CORRESPONDENCE

Benznidazole for Chronic Chagas' Cardiomyopathy

TO THE EDITOR: The Benznidazole Evaluation for Interrupting Trypanosomiasis (BENEFIT) trial, reported by Morillo et al. (Oct. 1 issue),[1] showed that trypanocidal therapy with benznidazole in patients with Chagas' cardiomyopathy significantly reduced polymerase-chain-reaction (PCR)–based parasite detection in serum samples but did not significantly reduce clinical deterioration of cardiac function through 5 years of follow-up. However, after benznidazole treatment, the PCR conversion rate was only modest, at 66.2%, which suggests that the parasite persisted in a considerable proportion of patients. This modest PCR conversion rate raises the question of whether drug exposure was adequate. First, the regimen was modified from 5 mg per kilogram of body weight per day for 60 days to a fixed dose of 300 mg per day with variable duration, with the authors citing only anecdotal experience without providing evidence for equivalence.[2,3] Second, dose–response relationships as assessed by measurement of serum drug concentrations were not evaluated. This is particularly relevant because side effects led to frequent therapy interruptions. Third, reinfection due to ongoing vector exposure or reactivation may have contributed to the increase in positive PCR assay results over time.[4,5] Despite the disappointing trial findings, it is, in our view, premature to dismiss the possibility that benznidazole treatment has long-term clinical benefits beyond the relatively short follow-up period of 5 years. In our opinion, in the absence of alternative treatment options, benznidazole for Chagas' cardiomyopathy should not be precluded.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Morillo et al. report that a short course of benznidazole had no significant effect on the progression of heart disease in patients with established Chagas' cardiomyopathy. On the basis of PCR assay results, the authors argue against a possible association between the eradication of *Trypanosoma cruzi* and more favorable clinical outcomes. However, the well-recognized strength of PCR in assessing Chagas' disease re-

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mains its ability to detect trypanocidal treatment failure.[1] Because low intermittent parasitemia is characteristic of Chagas' disease in the chronic phase, a single negative PCR assay result is unreliable for the assessment of trypanocidal treatment efficacy. Hence, the authors' assumption that parasite clearance does not lead to clinical improvement seems unfounded. The study by Morillo et al. should be viewed as a pragmatic trial that shows that benznidazole is ineffective in the prevention of clinical deterioration in patients with advanced Chagas' infection. With respect to younger patients with little or no evidence of established cardiomyopathy, trypanocidal treatment with benznidazole remains a plausible option.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Morillo et al. conclude that benznidazole treatment has no significant effect on the clinical progression of Chagas' cardiomyopathy, despite significantly reducing the circulating parasite load. Given the broad implications of these findings, further data analyses and new clinical studies are necessary.

In the study by Morillo et al., the PCR conversion rates in the placebo group were markedly higher than the rates reported in other recent studies,[1] which suggests that PCR evaluation was conducted at a lower sensitivity, potentially leading to an overestimation of the trypanocidal effect of benznidazole. In addition, the authors should focus on the proportion of patients who had persistently negative PCR assay results after antiparasitic treatment, rather than on the overall proportion of patients who have a negative PCR assay result at each time point. Clinical progression should be assessed among the patients who had or did not have a response to benznidazole treatment, as compared with those who received placebo. Finally, the lack of correlation between the trypanocidal effect of benznidazole and the clinical evolution of the disease may be related to limited drug access or activity in the inflammatory and fibrotic foci of Chagas' cardiomyopathy, a lack of reversibility of these lesions, or both.[1-3] In addition, this lack of correlation highlights the need for early diagnosis and treatment of patients with chronic indeterminate Chagas' disease and for the assessment of new drugs and treatment strategies,[2] as well as the need for future studies of the effects of benznidazole on the clinical progression of chronic indeterminate Chagas' disease.[4]

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Dr. Ribeiro reports being head of the Chagas Disease Area at the Drugs for Neglected Diseases initiative, a not-for-profit product development partnership that develops new treatments for neglected patients, including those affected by Chagas' disease. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Hamers et al. raise issues regarding the dosing regimen of benznidazole and why this was changed. Modification of the benznidazole regimen was necessary because of changes in the production of benznidazole that occurred during the course of the trial, as explained in the Supplementary Appendix accompanying our article (available at NEJM.org). In making the modifications, we ensured that the total dose of the two regimens given to the patients was similar. Preliminary data from our study indicate a similar effect of these two regimens on the rates of conversion to a negative PCR result, clinical outcomes, and side effects,

the rate of which was lower than reported previously. Overall, our rate of permanent discontinuation of benznidazole was substantially lower than the rates reported previously.[1,2] We did not measure serum drug concentrations because this would have been costly and impractical in a large randomized trial. We believe that reinfection was unlikely because only 2.6% of the patients lived in an infested house. The mean duration of follow-up in our trial was 5.4 years; however, 75% of the patients were followed for up to 7 years. Although this is a short period as compared with the long natural history of Chagas' disease, it is unknown whether extended follow-up would change our conclusions in the overall population studied.

Cordeiro questions the validity of PCR assay as a marker of therapeutic efficacy or failure. We used it simply to show that benznidazole has an effect on this measure in chronic Chagas' cardiomyopathy, but the effect was indeed more modest than it is in the indeterminate stage of the disease.[3] We agree that PCR-based detection of circulating *T. cruzi* is a useful method for denoting treatment failure. However, BENEFIT was a pragmatic trial, and we do not assert that parasite clearance from the blood would not lead to clinical improvement. Our data suggest that the currently used regimen that is recommended by most guidelines[4,5] may be inadequate. It is possible that in younger patients with no evidence of cardiomyopathy, etiologic treatment to remove or correct the cause of the disease may be more effective, but this determination requires prospective evaluation in larger and longer-term randomized trials.

Urbina et al. raise several issues. PCR conversion rates in the placebo group were higher in our trial than in previously reported studies, but most of the data from those studies were obtained from patients in the indeterminate stage of Chagas' cardiomyopathy and were based on the inclusion of patients with multiple positive PCR measurements; therefore, those studies cannot be directly compared with ours. With respect to the other issues raised, it is uncertain whether focusing on patients who have a response to treatment as detected by PCR assay would identify a subgroup of the population that would benefit from treatment. Whether newer regimens of trypanocidal drugs, given alone or in combination, or whether repeated dosing or intervening at an earlier stage of the disease would be associated with greater benefit is also uncertain and needs to be explored further. Our study emphasizes the need to test hypotheses, however attractive, in large randomized trials that can provide reliable information on the effects of treatment on clinical outcomes.

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Since publication of their article, the authors report no further potential conflict of interest.

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FTO Obesity Variant and Adipocyte Browning in Humans

TO THE EDITOR: Different polymorphisms in the fat-mass and obesity-associated gene (*FTO*) have been consistently associated with traits related to obesity and were sensibly scrutinized by Claussnitzer et al. (Sept. 3 issue)[1] by means of genetic and genomic approaches. The authors reported the regulatory importance of the *FTO* locus in early adipocyte differentiation and the causal role of a risk-conferring *FTO* variant (rs1421085) on adiposity, which is believed to act by disrupt-