Use of benznidazole to treat chronic Chagas’ disease: a systematic review with a meta-analysis

CRD summary
The effectiveness of benznidazole for treating chronic Chagas’ disease was uncertain and observed benefits could be marginal. There was a lack of randomised evidence on treatment in the late chronic stage of the disease. Although the review was limited by a failure to formally assess study validity and report review processes, the authors’ cautious conclusions appear reliable.

Authors’ objectives
To evaluate the effectiveness of benznidazole for treating chronic Chagas’ disease.

Searching
MEDLINE, EMBASE, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to October 2008 without language restrictions. Search terms were reported. Reference lists of included studies and of other relevant literature were checked. The search was restricted to published literature.

Study selection
Controlled studies that compared treatment with benznidazole versus placebo or no treatment for patients of any age with chronic Chagas’ disease in the indeterminate phase or with visceral involvement were eligible for inclusion. The primary review outcome was serological, parasitological or clinical response to therapy as defined in the primary study. Clinical response (non-progression or cure) was a separate outcome. Studies of acute or congenital infection were excluded.

Participants in the review were children or adults (overall age range one to 79 years) with chronic Chagas’ disease in the earlier or later stage. Most participants were symptomatic and some had organ involvement. The most commonly used dose of benznidazole was 5mg/kg daily (range 4mg/kg to 10mg/kg). Response rate was measured by negative serology in most studies; other measures were xenodiagnosis, blood culture, polymerase chain reaction (PCR) and clinical events. Adverse reactions were reported in the review. Median study duration was four years (range one to four years in randomised studies and two to 21 years in observational studies).

The authors did not state how the papers were selected for the review.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Odds ratios (ORs) and 95% confidence intervals (CIs) were extracted or calculated from event rates in the two groups. Data were extracted in duplicate using a standardised format.

Methods of synthesis
Studies were combined to calculate pooled odds ratios and 95% CIs by means of a random-effects model. Negative serology results were the preferred measure for the primary outcome (where there was a choice). Sensitivity analyses were conducted to examine the effects of study design, participant age (child/adult) and choice of outcome measure. Heterogeneity was assessed using $\chi^2$ and $I^2$ tests. Publication bias was assessed by estimating the additional number of studies with null or statistically non-significant findings that would be required to render the analysis statistically non-significant.

Results of the review
Nine studies were included in the review (n=1,924): three double-blinded randomised controlled trials (RCTs) (n=285)
and six observational studies (n=1,639)

**Treatment response**: All analyses significantly favoured the intervention over controls for this outcome, but with substantial heterogeneity in most cases. When all nine studies were pooled, the odds ratio was 18.8 (95% CI 5.2 to 68.3, I²=76%; nine studies). The most marked effect was in RCTs (OR 70.8, 95% CI 16 to 314, I²=36%; three RCTs); restricting this analysis to RCTs of children reduced heterogeneity (OR 38.4, 95% CI 10.7 to 137.0, I²=8%). The odds ratio for observational studies was 7.8 (95% CI 2.1 to 28.9, I²=59%; six studies); restricting analysis to observational studies of adults reduced the odds ratio to 6.3 (95% CI 1.6 to 24.7, I²=60%).

Assessment for publication bias indicated that 223 statistically insignificant unpublished studies would be required to negate the statistical significance of these findings.

**Clinical response**: The intervention significantly lowered the risk of a clinical event (heart disease or mortality) (OR 0.29, 95% CI 0.16 to 0.53, I²=0%; two observational studies)

**Adverse reactions**: A median of 10% of participants (range 1% to 18%) discontinued treatment due to toxicity (most commonly cutaneous or gastrointestinal). Adverse reactions were less common in children than adults. Reporting was poor for this outcome.

**Authors' conclusions**
The effectiveness of benznidazole for treating chronic Chagas' disease was uncertain and the observed benefits could be marginal. There was a lack of randomised evidence relating to the late chronic stage of the disease.

**CRD commentary**
The objectives and inclusion criteria of the review were clear and relevant sources were searched for studies in any language. The restriction by publication status meant that the review was subject to publication bias, although formal assessment was not strongly suggestive of such bias. No systematic assessment of study validity was reported and designs of observational studies were not described in detail. It was unclear whether steps were taken to minimise risks of bias and error by having more than one reviewer independently select the studies, although this precaution apparently applied to data extraction. These factors made it difficult to determine the reliability of the review findings. The statistical techniques used to combine studies and assess for heterogeneity appeared appropriate. The authors discussed potential sources of heterogeneity between studies and provided a plausible explanation for the variable findings. They also noted that the surrogate markers used in most studies were not reliable predictors of clinical events. Although the review was limited by the failure to formally assess study validity or report review processes, the authors' cautious conclusions appear reliable.

**Implications of the review for practice and research**
**Practice**: The authors stated that treatment of Chagas' disease with benznidazole was indicated in acute infections and the early chronic stage of the disease (children aged up to 12 years), but its risk-benefit ratio was doubtful in asymptomatic individuals and those aged over 50 years.

The authors did not state any implications for further research.

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**Bibliographic details**

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.