Reviewer's report

Title: Immunological and parasitological response in chronic Chagas patients 3 years after nifurtimox treatment

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Reviewer: Andrea Angheben

Reviewer's report:

This is an interesting study on the response to nifurtimox three years after treatment of patient affected by chronic Chagas disease. The topic and the particular focus on treatment failure/assessment may well interest BMC Infectious Disease readers. The following comments represent corrections, concerns or issues related to the paper:

a) discretionary revisions:

- Title and Page 2 line 4 “immunological”: when I read “immunological” I do not think only to “serological” response as it is further shown in the paper but also to cytokines cascade/interaction/titer or other immune biomarkers evolution after treatment; so I would prefer "serological" than "immunological"; if authors do not want to change the title at least in the abstract… Rest of the abstract is really well written and informative.

- Page 11 line 4 I would add to “but a study”: "but a non-randomized study" which can better summarize to readers not deeply interested in Chagas disease literature

- Page 11 line 14 “Stat-Pak cannot be used”, why not “cannot be suggested as a test of cure”?

- Page 11 line 2: low agreement …demonstrates the lack of utility:I would be less absolute saying “tend to demonstrate” the lack of utility…

b) minor essential revisions:

- Page 2, line 3 recommandations should be corrected “recommendation”; treatement # treatment;

- Page 9 line 4: the final “point” misses.

- Through the paper when regarding the two ELISA tests authors must write ELISAs, the “s” is frequently missing indicating the plural.

- Page 10 line 6: maker # marker.

- Page 13 last paragraph: authors provide a list of new diagnostic techniques, omitting serological approach as a result of their data; I do not ask for change here, since conclusion is clearly following author’s data and discussion, but I would prefer a line to be dedicated (eventually in the discussion) to the more recent serological/antigenic approaches to cure assessment (for instance multiplex serology, ref 9 of the manuscript or for antigen detection Ana
- Table 2: percentage is reported between () but not specified as 100% or as (%) in the first line of the table.

- Last minor essential note: in the bibliography some journal are reported with shortened name (Lancet, JAMA, Mem Inst Oswaldo Cruz) and other with the complete one: needs review paying attention to the editor rules.

c) major compulsory revisions:

- Page 4 line 17: authors state that RDTs have proved sensitive and specific in adults screening for Chagas disease, referring to two good works where only one commercially available RDT has been evaluated (Stat-Pak); I would not be so absolute in affirming that RDTs in general are both sensitive and highly specific, while their utility in screening procedure in hard-to-reach population can be acceptable. Stat-Pak is currently the "most evaluated" RDT but we cannot pass the message than can be enough in screening procedures. I would ask for a more prudent formulation of the concept.

- Page 9 paragraph “ELISA and rapid immunochromatographic tests”: I would ask what authors means and therefore ask for more details in the text about “significant lower OD”: 10% or 20% or 50% drop down of OD?

- Table 1: I do not understand “duration of treatment” data: patients are 37, 25 took treatment for 60 days, 28 from 31 to 60: why not 31 to 59? Moreover 25+28+9=62, not 37 is this cumulative data? I need clarification/comment on that…

- Page 10 second paragraph: author clarify the central concept of the paper which is the lack of utility of serology as cure marker after ethiological treatment of Chagas disease: although this is probably true, some limitations/features of the study should be better highlighted: it is a fact that no studies on nifurtimox cure assessment has been published in non endemic countries and few in the endemic ones, therefore serological answer to this drug is not well known and cannot be generalized to benznidazole also; moreover, sample size of the present study is not big. I would prefer therefore to say that study findings pose in serious doubt the utility of serology as cure marker after treatment, considering that for instance some studies favour its use (see after and reference 9 of the manuscript) but other concerns can grow from its use in the management of and informed consent to patients. The study contributes to put under discussion the use of serology as marker of cure in Chagas disease management.

Cançado et al reported a cure rate of around 9% in chronically infected patients after a follow-up of 6-18 years. More recently, Viotti et al (ref. 9) have shown in a prospective study with a 3-years follow-up a higher seronegative conversion in a group of 53 treated patients compared to 89 untreated patients.

Krettli et al. proposed that lytic antibodies measured through a complement mediated lysis test could be a marker of follow-up of Chagas disease. Another study with a follow-up of 10 years suggested that patients with Chagas disease treated with benznidazole or nifurtimox may be considered cured due to a negative CoML, despite conventional serology remained positive (Galvao et al
In conclusion, I find this article very interesting, clear and direct, unique in the evaluation of nifurtimox treatment which is commonly paired/assimilate to the benznidazole one without consistent comparative data. It has been focused on a key issue in Chagas disease topic, that is the cure efficacy assessment, currently based on weak arguments in the context of poor evidence in favour of the treatment of chronic Chagas disease patients. I particularly appreciate author’s comments on the impact of these gaps in the common clinical practice.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests'