

Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)

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Should trypanocidal therapy be used to treat patients in the chronic phase of Chagas disease?

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Abstract

Antiparasitic treatment of patients with Chagas' disease in chronic stage could prevent the complications related to the disease. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified five systematic reviews including eight randomized trials and 11 observational studies. We combined the evidence using meta-analysis and generated a summary of findings table following the GRADE approach. We concluded it is not clear whether antiparasitic treatment improves survival or reduces complications related to chronic Chagas' disease because the certainty of the evidence is very low.

Problem

Chagas' disease represents the third largest parasitic disease burden globally and the first in Latin America[1]. Chronic Chagas' cardiomyopathy is the most common form of non-ischemic cardiomyopathy worldwide, and one of the leading causes of morbidity and death in Latin America [2]. Chagas' disease has two clinical phases, acute infection that may be manifested by a self-limited febrile illness that lasts 4 to 8 weeks, and chronic phase characterized by an indeterminate stage in which patients are asymptomatic and free of complications that can last their whole life [3]. Ten to thirty years after the acute infection, about one third of the patients in chronic phase of Chagas' disease develop cardiac or digestive complications. At the present time, the mechanism responsible for the mentioned complications is believed to be related to the presence of chronic parasitemia and its corresponding inflammatory

reaction [4]. In this context, antiparasitic treatment for patients with Chagas' disease in the chronic phase is proposed as a measure to prevent the disease's visceral complications and their consequences.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information, we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- Trypanocidal therapy probably does not improve survival nor reduces cardiomyopathy progression in patients with chronic Chagas’ heart disease.
- Trypanocidal therapy probably reduces the risk of congenital transmission in young women with chronic Chagas’ disease.
- It is not clear whether antiparasitic treatment improves survival or reduces complications related to chronic Chagas’ disease in patients with early stages of chronic Chagas’ disease (no visceral involvement) because the certainty of the evidence in this scenario is very low.
- Antiparasitic treatment probably increases the risk of adverse effects that leads to treatment discontinuation

About the body of evidence for this question

<p>What is the evidence. See evidence matrix in Epistemonikos later</p>	<p>We found five systematic reviews [5],[6],[7],[8],[9] considering 19 primary studies [10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28], including eight randomized controlled trials [10],[11],[12],[13],[15],[18],[21],[26], and 11 observational studies. We also identified two recently published primary studies (one randomized [29]and one observational [30]), not included in any systematic review.</p>
<p>What types of patients were included</p>	<p>Patients with Chagas’ disease in chronic phase indeterminate stage or chronic phase with visceral compromise.</p>
<p>What types of interventions were included</p>	<p>Benznidazole, nifurtimox, allopurinol or itraconazole for 30 to 60 days.</p>
<p>What types of outcomes were measured</p>	<p>Death from any cause; cardiac disease progression; congenital transmission; electrocardiographic abnormalities; serological tests negativization; xenodiagnosis negativization; polymerase chain reaction negativization; adverse effects leading to treatment discontinuation</p>

Summary of findings

The information about the antiparasitic effects is based on eight randomized controlled trials and eleven observational studies that included 7772 patients. Eight studies (one randomized and seven observational studies) reported death from any cause, six studies (one randomized and five observational studies) reported cardiac disease progression, one observational study reported congenital transmission, eleven studies (six randomized and five observational studies) reported adverse effects that lead to treatment discontinuation, four studies (three randomized and one observational study) reported electrocardiographic abnormalities, ten studies (three randomized and seven observational studies) reported serological tests negativization, four studies (two randomized and two observational studies) reported polymerase chain reaction negativization and seven studies (four randomized and three observational studies) reported xenodiagnosis negativization.

- Benznidazole therapy probably does not improve survival in patients with chronic Chagas' heart disease. It is not clear whether other antiparasitic drugs affect survival or cardiomyopathy progression because the certainty of the evidence is very low.
- Benznidazole therapy probably does not reduce cardiomyopathy progression in patients with chronic Chagas' heart disease. It is not clear whether other antiparasitic drugs affect cardiomyopathy progression because the certainty of the evidence is very low.
- Trypanocidal therapy probably reduces the risk of congenital transmission in young women with chronic Chagas' disease. The certainty of the evidence is moderate.
- It is not clear whether antiparasitic treatment improves survival or reduces complications related to chronic Chagas' disease in patients with early stages of chronic Chagas' disease (no visceral involvement) because the certainty of the evidence in this scenario is very low.
- Antiparasitic treatment probably increases the risk of adverse effects that leads to treatment discontinuation. The certainty of the evidence is moderate.

Antiparasitic for Chagas' disease in chronic phase				
Patients		Patients with Chagas' disease in chronic phase		
Intervention		Antiparasitic treatment		
Comparison		Placebo		
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT antiparasitic treatment	WITH antiparasitic treatment		
	Difference: patients per 1000			
Death	Benznidazole		RR 0.94 (0.78 to 1.14)	⊕⊕⊕○ ¹ Moderate
	180 per 1000	169 per 1000		
	Difference: 11 patients less per 1000 (Margin of error: 40 less to 25 more)			
	Nifurtimox		RR 1.36 (0.4 to 4.5)	⊕○○○ ^{1,2} Very low
	40 per 1000	54 per 1000		
	Difference: 14 patients more per 1000 (Margin of error: 24 less to 139 more)			
	Allopurinol		RR 0.16 (0.04 to 0.66)	⊕○○○ ^{1,2} Very low
	40 per 1000	6 per 1000		
	Difference: 34 patients less per 1000 (Margin of error: 39 to 18 less)			
Cardiac disease progression	Benznidazole		RR 0.88 (0.67 to 1.15)	⊕⊕⊕○ ¹ Moderate
	87 per 1000	76 per 1000		
	Difference: 11 patients less per 1000 (Margin of error: 29 less to 13 more)			
	Allopurinol		RR 1.09 (0.73 to 1.64)	⊕○○○ ^{1,2} Very low
	130 per 1000	142 per 1000		
Difference: 12 patients more per 1000 (Margin of error: 35 less to 83 more)				
Congenital transmission	Benznidazole or Nifurtimox		RR 0.04 (0.012 to 0.166)	⊕⊕⊕○ ^{2,3} Moderate
	203 per 1000	8 per 1000		
	Difference: 195 infections less per 1000 (Margin of error: 201 to 171 less)			
Adverse effects related to antiparasitic treatment leading to treatment discontinuation	38 per 1000	99 per 1000	RR 2.61 (1.07 to 6.4)	⊕⊕⊕○ ¹ Moderate
	Difference: 61 patients more per 1000 (Margin of error: 2 to 205 more)			

RR: Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risk **WITHOUT antiparasitic** is based on the risk in the control group of the trials. The risk **WITH antiparasitic** (and its margin of error) is calculated from relative effect (and its margin of error).

¹ There is important imprecision. The decision would substantially vary in both extremes of the confidence interval or the results are fragile [31] (fragility index for the effect allopurinol on death is 3).
² Studies that reported this outcome are observational.
³ Confidence in the estimates of effect was upgraded because of a large magnitude of effect.

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕

High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕○

Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕○○

Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕○○○

Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- The evidence applies to patients with Chagas' disease in chronic phase.
- The evidence does not apply to patients with Chagas' disease in acute phase, early congenital Chagas' disease or reactivated Chagas' disease.

About the outcomes included in this summary

- Two of the efficacy outcomes that we considered as critical (survival and visceral compromise) were reported by only one randomized controlled trial [29] that informed absence of significant benefits. However that study included patients with Chagas' disease in chronic phase with confirmed cardiac compromise and the results are not directly applicable to patients at early stage (no visceral compromise). The latter subgroup of patients was only included in observational studies with inconsistent results (very low certainty evidence) [14],[17],[20],[24],[27].
- One observational study [30] compared the incidence of congenital Chagas' disease in newborns of women with chronic Chagas' disease that had received and not received antiparasitic treatment. The results showed a considerable reduction in congenital infections.
- Most of the efficacy outcomes reported in the randomized controlled trials were surrogate, their results suggest antiparasitic treatment with benznidazole, nifurtimox or allopurinol probably reduces the chance of xenodiagnosis positivity (308 less per 1000; 95% CI 56 to 390 less, [MODERATE certainty]. Treatment with benznidazole also probably reduces the chance of polymerase chain reaction positivity (152 less per 1000; 95% CI 93 less to 178 less, [MODERATE certainty]).

Balance between benefits and risks, and certainty of the evidence

- The absence of benefits in terms of survival or cardiac disease progression in patients with confirmed visceral compromise (MODERATE certainty) determines that the risks (increase in morbidity related to adverse effects, MODERATE certainty) predominate in the trade-off analysis.
- In patients with early stage chronic Chagas' disease (no visceral compromise) it is not clear if antiparasitic treatment affects clinically important outcomes (observational studies with inconsistent results or indirect evidence from surrogate outcomes).
- In young women with Chronic Chagas' disease antiparasitic treatment probably reduces the risk of congenital transmission (MODERATE certainty) hence the trade-off analysis favors benefits over risks.

What would patients and their doctors think about this intervention

- Considering the existing uncertainty related to the efficacy of antiparasitic treatment we assume that significant variability in patients values and preferences could exist. Although we consider that the majority would choose no to be exposed to an intervention related to significant adverse effects whose benefits have not been proved, some could put more weight in the possibility of obtaining those benefits and choose the opposite.

Resource considerations

- In the context of an intervention whose benefits are dubious, costs could be relevant in reaching a decision.

Differences between this summary and other sources

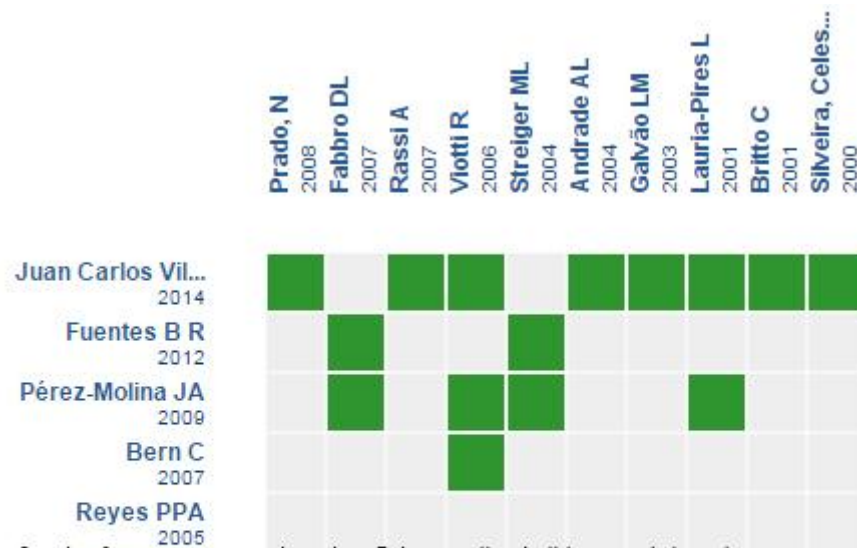
- The conclusions of the present analysis are consistent with the conclusions of most published systematic reviews [5],[6],[7],[8] but are discordant with one of them in which the authors recommend antiparasitic treatment for most Trypanosoma cruzi infected patients [9].
- Our conclusions are partially discordant with the main clinical practice guidelines which recommend to consider antiparasitic treatment for children or young adults with Chagas' disease in chronic phase [32],[33],[34].

Could this evidence change in the future?

- The probability that future evidence significantly modifies the information presented in the present summary is high because of the uncertainty that exists in relation to the main outcomes in the subgroup of patients with early stage Chronic Chagas' disease (no visceral compromise).
-

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.

The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.

The rows represent systematic reviews that share at least one primary study, and columns display the studies.

The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version**: [Trypanocidal therapy to prevent chagasic cardiomyopathy](#)

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears. The details about the methods used to produce these summaries are described here

<http://dx.doi.org/10.5867/medwave.2014.06.5997>.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org). These summaries follow a rigorous process of internal peer review.

Conflicts of interest

The authors do not have relevant interests to declare.

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