3 and more of these AEs (hazard ratio [HR], 8.4; 95% CI, 1.6–45.5; P = .01) but not in presence of 1 AE (HR, 0.4; 95% CI, 0.04–5.0; P = .51) or 2 AEs (HR, 0.6; 95% CI, 0.1–7.3; P = .72). In addition, temporary treatment interruption and reduction of drug daily doses were common (28.8% and 17.8%, respectively).

DISCUSSION

This study shows that nifurtimox treatment in adult Latin American migrants infected with *T. cruzi* is poorly tolerated and is associated with a significant risk of serious AEs. Nifurtimox was administered at the usual dose and for the recommended duration in ambulatory care. Only 56.2% patients completed the full 60-day course, and 28.8% did not tolerate treatment for >30 days. Although most AEs were graded as mild or moderate, the majority of patients endured several AEs concomittantly, which contributed to the high rate of premature treatment termination. A substantial proportion of patients experienced treatment interruption or needed dose reduction at some point. Most AEs occurred early during the treatment course, suggesting that most AEs with nifurtimox do not depend on cumulative doses. Digestive symptoms were the most frequent, whereas neurological symptoms were the most persistant. Because most AEs were mild in intensity, symptomatic treatment was prescribed. When AEs were more severe, nifurtimox dose was temporarily reduced or the drug was suspended until the patient recovered with the appropriate treatment.

Even after 40 years of use, published data on nifurtimox

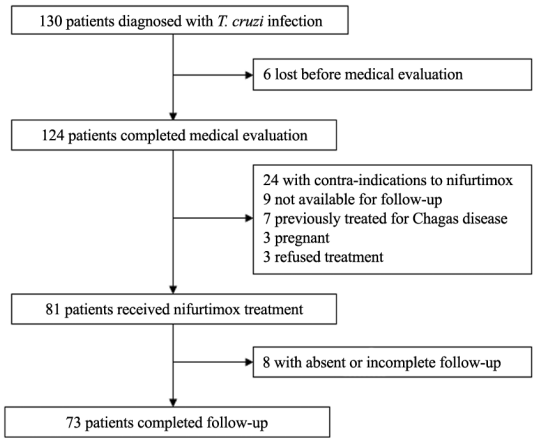

Figure 1. Flow diagram of the study participants.

Table 2. Description of Expected Adverse Events among 81 *Trypanosoma cruzi*–Infected Patients Treated with Nifurtimox in Geneva, Switzerland

Adverse event	Frequency, no. (%)	Grade of severity,[a] %				Time of onset, median days (IQR)	Duration of illness, median days (IQR)
		1	2	3	4		
Gastrointestinal							
Anorexia	59 (74.7)	89.8	10.2	0	0	9 (2–13)	42 (17.5–62.5)
Nausea	44 (54.3)	81.4	11.6	4.7	2.3	3 (1–9)	14 (3–47)
Abdominal pain	32 (39.5)	87.1	3.2	6.5	3.2	8.5 (2–18)	7 (2–15)
Vomiting	21 (25.9)	76.2	14.3	9.5	0	11 (3–29)	2 (1.5–16.5)
Diarrhea	14 (17.2)	85.7	7.2	0	7.1	11 (5.5–19.5)	3 (1–11)
Neurological							
Headaches	59 (72.8)	69.5	23.7	6.8	0	4 (1–11)	13 (6–30)
Mood alteration	40 (49.4)	91.9	8.1	0	0	7 (2–23)	25 (17–58)
Dizziness	27 (33.3)	69.2	15.4	15.4	0	6 (1–12)	6 (25–12.5)
Sensitive neuropathy	4 (4.9)	100	0	0	0	44 (18–52)	26.50 (7.5- 52.5)
Constitutional							
Fatigue	56 (69.1)	78.6	14.3	7.1	0	8 (2–15)	23 (8–51)
Insomnia	44 (54.3)	95.5	4.5	0	0	5 (2–20)	33 (11- 59)
Musculoskeletal							
Arthralgia	27 (33.3)	84.6	7.7	7.7	0	11 (5.5–15.5)	4.5 (2–10)
Myalgia	24 (29.6)	75.0	16.7	8.3	0	11 (8–22)	5 (3–11)
Dermatological							
Prurit	19 (23.5)	76.5	23.5	0	0	6 (3–17)	7.5 (2–23)
Rash	14 (17.2)	61.5	23.1	15.4	0	9 (5.5–13.5)	4 (1–6)

NOTE. IQR, interquartile range.

[a] Severity was graded from 1 (mild) to 5 (fatal), according to Common Terminology Criteria for Adverse Events, version 3.0.

safety and tolerance in adults are scarce. In Brazil, Coura et al [14] reported a 29.9% rate of premature treatment termination due to AEs among 27 adults treated with low-dose nifurtimox (5 mg/kg/day) for 30 days. The most frequent AEs were digestive, neurologic, and psychiatric. Levi et al [16] administered nifurtimox at various doses (5–17 mg/kg/day) for up to 120 days in 8 patients and reported premature treatment termination in six (75%) patients because of severe AEs (nausea, vomiting, weight loss, neuropathy, and psychiatric disturbance). No data are available from other countries—in particular Bolivia, where benznidazole has been most frequently used. Some investigators mention that tolerance to nifurtimox varies between ethnic and age groups and that children appear to tolerate it better than adults [17, 18]. In our adult cohort, age was not associated with premature treatment termination.

Of concern, six (7.4%) patients suffered from nonfatal SUSARs. DRESS, Quincke edema, myocarditis, and grade 3 anaphylaxis reactions are described in relation with nifurtimox for the first time, to our knowledge. DRESS, which has been described mostly with aromatic anticonvulsivants and sulphonamides, usually begins 2–6 weeks after treatment initiation but may also occur after treatment discontinuation, which happened with one of our patients [21]. The case of myocarditis occurred in a previously healthy young woman who did not have previous evidence of chagasic chronic cardiopathy. In the absence of a proven alternative etiology and endomyocardial biopsy, direct myocardial nifurtimox toxicity was only considered as a possible cause. A possible explanation could be an acute intramyocardial inflammatory reaction secondary to parasitic antigen release. More studies are needed to assess the potential myocardial toxicity of nifurtimox in *T. cruzi*–infected patients. Two patients with no history of allergy suffered from severe allergic reactions (Quicke edema and grade 3 anaphylaxis) within the first 2 weeks of treatment. In the absence of concomitant exposition to any other significant allergens, nifurtimox was considered the most probable cause of these reactions.

Rassi et al [22] reported the use of a combination of nifurtimox and betametasone. Steroids were intended to increase *T. cruzi* parasitemia and thus enhance nifurtimox efficacy. The authors did not report better treatment tolerance in patients receiving steroids. Therefore, considering the nonimmunoallergic etiology of most AEs, we do not support the general use of prophylactic corticosteroids to improve nifurtimox tolerance. The systematic addition of antihistaminic drugs to prevent nifurtimox related AEs has not been evaluated, to our knowledge.

When considering the high rate of transient or definitive treatment interruption, the social condition of our patients should probably be taken into account. Almost all were un-

Table 3. Description of Suspected Unexpected Serious Adverse Reactions (SUSARs) during Nifurtimox Treatment ($n = 6$)

Patient sex (age in years)—MH	SUSAR	Clinical description	Day of onset	Outcome
Female (27)—healthy, no allergy, no treatment	Myocarditis	Febrile chest pain, negative T waves, elevated serum troponine I level, normal echocardiogram and 24-h holter recording results, negative viral serological and anti–nuclear factor results	10	Recovered with NSAIDs; second-line treatment with benznidazole interrupted at day 3 because of pruritic generalized maculopapular rash
Male (31)—healthy, no allergy, no treatment	DRESS	Febrile generalized maculopapular rash, adenopathies, blood eosinophilia, elevated liver enzyme levels, negative viral serological results	63[a]	Recovered with high-dose OCS
Female (38)—known asthma, no allergy, no treatment	DRESS	Fever, severe pruritus, tachypnea, adenopathies, blood eosinophilia	12	Recovered with high-dose OCS; definitive treatment interruption
Female (38)—known chronic lumbar pain, no allergy, no treatment	DRESS	Fever, dyspnea, generalized maculopapular rash, adenopathies (including mediastinal and hilar), blood eosinophilia, elevated liver enzyme levels, negative viral serological and anti–nuclear factor results, pulmonary infiltrate	21	Recovered with high-dose OCS; definitive treatment interruption
Female (39)—known gastritis, no allergy, intermittent esomeprazol treatment	Quincke edema	Dyspnea, dysphonia, normal blood oxygen saturation, vocal cord edema (laryngoscopy)	11	Recovered with high-dose OCS; completed 60-day benznidazole course
Female (40)—healthy, no allergy, no treatment	Anaphylaxis grade 3	Diffuse erythematous rash, dyspnea, dysphonia, low blood pressure, normal chest radiography and laryngoscopy results	9	Recovered with oral antihistaminics and intravenous corticosteroids; definitive treatment interruption

NOTE. DRESS, drug reaction with eosinophilia and systemic symptoms; MH, medical history; NSAIDs, nonstreroidal anti-inflammatory drugs; OCS, oral corticosteroids.

[a] Three days after treatment termination.

Table 4. Observed Duration of Nifurtimox Treatment among 73 Patients with *Trypanosoma cruzi* Infection in Geneva, Switzerland

Duration	Patients, no. (%)
60 days	41 (56.2)
⩾53 days (90% of recommended duration)	47 (64.4)
⩾45 days (75% of recommended duration)	50 (68.4)
⩾30 days (50% of recommended duration)	52 (71.2)

documented migrants living in Geneva with very low socioeconomic status and poor social support. Prior studies conducted among this population showed that the constant stress to earn a daily income resulted in frequent mental health problems and poor health perception [23]. Therefore, nifurtimox tolerance may differ in this vulnerable population relative to patients living in their home country with more social support. Considering the current migration flows and the changing epidemiology of Chagas disease, the influence of social determinants on treatment tolerance deserves further investigations.

Most patients in our cohort were Bolivians, which may limit the generalizability of our observations. At present, there is no evidence for a genetic influence on tolerance to nifurtimox, despite suggestions that tolerance in Central and South America may differ [17]. This important topic should be further studied, because it may eventually lead to distinct pharmacological recommendations. Nevertheless, Bolivians are the most affected by Chagas disease, and several countries outside Latin America harbor large communities of Bolivian migrants [2]. In fact, most published cases of Chagas disease outside the Americas occurred in Bolivian migrants [3, 13, 15].

Our results call into question the safety of large-scale use of nifurtimox among adult patients in settings with difficult access to medical care, such as poor rural areas of South America. Treatment risks and benefits should be thoroughly discussed with patients before initiation. Easily accessible medical care and close clinical follow-up appear to be prerequisite to nifurtimox treatment. In addition, patients should be educated regarding identification of early symptoms of serious AEs. To further define nifurtimox tolerance in different settings, all relevant AEs should be reported to pharmacovigilance systems. Pharmacovigilance for nifurtimox and benznidazole in Europe is currently not sufficient and should be enhanced to collect appropriate and extensive safety data.

It is not known weather benznidazole is better tolerated than nifurtimox in adult *T. cruzi*–infected patients, because the 2 drugs have not been properly compared. In a retrospective study conducted among 1047 adults treated with benznidazole for 30 days, Viotti et al [19] reported a 17.2% rate of premature treatment termination caused by AEs. A higher rate (27%) was reported among 11 patients receiving benznidazole for a longer period (60 days) [20]. Cutaneous, hematological, or neurological AEs are frequent and may be life-threatening [24]. Considering the lack of current therapeutic alternatives, a clinical trial comparing the safety and efficacy of benznidazole and nifurtimox is needed to foster better evidence-based therapeutic recommendations.

Because 70% of our patients achieved at least 30 days of treatment, the clinical (ie, incidence of *T. cruzi*–related organ damage) and parasitological efficacy of a 30-day nifurtimox regimen could be evaluated. However, this treatment duration is unlikely to lead to a significant decrease in serious AEs, because the majority occur during the first month of treatment. Other potential strategies to improve nifurtimox tolerance include prolonged treatment with a reduced daily dose, an alternate-day regimen, or combination therapy with other try-

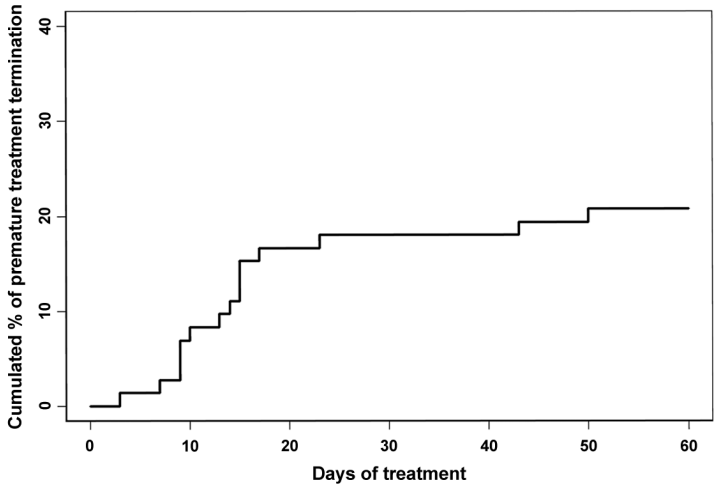

Figure 2. Kaplan-Meier curve for the occurrence of premature treatment termination among 73 *Trypanosoma cruzi*–infected patients treated with nifurtimox in Geneva, Switzerland.

panocidal drugs (eg, benznidazole) to reduce dose and/or duration [12, 13]. The ongoing development of new drugs for this neglected tropical disease provides some hope [25, 26]. More than a century after Carlos Chagas' discovery, patients and clinicians still await an efficient, safe, and accessible drug.

Acknowledgments

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Potential conflicts of interest. All authors: no conflicts.

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