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Tolerance of Benznidazole in Treatment of Chagas' Disease in Adults▽

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Chagas' disease is an emerging public health problem in areas where the disease is not endemic. Treatment with benznidazole has shown efficacy in the acute stage of the disease, but its efficacy in the chronic stage remains controversial, and unwanted side effects are more frequent and severe in adults than in children. This study describes the profile of side effects of benznidazole in a cohort of *Trypanosoma cruzi*-infected patients in a European country.

Chagas' disease is a traditionally rural Latin American disease that affects 8 to 10 million people (12). Its causal agent, *Trypanosoma cruzi*, is mainly transmitted by a triatomid vector that is endemic in most countries of Latin America. Other routes of transmission, which can also occur in countries where the vector is not present, are blood transfusion, organ transplant, and mother-to-child transmission (14). The acute phase of Chagas' disease usually presents few or no symptoms; some patients experience fever, lymphadenopathy, splenomegaly, and/or edema, but rarely severe disease. Without treatment, around 5 to 10% of patients with severe disease die (14). After the acute phase, *T. cruzi*-infected individuals pass into a clinically silent chronic phase (14). However, over a period of 10 to 30 years, 20 to 35% of patients develop symptomatic chronic Chagas' disease that is mainly characterized by cardiac and/or gastrointestinal disorders.

Treatment with the currently used drugs (benznidazole and nifurtimox) in this phase of the disease provides cure rates of close to 100% in infants (16) and around 60% in children and adults with recent infection (4, 19). The efficacy of drug therapy declines with the duration of infection and is still a matter of debate in the late chronic phase of Chagas' disease (18).

Chagas' disease is no longer limited to areas of endemicity and has recently become a public health problem in the United States and in most European countries receiving immigrants from Latin America, where the disease is endemic (8, 11). The most widely available drug for treating the disease is benznidazole.

In adults, benznidazole has a high rate of adverse effects, which can be classified into three groups: (i) hypersensitivity, including dermatitis with cutaneous eruptions (usually appearing between days 7 and 10), myalgias, arthralgias, and lymphadenopathy; (ii) polyneuropathy, paresthesias, and polyneuritis (usually during the 4th week of treatment); and (iii) bone marrow disorders, such as thrombopenic purpura and agranulocytosis (usually after the second week of treatment) (17).

Despite the high efficacy in acute infections, treatment in chronic stages is controversial and the true efficacy in these stages is unknown (10). However, recent studies have demonstrated that treatment with benznidazole can restrict the progression of Chagas' disease (23) and increase long-term negative seroconversion in patients in an early indeterminate phase (4).

The main aim of this study was to describe and discuss the side effects of benznidazole in a cohort of *T. cruzi*-infected patients in chronic and indeterminate stages living in Barcelona, Spain.

We performed a descriptive observational study in the Center for International Health, in the Hospital Clinic, a university hospital in the center of Barcelona. At the time the study was performed, around 67,000 Latin American migrants lived in this city. The majority of the migrant population attending the Center for International Health came from Latin America, in particular from Bolivia.

Participants were selected from the Latin American population attending the clinical unit, regardless of the reason for the visit, from June 2005 to November 2008. Participants were included in the study if they fulfilled the following four inclusion criteria: (i) having been born in a country where Chagas' disease is endemic (ii) having a confirmed diagnosis of *T. cruzi* infection (by two serological enzyme-linked immunosorbent assays [ELISAs], following international recommendations [24]), (iii) having consented to receive treatment with benznidazole during the study term, and (iv) having signed the informed-consent form. Patients that had previously received treatment with benznidazole or nifurtimox were excluded. Participants were followed by clinicians for up to 60 days.

According to the in-hospital protocol for Chagas' disease treatment, an electrocardiogram and a chest X-ray were per-

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TABLE 1. Adverse events related to antiparasitic treatment with benznidazol in *T. cruzi*-infected patients

Adverse event	No. of patients with event (%)	No. who stopped treatment
Headache	59 (56.2)	None
Dermatological	53 (50.5)	8
Urticaria	23/53 (43.4)	8
Petechial rash	19/53 (35.8)	None
Itching	7/53 (13.2)	None
Palmar-plantar rash	6/53	None
Edema	2/53	None
Dyshidrosis	2/53	None
Hyperpigmentation	2/53	None
Erythema nodosum	1/53	None
Mucositis	1/53	None
Anorexia	42 (40)	None
Weakness	32 (30)	None
Fever	12 (11)	6[a]
Articular involvement	38 (36.2)	None
Arthromyalgia	37/38	None
Arthritis	1/38	None
Paresthesia	29 (27.6)	None
Gastrointestinal disorders	16 (15)	2
Epigastralgia	8/16	2
Nausea	2/16	2
Dysphagia	2/16	None
Abdominal bloating	1/16	None
Heartburn	1/16	None
Vomiting	1/16	2
Diarrhea	1/16	None
Aphthous stomatitis	1 (1)	None
Hearing impairment	1 (1)	None

[a] Six out of eight patients with urticaria presented with fever.

formed for all patients. An esophagogram and a barium enema were only prescribed for patients with gastrointestinal symptoms. In addition, a real-time PCR (RT-PCR) (13) was performed on blood samples of all patients before and 6 months after treatment. All patients were treated with 5 mg/kg of body weight/day of benznidazole for 60 days, with fortnightly medical visits, including a hemogram and biochemistry tests (including hepatic and renal function).

A descriptive analysis was performed. Frequencies, means, and standard deviations were calculated using Stata 9 (20).

All patients invited to participate accepted to sign the informed consent form after receiving the information. A total of 105 participants received benznidazole 5 mg/kg/day (100 mg/tablet; Radanil, Roche) for 60 days. Most of them were women (85/105, 80%), and they had a mean age of 38.7 years (range, 16 to 58). The most frequent country of origin was Bolivia (85.7%), followed by Argentina (9.5%), with only one case each from Colombia, Ecuador, Paraguay, and Peru. All participants were in the chronic stage of the disease. Thirteen (12.4%) had cardiac disorders, and 3 (2.8%) digestive disorders (one with degree I esophagopathy and two with dolichocolon). Sixty of the 105 (57.1%) patients presented one or more adverse events, and 45 of 105 (42.9%) were asymptomatic during the follow-up. Forty-five percent (27 of 60) of the patients presenting with adverse events presented more than one symptom attributed to benznidazole during the treatment period. Side effects during the treatment are shown in Table 1, and examples of the most common skin presentations in Fig. 1 and 2.

Eighty-nine patients (83.8%) completed treatment, while 8 patients (7.6%) had to discontinue due to fever and severe urticaria and 2 other cases (1.4%) due to poor gastrointestinal tolerance (both were in the indeterminate stage of the disease, without pretherapy digestive involvement). Four patients were lost to follow-up after starting treatment.

26 patients had positive blood RT-PCRs for *T. cruzi* before treatment, 5 of which remained positive after completing full treatment, indicating therapeutic failure. In 3 of these 5 patients, the first RT-PCR after treatment was positive, but in the other two patients, RT-PCR was positive 2 years later during the follow-up.

The emergence of Chagas' disease in areas where it is not endemic is currently a public health challenge, and one of the main limitations is the lack of experience in managing adverse events caused by specific treatment against *T. cruzi.* A wide range of side effects were found in the 105 patients treated with

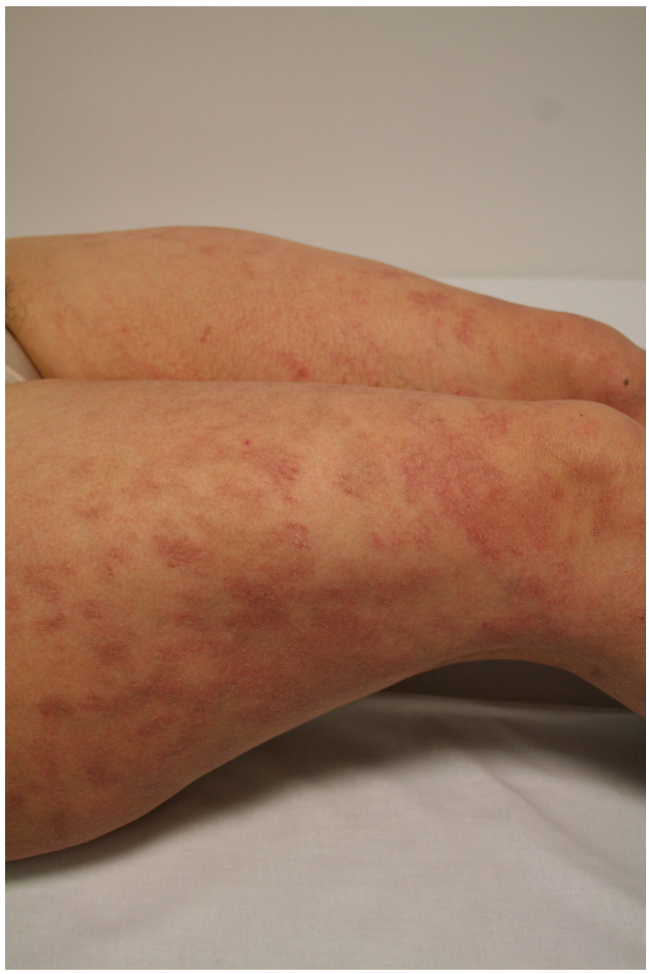

FIG. 1. Pruriginous maculopapular rash on limbs of a patient receiving benznidazole.

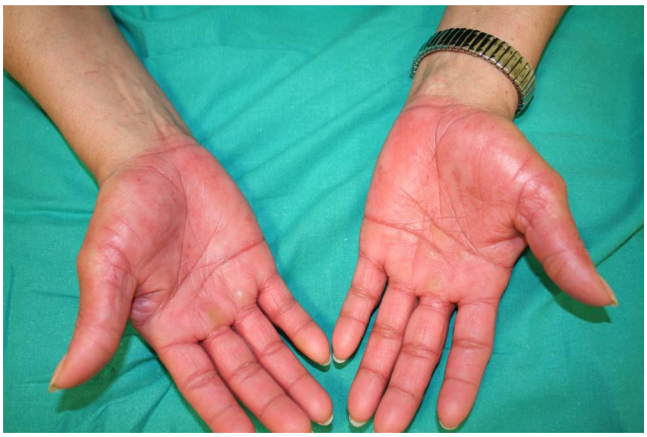

FIG. 2. Palmar rash in a patient receiving benznidazole, a concomitant manifestation with micropapular rash and urticaria.

benznidazole in this geographic area where *T. cruzi* is not endemic, with an incidence similar to and even higher than those previously reported (22). Nonetheless, our results are similar to those obtained in systematically controlled trials designed specifically for this purpose (17), probably due to the close follow-up (every 15 days during treatment) and the application of questionnaires to check for the appearance of side effects on each visit.

The use of RT-PCR allowed us to confirm treatment failure in 5 of 26 (19.2%) of patients. As shown by other studies, repeated PCR testing may indicate that the true treatment failure rate is higher (6).

Though adverse events related to benznidazole have been described mainly in the first 2 weeks of treatment (22), we observed that they appeared during the whole treatment.

Not many studies describing adverse events related to benznidazole in *T. cruzi*-infected adults in the chronic or indeterminate stage of the disease have been reported. Before 1990, small studies with various regimens of drug administration were published (2, 7, 9). Since 1990, larger studies have been reported (1, 5, 17, 21, 23, 25). The most common adverse event related to benznidazole in our study was headache, described in other studies but not so frequently, with an incidence of 2 to 18% (9, 21, 23). It mainly appeared during the first 15 days and was usually well controlled by symptomatic treatment, but it could persist while benznidazole was being administered.

Dermatological events have been described in other works as the main side effect of this drug. Urticaria, the most common dermatological side effect, has been described to appear in 18 to 56% of patients during the first 10 days of treatment with benznidazole (1, 2, 3, 5, 7, 9, 21, 23, 25). We observed that in 13 of 23 patients, urticaria appeared in this 15-day period, but in 6 of 23 patients, urticaria appeared in the second fortnight, and in 4 of 23, in the second month of treatment.

Articular involvement and paresthesia (as a symptom of peripheral polyneuritis), are serious toxic effects induced by benznidazole, appearing mainly at the end of the treatment, as has been described previously (1). We observed a higher rate of patients with this toxic event than has been described in other studies, which reported it in 10 to 18% of patients (25). In studies previous to 1990, a high rate of this adverse event was recorded (25 to 45%), probably due to high dose regimens used in those studies (2, 9).

Gastrointestinal disorders were not as common in our study as in other studies, in which they have been described to appear in 13 to 27% of patients (9, 17, 25). Viotti et al. described a 5% incidence of digestive side effects (23), which appeared only when the patients did not follow a specific diet indicated during the treatment, and anorexia, which was observed in 40% of our patients, was not recorded in any patient in Viotti's studies.

The appearance of fever in patients treated with benznidazole is a criterion of severity. In other reports, it was described as a symptom that appeared with dermatological events (1, 3, 25), but Viotti et al. (23) described fever in 0.9% of patients and Sosa Estani et al. in 6% (17) of patients. In our study, it was recorded in 12 (11%) patients, and in 6 cases, it presented with urticaria.

Our results concur with the fact that no cumulative effect of benznidazole serum concentrations is expected during treatment, so the probability of side effects appearing might be similar over time (15), unless the side effect that appears is a hypersensitivity reaction.

In most cases, the side effects were well controlled with symptomatic treatment. Treatment was stopped in 9% of patients, fewer than reported in previous studies with benznidazole (17, 22), but no life-threatening side effects were observed. Only one patient who had to stop the treatment was in the chronic stage of the disease, with digestive involvement in particular, but the reason for stopping benznidazole was a severe urticaria with fever. The results of our study may be explained by the fact that we recorded clinically observed side effects and specific medical histories every 15 days.

Little is known about the pharmacokinetics of benznidazole. To date, the therapeutic range has been defined as 3 to 6 mg/liter, and serum concentrations >20 mg/liter seem to be associated with more side effects (15). Based on the pharmacokinetic profile of benznidazole, serum drug concentrations are expected to be lower than 20 mg/liter (15) with the current regime of 5 mg/kg/day (split into two doses, every 12 h). Nonetheless, there is a high incidence of side events that can be severe in some patients.

Until new, better drugs or combined therapies become available for Chagas' disease treatment, the current treatment with benznidazole and nifurtimox must be improved and patients treated with these drugs must be strictly monitored during the follow-up.

Our study was carried out in Barcelona, an urban area with good access to health services where Chagas' disease is not endemic. The conclusions and lessons of our study are difficult to replicate in rural areas of endemicity, where the access of patients to the health system is usually limited.

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All the authors contributed to the literature search and writing the text. María-Jesús Pinazo, José Muñoz, Elizabeth Posada, and Joaquim Gascon led the clinical management of the patients and designed the study. Elena del Cacho and Dolors Soy contributed to the design of the study and conducted the critical review of drug side effects based on

their previous experience in antiparasitic drugs. Montserrat Gállego and Paulo López-Chejade performed laboratory support for *T. cruzi* serology and RT-PCR. Edgar Ayala analyzed and interpreted the data.

The authors have no conflicts of interest.

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