Efficacy of Oral Administration of E1224 in Combination with Benznidazole on Experimental Trypanosoma cruzi Infection

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Introduction and Objectives

Chagas disease remains a challenging infection due to the unavailability of well tolerated and easy-to-use treatments, and consistently efficacious drugs. Combination therapy is proposed as an alternative therapeutic approach, as it may improve treatment efficacy whilst decreasing toxicity, with potential impact on the developments of resistance.

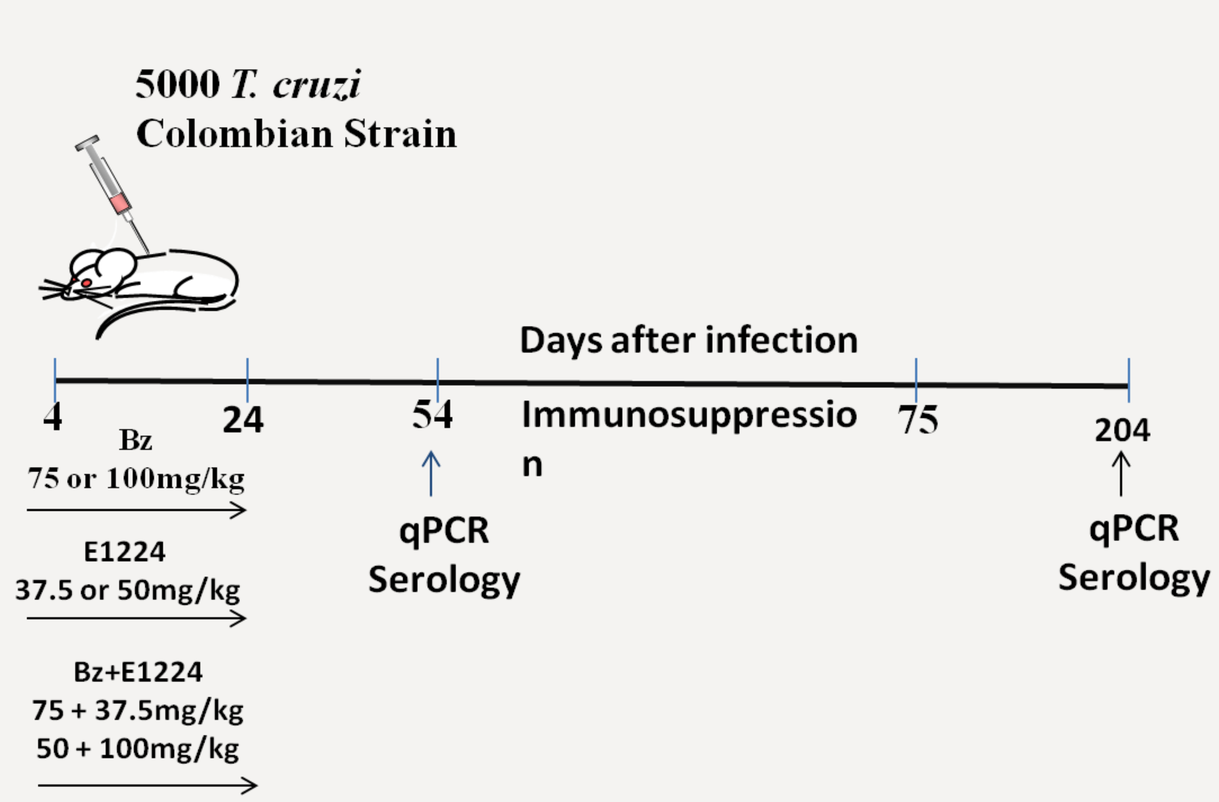
In this study, we evaluated the effect of treatment with benznidazole (Bz) when combined with E1224 (pro-drug of ravuconazole) in experimental acute murine infection.

Methods

Parasite: Colombian *T. cruzi* strain (DTU I), highly resistant to benznidazole .

Drugs: E1224, which is a pro-drug of ravuconazole ([R-(R*,R*)]-4-[2-[2-(2,4-difluorophenyil)-2-hydroxy-1-metlyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-thiazolyl]benzonitrile, Eisai, Japão) and benznidazole (2-nitroimidazole-(N-benzil-2-nitzo-1-imidazoleacetamide; Lafepe, Brazil).

Study design



Results

Bz/E1224 combinations were well tolerated and all treatments, in monotherapy or combinations, prevented the death of infected animals, while the mortality in the control group was 80%. Both drugs were very effective in suppressing parasitemia during the treatment period. However, after the end of the treatment, parasitological and PCR assays indicated no cure among animals treated with different doses of E1224 or Bz in monotherapy. Combination therapy using E1224 at 50mg/kg plus Bz100 mg/kgmpk and E1224 at 37.5mpk plus Bz 75mpk induced 100% and 40% cure rates, respectively (Table 1).

Table 1 - Efficacy of E1224 in monotherapy or in benznidazol combination treatment for 20 days in *Trypanosoma cruzi drug*-resistant murine model[1]

Experimental groups	Number of surviving/ total mice[3]	Total negative assays/ total mice[4]
Untreated	2/8 (25%)	0/8 (0%)
Bz – 75mk/kg	7/7 (100%)	0/7 (0%)
E1224 37.5mg/kg	7/7 (1005)	0/7 (0%)
E1224 + Bz (37.5 + 75 mg/kg)	10/10 (100%)	4/10 (40%)
Bz – 100mk/kg	8/8 (100%)	6/8 (25%)
E1224 50mg/kg	9/9 (100%)	0/9 (0%)
E1224 + Bz (50 + 100mg/kg)	10/10 (100%)	10/10 (100%)

[1]Swiss female (7 to 10/group) weight 20 to 24g were inoculated with $5x10^3$ trypomastigotes of Colombian strain.
[2]Treatment was initiated at 4 days after inoculation followed by 20 days and it was administered per oral route.
[3] Survival until 30 days after treatment
[4]Negative results in fresh blood examination performed before and after cyclophosphamide immunosuppression and in PCR assay performed in the 1st and 6th month after treatment.

Furthermore, cured animals had significantly lower levels of serum anti- *T. cruzi* IgG than those of the untreated animals, and similar to healthy mice (Figure 1)

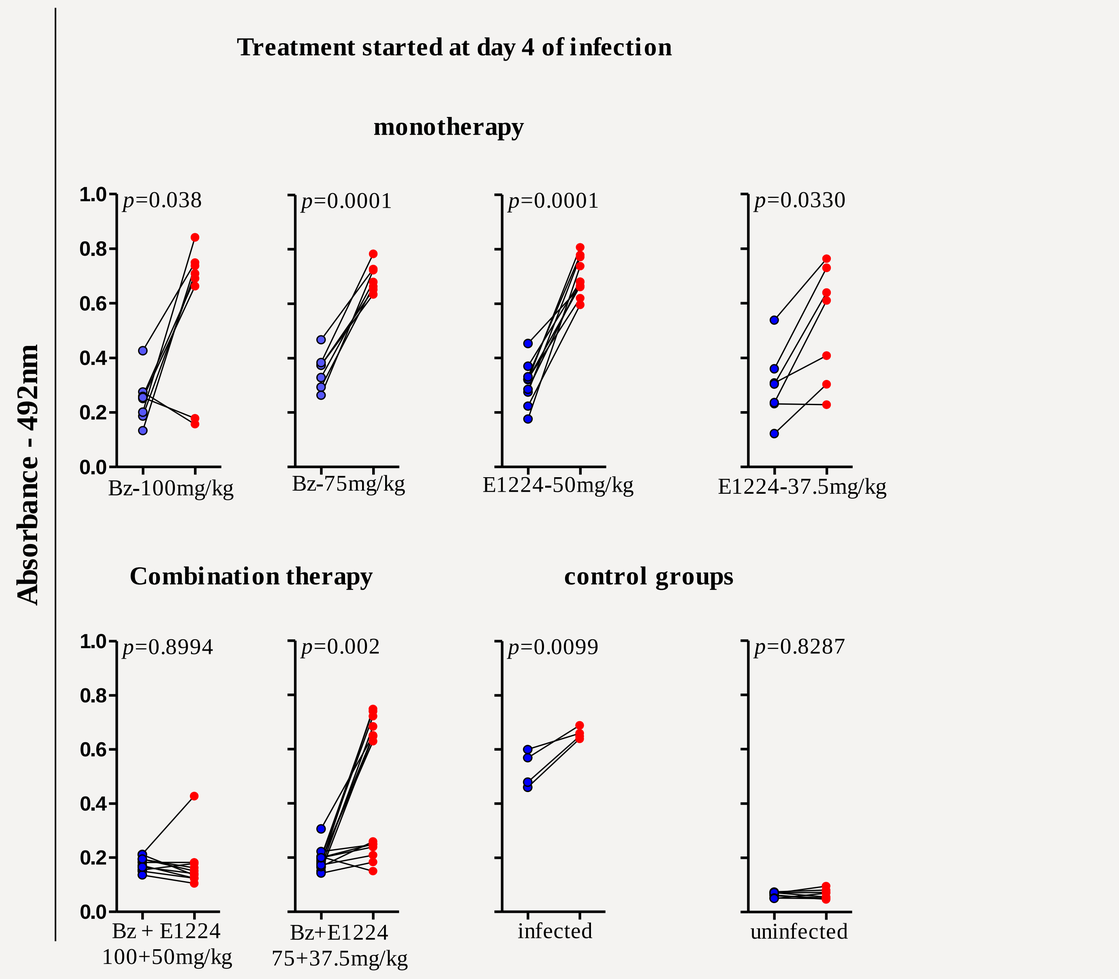


Figure1: IgG, antibodies in sera of mice infected with 5000 trypomastigotes of *T. cruzi* Colombian strain and treated daily with 37.5 and 50 mg/kg/day of E1224 in combination of 50 and 100 mpk of benznidazole for 20 consecutive days. Treatments were started at day 4 of infection. Blue circles represent the IgG levels 30 days after treatment red circles IgG levels 180 days after treatment.

Conclusions

Our results demonstrated a positive interaction between E1224 and Bz in the treatment of *T.cruzi* murine infection. In addition, this study expands the available preclinical data on drug combinations on azole and Bz compounds and provides support for the evaluation of new anti-*T.cruzi* treatment regimens.

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