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Tolerance to nifurtimox and benznidazole in adult patients with chronic Chagas' disease

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Background: Current options for Chagas' disease treatment are restricted to benznidazole and nifurtimox. To the best of our knowledge, no study has ever compared their tolerance in adults in a non-endemic country.

Objectives: To compare the completion rates and drug tolerance in a cohort of patients treated according to current guidelines.

Patients and methods: We analysed the medical records of all Chagas' disease patients aged 18 years or over who started antiparasitic treatment at the Geneva University Hospitals, Switzerland, from 2008 to 2016. We recorded treatment duration and all adverse events.

Results: We included 176 patients, 92 and 84 of whom received benznidazole or nifurtimox, respectively. The overall treatment completion rate was 62.5%, without a significant difference between the groups (P=0.436). Most patients (89.8%) suffered at least one adverse event. Those receiving nifurtimox had more events (6.2 versus 3.5, P<0.001). Mucocutaneous symptoms predominated in the benznidazole group, whereas digestive symptoms were most frequent with nifurtimox. Neuropsychiatric events frequently occurred in both groups, most notably in patients receiving nifurtimox. Arthralgia, dyspnoea, sensitive neuropathy and pruritus were independent predictors of treatment interruption.

Conclusions: Currently recommended drug regimens for Chagas' disease are not well tolerated and entail frequent treatment discontinuation irrespective of the drug used. This highlights the need to improve treatment tolerance in adults with Chagas' disease with new therapeutic options.

Introduction

Chagas' disease results from human infection with *Trypanosoma cruzi*, a flagellated protozoan whose vector-borne transmission is endemic in Latin America. It is estimated that 6–8 million persons are affected worldwide.[1] The disease's epidemiology has changed in recent decades, with a majority of cases now being identified in urban settings in the Americas and with a growing number of affected persons being clinically managed in non-endemic countries outside Latin America.[2,3]

Only two drugs are currently recommended for the treatment of Chagas' disease. Nifurtimox and benznidazole have been in use since the late 1960s, but their availability has repeatedly been compounded by shortages in production and distribution problems both in endemic and non-endemic regions, with a negative impact on patient access to therapy.[4,5] To date, the FDA has only granted approval to benznidazole in the USA, but nifurtimox can be accessed through the WHO. Only a few trials have been conducted to assess treatment efficacy in humans, but current evidence points to satisfactory efficacy in the acute phase, including following congenital infection, and the early chronic phases of the disease and in the case of *T. cruzi* reactivation.[6] While the recommendation to administer antiparasitic therapy had long been restricted to newborns and children, a paradigm shift has recently occurred, with increasing evidence supporting treatment in adults with a chronic infection as well.[6–8] Subsequently, some authors have called for starting antiparasitic therapy in all patients with chronic infection, irrespective of age.[9] Yet, access to the drugs, their limited tolerance and difficulties in evaluating their efficacy in individual cases remain key challenges in expanding this treatment.[6,10,11]

The few available sources of evidence have shown that tolerance to both antiparasitic drugs is limited and frequently results in treatment interruption.[6,12–14] The data published on the safety and efficacy of nifurtimox and benznidazole do not allow a clear conclusion to be drawn regarding which of the two is superior. While WHO guidelines in 2002 and the Pan American Health Organization (PAHO) in 2019 do not favour one drug over the other as first choice, most experts prefer benznidazole as a first-line therapy.[6,15–18] Yet, few comparative studies have been conducted in a clinical setting and none has been conducted outside endemic areas. We aimed to describe the real-life tolerance and compliance for each drug in adult patients who were treated in a European reference centre.

Patients and methods

Ethics

This study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. It received ethical clearance from the Geneva Canton Research Board (Project 07-285). All data analysed were anonymized.

Setting

This retrospective study was conducted at the Geneva University Hospital (HUG; Switzerland), which acts as the reference centre for the management of Chagas' disease in the Canton of Geneva (population: ∼500 000). Following an epidemiological survey conducted in 2008 that highlighted the emergence of cases of Chagas' disease in Geneva, screening programmes and clinical management strategies were implemented in the community and at HUG, notably in the divisions of primary care and obstetrics.[19]

Participants and procedures

We extracted clinical data from the electronic medical files of all adult patients with Chagas' disease who had started antiparasitic therapy with nifurtimox or benznidazole at HUG between 2008 and 2016. Diagnosis was based on positive results in at least two serological tests (ELISA cruzi®, bioMérieux; BioElisa Chagas®, Biokit; Stat-Pak®, Chembio) using different techniques and antigens, in accordance with WHO guidelines. Seropositive patients underwent standardized medical management, which included clinical staging, evaluation of eligibility for treatment, shared decision-making before starting treatment and follow-up during antiparasitic therapy.

Disease staging relied on a thorough medical history, physical examination and 12-lead ECG. The presence of electrocardiographic abnormalities or persistent clinical symptoms prompted further cardiological (24 h Holter, echocardiogram) and/or digestive (barium studies) investigations. After careful exclusion of contraindications, patients eligible for treatment received extensive information and, upon acceptance, started treatment with either nifurtimox 10 mg/kg/day divided into three doses or benznidazole 5 mg/kg/day in two or three doses with a maximum dose of 300 mg per day. Both drugs were prescribed for 60 days. We followed Bern's recommendation of not starting treatment in patients aged 50 years or older, but made exceptions in individual situations.[17] The choice of the first-line drug was mainly determined by availability of the medicine. While we aimed at following the WHO recommendation of using benznidazole as first-line therapy, recurrent periods of supply shortage and drug unavailability in Switzerland constrained us to use nifurtimox as first-line therapy during the years 2008 to 2010.[15,20,21] Patients underwent standardized clinical follow-up during treatment on Days 7, 21 and 60, which included a review of newly occurring symptoms, physical examination and laboratory tests when clinically required. Additional follow-up visits were made at any time during the treatment in the case of new symptoms. When necessary, decisions regarding temporary or definitive treatment interruption were made jointly with the patient. After a decision of definitive treatment interruption, clinicians were free to propose a second-line therapy with the alternative drug.

Adverse events were considered to be any new symptom occurring during therapy and not explained by obvious alternative causes (e.g. cold, injury). The timings of occurrence of the adverse events were categorized (Days 1 to 7, 8 to 14, 15 to 30 or 31 to 60). Adverse event severity was not systematically graded and recorded, and was therefore not included in the analysis.

Statistical methods

We described the patients' characteristics, their disease stage and the first-line treatment received (benznidazole versus nifurtimox). We reported the occurrence of adverse events, globally and stratified by first-line treatment. We obtained Kaplan–Meier estimates of time to the interruption of treatment, by first-line treatment received. To identify risk factors for interruption of treatment, we cross-tabulated the non-completion of 60 days of treatment with first-line treatment, patient characteristics and reports of adverse events. For all comparisons of proportions we used Fisher's exact test.

To model the associations between adverse events and non-completion of treatment more precisely, we used time-dependent Cox regression models. The moment of occurrence of any adverse event was classified into four time brackets as mentioned above. We used time-dependent Cox models for univariate analysis (one adverse event at a time) and retained significantly associated events (univariate $P<0.05$) for a multivariate model. We used a fairly strict criterion for inclusion at this stage because the number of adverse events was large in relation to the number of non-completion events. The treatment type was also included in the multivariate model, to establish whether adverse events explained any difference in completion rates between the two treatments.

Table 1. Sociodemographic and disease characteristics of the patients

	All (*N*=176), *n* (%) or median (IQR)	Benznidazole (*N*=92), *n* (%) or median (IQR)	Nifurtimox (*N*=84), *n* (%) or median (IQR)	*P*
Female	143 (81.3)	75 (81.5)	68 (81)	1.000
Bolivian	173 (98.3)	91 (98.9)	82 (97.6)	0.606
Age (years)	40 (13)	43 (12)	38 (13)	0.009
Stage				0.198
indeterminate	142 (80.7)	71 (77.2)	71 (84.5)	
cardiopathy	31 (17.6)	19 (20.7)	12 (14.3)	
digestive	2 (1.1)	2 (2.2)	0 (0)	
cardiodigestive	1 (0.6)	0 (0)	1 (1.2)	

Continuous variables are presented as the mean with standard deviation (for normally distributed variables) or the median and IQR for skewed variables, whereas categorical variables are listed as proportions with percentages. Continuous variables were compared using Student's *t*-test. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. The significance level was set at 0.05.

Results

Patient characteristics

Overall, 355 adult patients with Chagas' disease were seen at HUG between 2008 and 2016. One hundred and seventy-nine were not treated with antiparasitic therapy because of older age (n=74), follow-up discontinuation after the initial clinical encounter (n=59), refusal (n=38), previous antiparasitic therapy (n=4) or medical contraindication (n=4). The present study includes the 176 eligible patients who initiated treatment. Of these, 92 and 84 received benznidazole and nifurtimox as first-line antiparasitic therapy, respectively. Overall, patients were predominantly young to middle-aged women originating from Bolivia and presenting with chronic Chagas' disease at the indeterminate phase (Table 1). Older age of the benznidazole-treated patients (43 versus 38 years, P=0.009) was the only significant difference between groups.

Adverse events

A total of 158 (89.8%) patients suffered at least one adverse event during treatment. This proportion was significantly higher in the nifurtimox group compared with the benznidazole group (95.2% versus 84.8%, P=0.026). On average, patients receiving nifurtimox suffered more events (6.2 versus 3.5, P<0.001) than those in the benznidazole group and were more at risk of suffering five or more adverse events (69% versus 35.9%, P<0.001).

The profile of adverse events differed between treatment groups (Table 2). Mucocutaneous symptoms predominated in the benznidazole group, whereas digestive symptoms were more frequent with nifurtimox. Neuropsychiatric events frequently occurred in both groups.

Table 2. Frequency of adverse events in 176 adult patients with Chagas' disease treated with benznidazole or nifurtimox

Adverse event	Benznidazole (N=92), n (%)	Nifurtimox (N=84), n (%)	P
Mucocutaneous			
pruritus	34 (37.0)	17 (20.2)	0.020
rash	27 (29.3)	12 (14.3)	0.019
alopecia	1 (1.1)	0 (0)	1.00
angioedema	2 (2.2)	0 (0)	0.50
Digestive			
anorexia	20 (21.7)	62 (73.8)	<0.001
nausea	33 (35.9)	46 (54.8)	0.015
abdominal pain	20 (21.7)	33 (39.3)	0.014
vomiting	9 (9.8)	21 (25.0)	0.009
constipation	0 (0)	2 (2.4)	0.23
diarrhoea	0 (0)	13 (15.5)	<0.001
hepatitis	1 (1.1)	0 (0)	1.00
Neuropsychiatric			
headache	37 (40.2)	60 (71.4)	<0.001
mood changes	29 (31.5)	39 (46.4)	0.046
sensitive neuropathy	19 (20.7)	4 (4.8)	0.002
vertigo	6 (6.5)	23 (27.4)	<0.001
psychosis	1 (1.1)	1 (1.2)	1.00
convulsions	0 (0)	1 (1.2)	0.48
memory problems	0 (0)	11 (13.1)	<0.001
tremor	0 (0)	2 (2.4)	0.23
insomnia	24 (26.1)	42 (50.0)	0.002
dysgeusia	5 (5.4)	0 (0)	0.06
Systemic, constitutional			
fatigue	40 (43.5)	58 (69.0)	0.001
fever	0 (0)	12 (14.3)	<0.001
sweating	1 (1.1)	1 (1.2)	1.00
arthralgia	4 (4.3)	22 (26.2)	<0.001
myalgia	6 (6.5)	22 (26.2)	<0.001
chest pain	0 (0)	2 (2.4)	0.23
palpitations	1 (1.1)	1 (1.2)	1.00
parotid swelling	0 (0)	1 (1.2)	0.48
drug reaction with eosinophilia and systemic symptoms (DRESS)	0 (0)	1 (1.2)	1.00
Respiratory			
dyspnoea	3 (3.3)	8 (9.5)	0.12
laryngeal oedema (Quincke)	0 (0)	3 (3.6)	0.11
cough	2 (2.2)	3 (3.6)	1.00

Treatment completion

Overall, 110 (62.5%) patients completed the 60 day treatment, without a significant difference between groups (65.2% in the benznidazole group versus 59.5% in the nifurtimox group, P=0.436) (Figure 1). The median duration of treatment was 60 days in both groups. The mean treatment duration was not different between groups (47.6 with benznidazole versus 45.8 days with nifurtimox, P=0.571). Treatment interruptions occurred mainly during the first month in the nifurtimox group, in contrast to a more constant dropout rate in the benznidazole group. Temporary treatment interruption occurred more frequently among patients receiving nifurtimox (26.2% versus 8.7%, P=0.005). Overall, 13 patients started with a second-line treatment, but this allowed only four additional patients to reach a total of 60 days of antiparasitic therapy. Adverse events most frequently occurring before premature treatment termination were pruritus, rash and sensitive neuropathy in the benznidazole group and headaches, dyspnoea, pruritus and nausea in the nifurtimox group.

There was no association between the completion rate and sociodemographic or disease-related characteristics, or the occurrence of five or more adverse events. In contrast, non-completion was significantly associated with the occurrence of pruritus, sensitive neuropathy, dyspnoea and arthralgia during treatment (Table 3).

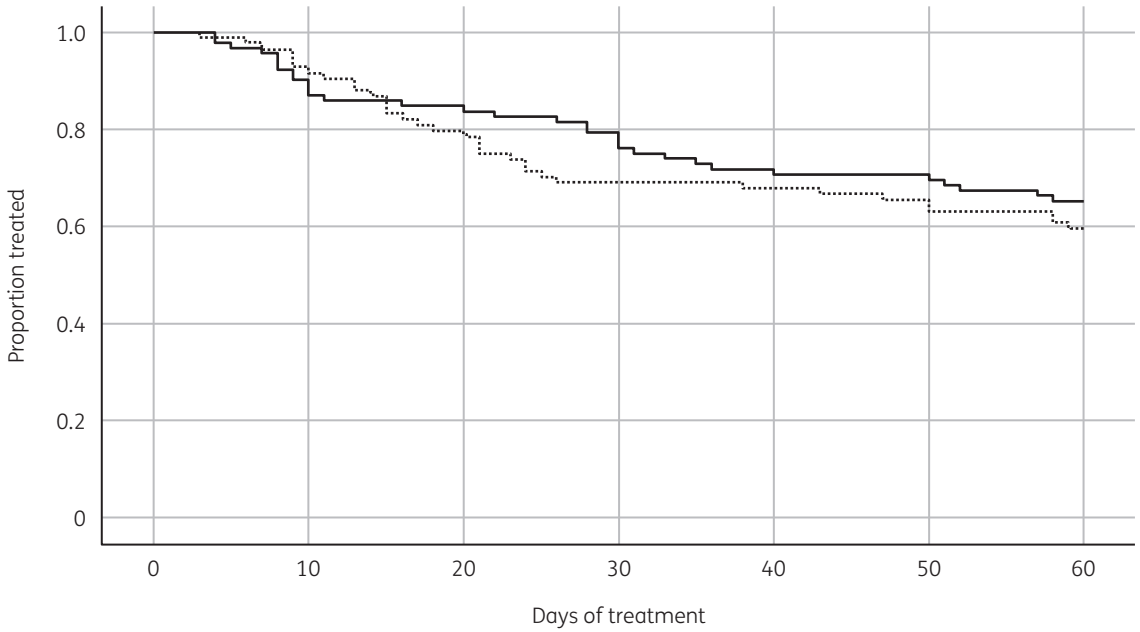

Figure 1. Kaplan–Meier estimates of time to treatment interruption in adult patients treated for Chagas' disease with benznidazole (n=92, continuous line) or nifurtimox (n=84, broken line) (log-rank test, P=0.436).

Factors predicting treatment non-completion

Demographic variables and clinical stage did not predict early termination of treatment, unlike pruritus, sensitive neuropathy, fever, arthralgia and dyspnoea. After adjustment for sociodemographic factors, treatment and stage of the disease, pruritus, sensitive neuropathy, arthralgia and dyspnoea remained a significant predictor for interruption (Table 4).

Discussion

We report here, to the best of our knowledge, the first comparative study on the tolerance of nifurtimox and benznidazole in adult patients with chronic Chagas' disease living in a non-endemic region. This single-centre retrospective study shows that nearly 40% of patients starting antiparasitic therapy for Chagas' disease did not complete the recommended 60 day regimen, irrespective of the compound used as first-line therapy. Moreover, this study provides evidence that, while nearly all patients present with adverse events during therapy, the number and type of such events differ between nifurtimox and benznidazole recipients, suggesting they were drug related. Whereas most adverse events were not associated with early treatment termination, pruritus, sensitive neuropathy, arthralgia and dyspnoea were predictors of treatment non-completion.

Both benznidazole and nifurtimox are better tolerated in children than in adults.[22,23] In adults, it is difficult to draw valid drug tolerance comparisons from the scientific literature, considering disparities in study settings and designs, drug dosages, treatment durations and methods of observation of tolerance. In addition, most studies have had a relatively small sample size and assessed only one drug. Safety studies with individual drugs recorded 70%–94.4% and 79%–100% completion rates with benznidazole and nifurtimox in the USA and in Spain.[24–28] In Geneva, we reported a completion rate of 56.2% with nifurtimox in a preliminary study.[14] Comparative studies conducted in Latin America showed wider ranges of completion rates, i.e. 58.6%–88.4% with benznidazole and 25%–96.3% with nifurtimox.[29–33] Factors associated with treatment interruption included higher drug dosage and the number and severity of adverse events. The low rate of treatment completion we observed in Geneva may be due to various factors such as high follow-up attendance, a cautious and conservative clinical approach in the management of adverse events, counselling and/or patient preferences. Indeed, the decision to stop treatment in the presence of adverse events was co-decided with patients after a thorough risk–benefit evaluation. We observed that patients in Geneva tend to have a rather negative perception of Chagas' disease treatment as being dangerous and poorly effective, which may negatively impact on their capacity and willingness to continue treatment despite the occurrence of side effects. Indeed, in our cohort of patients, treatment hesitancy or refusal was a frequent motive for not initiating therapy. This calls for a better understanding of patient knowledge and perception about treatment, and addressing fears and hesitancy during the clinical evaluation. Uncertainties over the efficacies and tolerance of both Chagas' disease treatments in adults, combined with problematic access to the drugs, all represent major limitations today. These constraints and limitations confirm the urgent need for different, shorter, better tolerated and more effective therapeutic options.

We found that nearly all patients suffered from adverse events during therapy and that patients treated with nifurtimox presented with more events. Previous studies showed large variations in the rate of adverse events in different settings. While 100% of patients in the USA showed adverse events with either of the two drugs, 27% and 32% of patients in Argentina, 91.5% and 83% in Colombia and 40% and 61.5% in Spain taking benznidazole and nifurtimox, respectively, presented with at least one adverse

Table 3. Factors associated with treatment completion in adult patients with Chagas' disease (N=176)

	Frequency, *n* (%)	Completed treatment, *n* (%)	*P*
Patient/treatment characteristics			
treatment			0.44
benznidazole	92 (52.3)	60 (65.2)	
nifurtimox	84 (47.7)	50 (59.5)	
sex			0.11
female	143 (81.3)	85 (59.4)	
male	33 (18.8)	25 (75.8)	
age (years)			0.88
18–39	83 (47.2)	51 (61.4)	
40–60	93 (52.8)	59 (63.4)	
disease stage			0.69
indeterminate	142 (80.7)	90 (63.4)	
cardiac or digestive	34 (19.3)	20 (58.8)	
Adverse event			
pruritus			0.025
no	125 (71.0)	85 (68.0)	
yes	51 (29.0)	25 (49.0)	
rash			0.13
no	137 (77.8)	90 (65.7)	
yes	39 (22.2)	20 (51.3)	
anorexia			0.64
no	94 (53.4)	57 (60.6)	
yes	82 (46.6)	53 (64.6)	
nausea			0.35
no	97 (55.1)	64 (66.0)	
yes	79 (44.9)	46 (58.2)	
abdominal pain			0.24
no	123 (69.9)	73 (59.3)	
yes	53 (30.1)	37 (69.8)	
vomiting			0.062
no	146 (83.0)	96 (65.8)	
yes	30 (17.0)	14 (46.7)	
diarrhoea			1.00
no	163 (92.6)	102 (62.6)	
yes	13 (7.4)	8 (61.5)	
headache			0.28
no	79 (44.9)	53 (67.1)	
yes	97 (55.1)	57 (58.8)	
mood changes			0.64
no	108 (61.4)	69 (63.9)	
yes	68 (38.6)	41 (60.3)	
sensitive neuropathy			0.02
no	153 (86.9)	102 (66.0)	
yes	23 (13.1)	9 (39.1)	
vertigo			0.21
no	147 (83.5)	95 (64.6)	
yes	29 (16.5)	15 (51.7)	
memory loss			0.54
no	165 (93.8)	102 (61.8)	
yes	11 (6.3)	8 (72.7)	
dysgeusia			0.36
no	171 (97.2)	108 (63.2)	
yes	5 (2.8)	2 (40.0)	
fatigue			0.76
no	78 (44.3)	50 (64.1)	
yes	98 (55.7)	60 (61.2)	
insomnia			0.87
no	110 (62.5)	68 (61.8)	
yes	66 (37.5)	42 (63.6)	
fever			0.059
no	164 (93.2)	106 (64.6)	
yes	12 (6.8)	4 (33.3)	
arthralgia			0.028
no	150 (85.2)	100 (66.0)	
yes	26 (14.8)	11 (42.3)	
myalgia			0.83
no	148 (84.1)	93 (62.8)	
yes	28 (15.9)	17 (60.7)	
dyspnoea			0.003
no	165 (93.8)	108 (65.5)	
yes	11 (6.3)	2 (18.2)	
Number of adverse events			0.28
0–4	85 (98.3)	57 (67.1)	
≥5	91 (51.7)	52 (57.2)	

event.[24–26,28,30,32,33] This may indicate differential susceptibility of patients or, more likely, variable methods of adverse events recording. Our findings indicate a distinct profile of adverse events for each drug. While nifurtimox was mainly associated with systemic/constitutional, gastrointestinal, neuropsychiatric and respiratory symptoms, benznidazole was more associated with mucocutaneous events, which agrees with previous reports.[12,27,34,35] Only a few adverse events were associated with early treatment termination in isolation, the majority of interruptions originating from the accumulation of adverse events. The range of events illustrates the challenge for adult patients to follow treatment, while working and managing family life. It calls for close clinical monitoring during treatment, adequate patient information and discussion of strategies to identify and manage events early. Recent pharmacological development regarding drug formulation, administration schedule and reduced dosage may open new avenues for better tolerated treatment regimens.[36–40]

This study entails some limitations such as the limited sample size, the lack of a placebo arm and the homogeneity of the studied population, which may restrict the validity of our findings in other settings. In Europe though, Bolivian middle-aged adults account for the large majority of patients with Chagas' disease seen in clinical settings, so we consider our findings fairly representative of the European situation.[2] Another main limitation pertains to our limited ability to retrieve information that would allow systematic grading of the severity of adverse events according to the common terminology criteria for adverse events used in other studies. We acknowledge that the same adverse event may entail different

Table 4. Univariate and adjusted associations between treatment type, patient characteristics and adverse events versus non-completion of 60 days of treatment (Cox regression with time-dependent covariates)

	Univariate		Adjusted for all variables in the table	
	relative hazard (95% CI)	*P*	relative hazard (95% CI)	*P*
Nifurtimox (versus benznidazole)	1.21 (0.75–1.96)	0.44	1.14 (0.65–2.01)	0.65
Female (versus male)	1.86 (0.89–3.91)	0.098	1.54 (0.72–3.28)	0.27
Age ≥40 years (versus younger)	0.92 (0.57–1.49)	0.73	0.85 (0.51–1.41)	0.53
Indeterminate stage (versus cardiac/digestive)	1.10 (0.61–1.99)	0.74	0.93 (0.49–1.75)	0.82
Pruritus	2.93 (1.56–5.45)	0.001	2.14 (1.08–4.24)	0.029
Sensitive neuropathy	4.04 (2.15–7.57)	<0.001	3.55 (1.74–7.25)	0.001
Fever	3.16 (1.43–6.97)	0.014	1.75 (0.69–4.45)	0.24
Arthralgia	3.55 (1.88–6.71)	<0.001	2.12 (1.02–4.39)	0.044
Dyspnoea	6.66 (3.14–14.12)	<0.001	3.79 (1.58–9.08)	0.003

discomfort and severity in different patients, thus influencing clinician and patient choice in the decision-making process about early treatment interruption. Of note, we used a conservative benznidazole total dosage below 18 g to account for potential risks of neuropathic and haematological toxicity. Therefore, our results may not be fully applicable to settings where higher benznidazole total doses are applied. Finally, we cannot draw conclusions regarding the clinical impact of premature treatment termination in the absence of systematic long-term post-treatment clinical follow-up and availability of valid biomarkers of cure.[41]

In conclusion, our results support efforts to find new therapeutic strategies using a shorter regimen, reduced dosage, drug combinations and/or new compounds in order to make Chagas' disease treatment better tolerated in real-life settings.

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Transparency declarations

None to declare.

Author contributions

Y.J. and F.C. designed the study. B.W. collected data. Y.J. and B.W. conducted the analysis. Y.J. drafted the manuscript. B.W. and F.C. proofread the manuscript.

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