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LETTER TO THE EDITOR

Response to `letter to the editor: 'Strategies to enhance access to diagnosis and treatment for Chagas disease patients in Latin America''

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Dear Editor,

We appreciate the comments on our recent review article about strategies to enhance access to diagnosis and treatment for Chagas disease patients [1,2]. We also appreciate the opportunity to respond to them, and expand the discussion on this crucial topic given that it is estimated that no more than 1% of the infected population by *Trypanosoma cruzi* (of ~7 million people) ultimately get access to treatment [3].

The letter comments mainly refer to two of the sections of the review article: diagnostics to detect the infection (section 2), and treatment opportunities and possibilities (section 7).

Regarding the first, we deeply agree with the concerns of the letter authors on the reduced access to Polymerase Chain Reaction (PCR) and conventional serology (ELISA) tests for the diagnosis of Chagas disease in many areas where the disease is highly endemic and only poorly equipped laboratories are available. In fact, our team at ISGlobal is working at present in a research line which aims to show that the use of alternative diagnostic methodologies, easier to use in those regions, can indeed substitute conventional diagnostics [4,5]. This is, in our opinion, the most urgent necessity in relation to Chagas disease diagnostics at the moment: validation and implementation of rapid diagnostic tests (RDTs) to diagnose chronic infections, and easy-to-use molecular tools such as loop mediated isothermal amplification (LAMP) to early detect congenital transmission events [6].

From our experience, the use of parasitological methods in regions with poorly equipped laboratories is primarily done for the detection of acute infections (such as congenital ones). However, without an appropriate screening of the mothers and considering that the acute stage of Chagas disease is usually asymptomatic or can be confounded with other diseases and go unnoticed, diagnosis is normally achieved at the chronic stage, either in the context of a screening campaign or because there is a clinical suspicion of the infection. By then parasitemia is low and intermittent and direct diagnosis is useless [7]; even if more sensitive molecular detection tools are used as the letter authors point out. Furthermore, it must be stressed that although finding trypomastigotes in a blood preparation is indeed a definitive proof of infection, it is no less true that the sensitivity of direct parasitological techniques is low and the algorithm to diagnose a congenital transmission, besides one or two micromethods, does comprise as well the serological determination of anti-*T. cruzi* immunoglobulins once maternal antibodies have waned [7]. So there is yet the urgency for a more sensitive and timely diagnosis of congenital (acute) infections as a very large percentage of children born to seropositive mothers are lost to follow-up and may only get diagnosed as chronically infected adults.

In truth, serological tests and PCR methods are more effective diagnostics than direct observation of circulating parasites. Current molecular amplification protocols have been developed taking into account *T. cruzi* genetic diversity [5,6]. In relation to serology-based diagnosis, cross-reactivity with host-derived moieties and antigens of related parasites (e.g. *Leishmania* spp.) has been described before [8]. But nowadays there are many commercially available tests based on recombinant *T. cruzi* antigens that have greatly overcome those limitations, as it can be observed in that very same reference [8]. In fact, as the letter authors comment, the agreement of two tests based on distinct antigen sets is still required for conclusive diagnosis of Chagas disease. This is, despite improvements in their performance, a practice that imposes extra costs in the diagnosis of the infection, and often entails delays in the turnaround of results with the risk of loss-to-treatment of infected subjects. Therefore considering the performance of presently available diagnostics, rather than suggesting further confirmation with immunoblots and PCRs, we would suggest to place the focus on the development and wider use of point-of-care diagnostics such as RDTs and LAMP, which would facilitate access to a diagnosis with the goal to ultimately simplify access to treatment [1].

In contrast we agree with the authors of the letter that the evaluation of parasite cure might not be the only way to ascertain therapeutic efficacy. Nonetheless, clear and defined readouts are required to be able to follow-up treatment

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response in the context of daily clinical management of patients or during the performance of clinical trials. Since confirmation of cure is currently difficult to ascertain as serological reversion can take over a decade to occur and this is not practical, molecular amplification of parasite DNA is taken as a surrogate of treatment failure and negative amplification is considered an indication of therapeutic response [7]. Molecular tools cannot fully assure that the treatment worked as a relapse may occur at any other time point sampled, so it is fundamental to develop and validate other biomarkers for the early assessment of treatment efficacy [9]. But it is understandable that if it is the presence of the parasite what is causing the damage (as it is well acknowledged by now), whatever intervention that stops or delays the advancement of the infection (be it chemotherapy, be it a vaccine, or its combination), will clearly be of benefit to the patients. This can be monitored to a certain extent with molecular tools, and there is plenty of evidence currently supporting these arguments [10–14].

On the other hand, with respect to the comments on treatment, the use of 'traditional' chemotherapy doses and regimens in clinical trials have been shown to be reasonable in order to compare them with new drugs under evaluation or with new regimens and doses of existing ones [11,12,14]. As for the controversy in the therapeutic effects when late chronic patients were treated, we are not sure whether the letter authors refer to the results of the BENEFIT trial or to the results of any of the other trials they mention (CHAGASAZOL or STOP-CHAGAS). If they meant the former, then it must be noted that rather than a cause-effect derived from early or late chronic infections being treated, the main issue with the BENEFIT trial design, in our opinion, which coincides with that expressed by others [15], is that it admitted subjects with advanced heart tissue damage [1]. We do not find any controversy related to the results from any of the other trials, including E1224 [11], where qPCR was the main tool to determine treatment failure or suggest treatment success at the particular time point when it was performed. These studies provided a range of response to the standard benznidazole treatment of 55% – 85% of the adults chronically infected with *T. cruzi* by twelve months post-treatment (see Table 1 in reference [1]). In light of these results, and with the support of pre-clinical and pharmacokinetic studies, the administration of reduced doses and/or alternative regimens of benznidazole and nifurtimox is being explored [1]. The outcome of these new trials will determine whether efficacy can be maintained or even increased and the advent of adverse events reduced, which would be greatly beneficial to all to-be-treated patients [1].

Meanwhile, as it has been proved that treatment of women at child-bearing age does significantly stop the transmission of congenital Chagas disease [16], and BENEFIT´s main lesson was that providing treatment to patients with advanced cardiac damage did not improve their status, administration of treatment should be done before the appearance of cardiac complications. Therefore, until new drugs or new regimens of existing ones are on the table, presently available treatment must be the prevailing option for those cases either indeterminate or with early cardiac involvement [17].

All the former said, we strongly disagree with the letter closing sentence. It is exactly because of all the aforementioned arguments that the therapeutic potential of treatment cannot be considered uncertain anymore. Of course, more effective and less toxic treatments would be of great importance and welcomed, especially for the chronic stage of the disease. But presently available drugs could already make a difference if access is increased and they would be made available to many more patients than they are now.

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Declaration of interest

J Gascon coordinates the NHEPACHA network and is member of the scientific committees of CEADES (Bolivia) and ISGLOBAL. J Alonso-Padilla, MJ Pinazo and S Sosa-Estani are members of the NHEPACHA scientific network. ME Botazzi and PJ Hotez are patent-holders and lead investigators of a program for the development of a therapeutic Chagas disease vaccine. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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