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Benznidazole treatment safety: the Médecins Sans Frontières experience in a large cohort of Bolivian patients with Chagas' disease

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Background: Up to half of patients with Chagas' disease under benznidazole treatment present adverse drug reactions (ADRs) and up to one-third do not complete standard treatment.

Objectives: To verify the incidence and possible factors associated with the suspension of benznidazole treatment in a large cohort of patients.

Methods: We included 2075 patients treated with benznidazole during the projects managed by the medical humanitarian organization Doctors Without Borders (Médecins Sans Frontières) in Bolivia from 2009 to 2013. Benznidazole treatment was provided two or three times per day for ∼60 days at 5–7.5 mg/kg/day. A multiple logistic regression model was developed to evaluate the factors associated with permanent suspension of benznidazole treatment.

Results: Permanent benznidazole treatment suspension occurred in 211 patients (10.2%) and the average time until permanent treatment suspension was 23 days. Multifactorial analysis revealed that female sex (adjusted OR = 1.70), moderate ADRs (adjusted OR = 10.57), mild ADRs (adjusted OR = 1.69) and skin disorders (adjusted OR = 4.18) were significantly associated with the permanent suspension of benznidazole treatment. Women with mild or moderate skin ADRs presented a probability of treatment interruption of 18.6% and 59.0%, respectively.

Conclusions: Benznidazole treatment was safe and a large proportion of patients were able to complete a full course of benznidazole treatment under close treatment surveillance. Female sex, skin disorders and mild and moderate ADRs were independently associated with the permanent suspension of benznidazole treatment. In particular, women with moderate skin ADRs had the highest risk of benznidazole treatment interruption.

Introduction

Chagas' disease (CD) is a neglected tropical disease caused by the protozoan *Trypanosoma cruzi*, which affects ∼6–7 million people worldwide.[1] Although most cases are concentrated in Latin America, migration and non-vector transmission routes have increased the number of reported cases in non-endemic areas, such as the USA and Europe.[2] Cardiovascular disorders are the most important clinical manifestations of CD, accounting for the disease's high morbidity and mortality rates.[3]

Following the identification of *T. cruzi* persistent infection within the myocardium of chronic patients, the paradigm of CD treatment in its chronic phase has shifted from symptomatic treatment towards treatment with anti-parasitic drugs. Although under debate,[4] aetiological treatment is indicated by many groups, including the US CDC, for patients <50 years old.[5–9] One of the main barriers for the widespread use of the main trypanocidal drug, benznidazole, is the high reported incidence of adverse drug reactions (ADRs), which affect up to 50% of treated patients.[10,11] However, only a small number of ADRs are severe (1%).[11] Even so, about one-third of the patients interrupt benznidazole treatment due to ADRs or other reasons.[11–13]

Since 1999, the international medical humanitarian organization Doctors Without Borders [Médecins Sans Frontières (MSF)] has run programmes for the diagnosis and treatment of CD in Latin

America with an initial focus on paediatric populations.[13] MSF treated a large population of patients with CD <18 years with a very low percentage of benznidazole suspension (ranging from 1.3% in Yoro, Honduras to 5.8% in Sucre, Bolivia), although the incidence of ADRs varied from 25.6% (Entre Rios, Bolivia) up to 50.8% (Olapa, Guatemala). Therefore, MSF's experience shows that benznidazole treatment can be safe for a young population. In addition, research conducted in the Oswaldo Cruz Foundation reached similar results in adults.[11] In 2009, MSF decided to include adult patients among those treated with benznidazole in their Latin American projects. Benznidazole intolerance is reported to be more frequent among adult populations and different rates of treatment suspension may be one of the reasons for the different results found in studies evaluating benznidazole effectiveness.[8,14] Therefore, it is imperative to identify the rate of benznidazole intolerance and the related ADRs in a large adult population and study the different factors associated with benznidazole suspension. Thus, the aim of the present study was to identify the rate and the factors associated with benznidazole treatment suspension in a large cohort of patients treated in an MSF programme developed in a rural area of Bolivia.

Patients and methods

Study population

Since the late 1990s, MSF has been working on the diagnosis and treatment of CD in Latin American countries. In 2009, MSF initiated collaboration with the Bolivian Ministry of Health and selected three rural districts (Aiquile, Omereque and Pasorapa) of the Cochabamba department to screen the general population for CD. The districts were selected based on previous reports of triatomines and/or exploratory MSF experiences.[13]

Patients included in the analyses had their CD diagnosis confirmed by two different serological tests (ELISA and indirect immunofluorescence assay) and were treated with benznidazole between 2009 and 2013. Before starting benznidazole treatment, clinical anamnesis and pregnancy tests were performed. Treatment was not initiated in women with a β-human chorionic gonadotrophin-positive test or breastfeeding or in patients with a history of allergy to benznidazole or kidney or liver failure.

Ethics

The present investigation is a retrospective study using secondary data collected from medical services provided by MSF. This study was approved by the Medical Director Operational Centre of MSF and fulfilled the exemption criteria set by the MSF Ethics Review Board for a posteriori analyses of routinely collected clinical data.

Benznidazole treatment and follow-up

The benznidazole regimen was 5–7.5 mg/kg/day for 60 days or more depending on patient weight: <40 kg, 7 mg/kg/day for 60 days; ≥40 kg and ≤60 kg, 5 mg/kg/day for 60 days; and >60 kg, 300 mg/day for an equivalent number of days according to his/her body weight, as reported by Yun *et al.*[13] in 2009. Treatment (at days 0, 7, 14, 21, 28, 35, 42, 49 and 60) was provided by a health professional and tablets were administered at home by the parents/guardians (in the case of children) or the patients themselves. Treatment adherence sheets were filled out by parents/guardians or patients, as previously reported.[13] Physicians or nurses accompanied patients weekly during benznidazole treatment and performed closer follow-up whenever necessary. Clinical evaluation also included anamnesis, physical examination, blood pressure, heart and breathing rate, and body temperature. Treatment was considered complete when patients had taken benznidazole during at least 55 of the 60 prescribed days.

Variables

Socio-demographic and clinical variables were obtained during medical appointments and included age, sex, municipality of residence, area of origin (urban/rural), presence of ECG abnormalities (first-, second- or third-degree atrioventricular block, complete or incomplete right bundle branch block, left anterior or posterior fascicular blocks, premature atrial or ventricular complexes, sinus bradycardia, left ventricular hypertrophy, atrial fibrillation or sinus tachycardia), cardiac symptoms (faintness, dizziness, dyspnoea, oedema, hepatomegaly and palpitation), skin disorders (directly related to benznidazole treatment such as maculopapular exanthema and/or pruritus), gastrointestinal disorders (epigastralgia, abdominal pain, nausea, vomiting and anorexia) and nervous system disorders (peripheral polyneuropathy manifested by tingling and discomfort on contact with cold water or cutting nails). The severity and the duration of benznidazole treatment ADRs were also evaluated.

The adverse event was considered a benznidazole-related ADR based on the compatibility of the time elapsed since benznidazole treatment initiation and the reaction's onset, nature of the event and medical or pharmacological plausibility.[13] ADRs were classified according to severity as mild (a minor short-lived reaction that may have required treatment but did not substantially affect the normal life of the patient and did not require treatment interruption), moderate (a reaction that interfered with the patient's normal daily activities and required temporary treatment interruption of no longer than 14 days) and severe (a reaction that threatened the patient's life and required definitive treatment interruption).[13] ADRs were also classified according to the affected organ as skin disorders, gastrointestinal disorders and nervous system disorders.

Whenever the patient presented a mild or moderate ADR, then counselling and specific ADR treatment were offered to restart benznidazole treatment whenever possible. Regarding skin disorders, treatment included use of topical creams with corticosteroids, which could be combined with oral administration of antihistamine drugs. In the case of severe skin disorders, oral systemic corticosteroids were prescribed. Regarding gastrointestinal disorders, dietary recommendations and a prokinetic drug, such as metoclopramide, were provided. Regarding nervous system disorders, benznidazole treatment was permanently suspended and symptomatic medication was provided together with rest of the affected limb.

The primary outcome (dependent variable) was benznidazole treatment suspension, which was defined as the interruption of benznidazole use within the first 55 days of treatment, determined by the physician according to his/her clinical judgement.

Data analysis

Descriptive statistics comprised mean (SD) for numerical variables and number of observations (percentage) for categorical variables. Logistic regression models were used to evaluate the influence of socio-demographic and clinical variables on benznidazole treatment suspension.

The construction of the final logistic regression model was performed in two steps. First, a univariate analysis was performed to identify variables that should be considered in the multivariate models, including all of those that showed $P < 0.20$ in the univariate model. Afterwards, a *backwards* method was used to maintain in the final regression model only the variables that provided a significant explanation of the outcome ($P < 0.05$). The contribution of each exploratory variable in the multiple logistic regression analysis was expressed as OR and 95% CI. The Hosmer and Lemeshow test and the area under the receiver operating characteristic (ROC) curve

Table 1. Socio-demographic and clinical characteristics in benznidazole treatment suspension in a large cohort ($N = 2075$) of Bolivian's with CD; factors associated with benznidazole suspension by univariate or multifactorial analysis

	Suspension, *n* (%)		Logistic regression	
Variable	no, 1864 (89.8)	yes, 211 (10.2)	OR[a] (95% CI; *P* value)	probability of benznidazole suspension
Age (years), mean (SD)	37.02 (13.53)	37.72 (11.83)	1.07[C] (0.88–1.31; 0.47)	
Sex, *n* (%)				
female	838 (45.0)	133 (63.0)	1.70[A] (1.22–2.37; 0.002)	0.03
Municipality of residence, *n* (%)				
Omereque	403 (21.6)	43 (20.4)	0.89[C] (0.62–1.28; 0.54)	
Pasorapa	263 (14.1)	25 (11.8)	0.79[C] (0.51–1.24; 0.32)	
Urban area of origin, *n* (%)	221 (11.9)	33 (15.6)	1.38[C] (0.93–2.05; 0.11)	
ECG results abnormal[b], *n* (%)	442 (29.7)	34 (20.6)	0.61[C] (0.42–0.91; 0.02)	
Cardiac symptoms, *n* (%)	114 (6.1)	14 (6.6)	1.09[C] (0.61–1.94; 0.77)	
ADR severity[c], *n* (%)				
moderate	154 (8.3)	109 (52.2)	10.57[A] (5.92–18.85; <0.0001)	0.17
mild	821 (44.0)	79 (37.8)	1.69[A] (0.97–2.97; 0.07)	0.03
Skin disorders, *n* (%)	386 (20.7)	148 (70.1)	4.18[A] (2.85–6.14; <0.0001)	0.07
Gastrointestinal disorders, *n* (%)	271 (14.5)	14 (6.6)	0.42[C] (0.24–0.73; 0.002)	
Nervous system disorders, *n* (%)	318 (17.1)	28 (13.3)	0.74[C] (0.49–1.13; 0.16)	

[a]Crude ORs (marked [C]) were estimated by univariate logistic regression; adjusted ORs (marked [A]) were estimated by multivariate logistic regression.
[b]ECG results were available for 1653 patients. ECG results abnormal were available for 476 patients.
[c]A total of 2073 cases of ADR severity entered in the logistic regression analysis. Moderate ADRs and mild ADRs were 263 and 900, respectively.

were performed to evaluate how adequately the model fitted the data. A level of significance $\leq$5% based on a two-sided test was considered statistically significant for all analyses. Microsoft access (version 2007) and R software (version 3.2.3) were used for data entry and analysis, respectively. Logistic regression model (lrm) and prediction functions of regression modelling strategy packages[15] were used to develop logistic regression models and to estimate the predicted probability, respectively, using R software (version 3.2.3).

Results

Among 14953 individuals screened for CD during the MSF mission in Bolivia, 2383 (15.9%) tested positive for *T. cruzi* infection and were recruited for clinical evaluation before starting benznidazole treatment. Patients who did not return to initial evaluation ($n = 308$) did not receive benznidazole treatment and were excluded from analysis. Therefore, a total of 2075 patients were treated with benznidazole and included in this analysis.

The sample consisted of 1104 men (53.2%) and 971 women (46.8%) with age ranging from 1 to 64 years (mean 37.1$\pm$13.4 years). Most patients lived in Aiquile ($n = 1341$; 64.6%) and came from rural areas ($n = 1821$; 87.8%). Treatment duration ranged from 2 to 122 days. Patients who underwent treatment for <60 days were those who had their treatment interrupted by physician's recommendation. Patients with treatment >60 days were those whose weight was >60 kg, as described in the Patients and methods section. The median time of follow-up was 63 days for those who completed benznidazole treatment and 26 days for those patients who had their treatment interrupted. ADRs occurred in 1165 patients (56.1%) and were classified as follows: 900 (43.4%) mild, 263 (12.7%) moderate and 2 (0.1%) severe. Benznidazole treatment was interrupted in 365 patients: 344 due to ADRs and 21 due to other reasons. Patients with a mild or moderate ADR were encouraged to restart benznidazole treatment after counselling and ADR treatment. From these, 154 restarted treatment and were able to finish the full course of treatment. Benznidazole treatment was definitely interrupted in 211 (10.2%) patients: 190 (9.2%) due to ADRs and 21 (1.0%) due to other reasons such as concomitant diseases, pregnancy during the benznidazole treatment and migratory movements. Regarding severity, ADR cases that required permanent benznidazole treatment interruption were classified as follows: mild = 79 (3.8%); moderate = 109 (5.3%); and severe= 2 (0.1%). Regarding clinical symptoms, ADRs that required permanent benznidazole treatment interruption were classified as follows: skin disorders, 148 (7.1%); gastrointestinal disorders, 14 (0.7%); and nervous system disorders, 28 (1.3%).

In univariate analysis, female sex, mild ADR, moderate ADR and skin disorders were positively associated with benznidazole treatment suspension, while ECG abnormalities and gastrointestinal disorders were inversely associated (Table 1).

After controlling for confounders, multiple logistic regression analysis indicated three variables associated with benznidazole treatment suspension: female sex, moderate ADR and skin disorders. A goodness-of-fit test (Hosmer and Lemeshow) demonstrated a good performance of the model ($P = 0.37$) with an area under the ROC curve of 0.82.

The estimated probabilities of benznidazole suspension for female patients, moderate ADRs, mild ADRs and skin disorders were 0.03, 0.17, 0.03 and 0.07, respectively. The estimated probability of

benznidazole suspension for female patients with moderate skin ADRs (female + skin disorders + moderate ADRs) was 0.59 and for female patients with mild skin ADRs (female + skin disorders + mild ADRs) was 0.19.

Discussion

This study shows that under close follow-up surveillance a large proportion of patients were able to complete benznidazole treatment (89.8%), even with an incidence of ADRs (56.1%) similar to that in previous studies.[10,11] These results are valid for both children and adult patients. A similar completion rate (82.1%) was observed by Tornheim *et al.*[16] when benznidazole was provided weekly to adult Bolivian patients. However, Tornheim *et al.*[16] reported a completion rate of only 65.1% when Bolivian patients returned at 2 week intervals without systematic provider intervention. Although the present study was not designed to evaluate different follow-up regimens, our results, together with those of Tornheim *et al.*,[16] suggest that a weekly follow-up surveillance could increase the completion rate of benznidazole treatment, probably due to an earlier identification of ADRs, prompt treatment and consequent lower abandonment rates. Furthermore, they also observed a higher probability for dermatological ADRs among female patients and recommended that patients should be screened for ADRs throughout the entire treatment course and that mild skin disorders should be managed with antihistamines. Additionally, they suggested that the most important clinical intervention for moderate or severe ADRs is withdrawal of the offending medication.

We used logistic regression analysis in a large sample of patients with a good discriminatory power of the described model. We have already used logistic regression analysis to evaluate suspension of benznidazole treatment due to ADRs in Brazilians with a similar result (ROC = 0.71).[17] However, some of the variables that constituted the model differed between these two studies. In the present study, sex, ADR severity and skin disorders significantly impacted on treatment suspension, while in Brazil, sex, demographic and socio-economic factors were associated with ADRs.[17] However, demographic and socio-economic factor data were limited in the present study. All patients had similar ethnic origin and lived in the same Bolivian department.

We and others[10,11,16] found that ADRs were more frequent among women. In consequence, women presented an increased chance of treatment suspension. Thong and Tan[18] published a review about risk factors for drug allergy and suggested that women had a higher incidence of self-reported drug allergy than men. Salvador *et al.*[19] suggested in a small cohort of 52 patients (75.0% women) that IgE-mediated hypersensitivity reactions or genetic or pharmacological factors were not associated with skin ADRs. They also suggested that the HLA-B*3505 allele presence could be associated with moderate–severe cutaneous reaction.[19] Age was not associated with the increased chances of treatment suspension after multiple logistic regression in the present study, while others have suggested a lower tolerance to benznidazole among elderly patients.[20]

In the present study, ADR severity was strongly associated with benznidazole treatment interruption as 8.8% and 41.4% of patients with mild and moderate ADR, respectively, did not complete standard benznidazole treatment. Moreover, regression modelling strategy[15] analysis demonstrated that moderate ADR was associated with a 17% estimated probability of benznidazole treatment suspension. However, a mild ADR, such as a skin disorder, may result in a higher probability of benznidazole treatment interruption than the one associated with a moderate ADR, in case it occurs associated with other risk factors such as female sex.

The third independent factor associated with benznidazole treatment interruption in this study was skin disorders. Based on a multiple logistic regression model, skin reactions are responsible for about 7% of the cases of benznidazole suspension. Accordingly, we and others have previously shown that skin disorders are the most frequent ADRs.[11,13,17]

Although others have found that patients with abnormal ECG had an increased risk of benznidazole-related ADRs,[16] we did not confirm such an association after multivariate regression analysis.

We have previously shown that benznidazole treatment may be safe[11] but requires a weekly follow-up as 1.6%–10.4% of ADRs can be severe.[13] Antihistamines and/or corticosteroids are normally used to treat moderate or severe skin disorders,[21] while patients with mild skin disorders do not need symptomatic treatment.[21] Our study showed that specific groups of patients, such as women with skin ADR, have a high probability of suspending benznidazole treatment. Viotti *et al.*[10] observed that 176 (98%) patients had dermatitis from hypersensitivity among 180 patients who interrupted benznidazole treatment. Pinazo *et al.*[22] also observed that women interrupted benznidazole treatment more frequently than men (11 patients, all women). Furthermore, the independent analysis of ADR showed that treatment interruption was more common in patients with skin disorders ($P = 0.0261$). Considering this difficult context, Górgolas *et al.*[23] reported that the combination of escalating benznidazole doses with oral steroids tapered within the following 9 days of benznidazole treatment could improve benznidazole tolerance in patients with CD. In fact, Rodríguez-Guardado *et al.*[24] also observed that the combination of escalating benznidazole doses and oral antihistamine (dexchlorpheniramine) was able to avoid skin disorders and allow a full course of 60 days of benznidazole treatment in 19 patients. Despite the limitations of these studies,[23,24] such as small sample size and lack of randomization, blinding or control group, their results suggest that escalating benznidazole doses along with prophylactic anti-allergy drugs for patients with an increased chance of moderate or severe ADRs could be a reasonable measure to avoid those reactions and increase the likelihood of treatment completion.

The results of our study are limited by the retrospective design of the study, absence of haematological or biochemical tests for all patients, incomplete ECG results and lack of information about the specific type of skin, gastrointestinal or neurological disorders. Although data analysis was done retrospectively, the close surveillance provided during benznidazole treatment allowed the occurrence of ADRs to be properly recorded for future analysis. ADR incidence could be higher if blood test results were available. However, few leucopenia cases are observed (2.6%)[25] and it is rarely a cause of benznidazole treatment interruption.[22] The same is observed for changes in liver blood tests, which warrant treatment suspension and occur in only up to 0.8%[20] of the patients treated with benznidazole. Information on ECG changes was not available for 20% of our patients and the specific change in the ECG presented by each patient was also not available. This fact precluded the classification of the CD clinical form of the patients of our study and we could not evaluate if the form of CD

(indeterminate or cardiac form) influenced the likelihood of developing ADRs during benznidazole treatment. The unavailability of data regarding schooling, financial status and social support also limited the results of our study. Our results may not apply to other populations, as all included patients were Bolivian. We also did not evaluate the clinical or parasitological (PCR) follow-up after benznidazole treatment.

CD treatment still faces many barriers such as its actual effectiveness,[8,12,26,27] safety[11,28,29] and sustainable benznidazole production.[30] Regarding clinical effectiveness, the BENEFIT clinical trial in individuals with established heart disease associated with CD demonstrated that benznidazole treatment decreased the number of patients with *T. cruzi* DNA detected by PCR but did not change the clinical outcome over 5 years of follow-up.[12] Therefore, the second Brazilian consensus on CD considers benznidazole treatment for chronic CD with no recent documented infection only in patients <50 years old without advanced heart disease.[27] A different scenario occurs in Bolivia, an endemic region of CD where patients are directly in contact with triatomine bugs and in many circumstances it is not possible to determine the time elapsed between last vector-borne *T. cruzi* exposure and CD clinical diagnosis. Regarding safety, previous studies pointed to a high proportion of treatment suspension and a consequent need for the development of alternative trypanocidal drugs.[10] However, our results suggest that a high proportion of benznidazole full treatment courses may be related to the strategy of close follow-up together with patient counselling and reassurance, and use of symptomatic medication. The safety of our strategy was tested in a large Bolivian population and corroborated by a minimum rate of severe ADRs (only 2 of 2075 patients). Therefore, we believe that our results could be an important contribution to overcome one of the barriers against widespread use of benznidazole to treat patients with CD.

In conclusion, this study showed that a large proportion of patients are able to complete a full course of benznidazole treatment with a very low incidence of severe ADRs (two cases) when a strategy of close follow-up together with patient counselling and reassurance, and symptomatic medication was used. This finding was observed in a large population of both children and adults living in Bolivian rural areas. Three variables were independently associated with the event of permanent benznidazole treatment interruption: female gender, ADR severity and skin disorders. Patients with moderate ADRs had the highest probability of suspending treatment. Moreover, the combination of different independent factors in the same patient greatly increased the likelihood of benznidazole treatment suspension. These patients should receive a close follow-up to evaluate for side effect severity to improve the likelihood of completing a full course of benznidazole treatment.

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Author contributions

R. A. M., C. P. F., J.-C. C. and L. M. B.-S. contributed to the design and execution of the study and collected data. G. M. S. d. S., M. F. F. M. and P. E. A. A. d. B. contributed to statistical analysis. G. M. S. d. S., M. F. F. M., A. M. H.-M., M. T. d. H., A. S. d. S., L. H. C. S., P. E. A. A. d. B. and R. M. S. contributed to interpretation and contextualization of the results and manuscript drafting.

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