Drug Susceptibility of Genetically Engineered Trypanosoma cruzi Strains and Sterile Cure in Animal Models as a Criterion for Potential Clinical Efficacy of Anti-T. cruzi Drugs

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The article by Francisco et al. (1) describes the use of a bioluminescence imaging system (2) to evaluate the efficacy of benznidazole, a 2-nitromidazolide, and posaconazole, an antifungal triazole, in murine models of acute and chronic Chagas disease. While the use of bioluminescence in Trypanosoma cruzi research has been reported before (3–6), the improved sensitivity of the red-shifted reporter facilitates following tissue distribution more accurately (2). However, there are issues concerning the nature and interpretation of the experimental results to consider.

(i) The finding that benznidazole induced a sterile parasitological cure in acutely or chronically infected mice using 20, 10, or just 5 daily doses of 100 mg/kg (see Fig. 1 to 4 in reference 1) is at odds with previous studies using the CL strain (7–10). CL was touted as a “benznidazole-susceptible strain,” but to induce a sterile cure, the treatment duration had to be extended to 40 days (7–10); the same duration of treatment was required to achieve a sterile cure with posaconazole at 20 mg/kg (8, 10). Such contrasting results suggest that the genetically engineered luminescent CL Brener clone used in this study may be hypersusceptible to benznidazole. Furthermore, the duration of the posaconazole treatment was suboptimal, leading to an overestimation of the efficacy of the former drug and an underestimation of that of the latter.

(ii) Of greater concern is the implication that a sterile cure is required for the clinical efficacy of any potential anti-T. cruzi drug. We still know too little about the clinical course of Chagas disease to make such a conclusion. If the parasite load is profoundly reduced but not eliminated by a drug, will an intact immune response keep the residual parasite load under control? According to the prevailing hypothesis of chronic Chagas disease (11–13), the reduction of >3 orders of magnitude of the parasite load induced by both benznidazole and posaconazole and sustained in the absence of immunosuppression (see Fig. 2 and 3 in reference 1) should lead to a profound reduction in the pathological manifestations of chronic Chagas disease. This interpretation is consistent with results from observational clinical studies (14).

(iii) Important consideration must also be given to the adverse side effects associated with benzimidazole treatment versus the excellent safety profile of posaconazole and analogs. Would the only drugs that can produce a sterile cure also have undesirable side effects? This is an unfortunate lesson from cancer chemotherapy.

Evaluation of the drug susceptibility of genetically engineered T. cruzi strains or clones is required in order to properly interpret the significance of the results of studies using such organisms. Furthermore, there is no evidence that a sterile cure is required for halting or slowing the clinical progression of Chagas disease. If a sterile cure becomes a “go/no go” criterion for drug development, we might never have a safe drug for etiological treatment of Chagas disease. Until there is a longitudinal study and a validated biomarker to show otherwise, the induction of a profound and sustained reduction of the parasite burden should realistically be the criterion for the advancement of potential anti-T. cruzi drugs or drug combinations to clinical development.

REFERENCES
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