Reviewer's report

Title: Benznidazole-treatment of late chronic Chagas' disease leads to an overall cytokine down-regulation that upon Trypanosoma cruzi antigen stimulation can be shifted towards a Type-1 modulated profile by monocytes, NK and CD8+ T-cells

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Reviewer: Mauricio Rodrigues

Reviewer's report:

1. Is the question posed by the authors well defined? See below.
2. Are the methods appropriate and well described? See below.
3. Are the data sound? Yes, it does
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes, it does.
5. Are the discussion and conclusions well balanced and adequately supported by the data? See below.
6. Are limitations of the work clearly stated? See below.
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes, it does.
8. Do the title and abstract accurately convey what has been found? Yes, it does.
9. Is the writing acceptable? Yes, it does.

The manuscript by Sathler-Avelar RT AL. is a large study comparing several parameters of the innate and acquired immune response of three groups of individuals: 1) untreated indeterminate Chagas disease patients; 2) Bz-treated indeterminate Chagas disease patients; 3) non-infected individuals. The authors evaluated the immune responses using cultures of PBMC unstimulated or stimulated with epimastigotes antigens.

The manuscript provides a lot of data that might be an important contribution considering the fact that these are relatively rare patient samples. The major shortcomings are:

1) Introduction: The manuscript lacks a clear hypothesis. What do they expect to find when they initiate the study? What type of modification of the immune response would be expected? There are examples of immune response modification after treatment in experimental models that could be used to predict these changes?

2) Material and Methods: The choice of epimastigote antigens should be clarified. This form of the parasite does not contain a very important group of antigens that are the trans-sialidases. Probably their results are restricted to the cystein
proteinase antigen which is the immunodominant antigen of epimastigotes. A comparison with trypomastigote and amastigote antigens should be provided for at least a group of patients.

3) Material and Methods: considering that they use PBMC, it is not clear whether it will reflect the myocardial infiltrated cells. It should be discussed.

4) Material and Methods: The groups of untreated indeterminate Chagas disease patients and Bz-treated indeterminate Chagas disease patients are not the same individuals. This type of problem could have been corrected by the analyses of a group of patients prior and after treatment.

5) Discussion: All the points raised above should be discussed as a limitation of the results provided.

6) Discussion: Based on the shift of the immune response caused by the treatment, would it be possible to vaccinate these individuals to further enhance the parasite clearance? I think that a major goal of this study would be to understand whether this is a viable possibility. It should be discussed and the recent papers on the subject should be cited: Quijano-Hernandez I, Dumonteil E. Advances and challenges towards a vaccine against Chagas disease. Hum Vaccin. 2011 7:1184-91. Vázquez-Chagoyán JC, Gupta S, Garg NJ. Vaccine development against Trypanosoma cruzi and Chagas disease. Adv Parasitol. 2011; 75:121-46.