An overview of Chagas disease treatment

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Chagas disease (American trypanosomiasis) is endemic in 21 countries of the Americas, where control is largely focused on elimination of the domestic insect vectors (Triatominae) coupled with measures to extend and improve the screening of blood donors in order to avoid transfusional transmission. Through national programmes and multinational initiatives coordinated by WHO-PAHO, much has been accomplished in these domains in terms of reducing transmission. Attention now turns to consolidating the successes in interrupting transmission, and improved treatment for those already infected and those who may become affected in the future. This article, based on technical discussions at the “Epidemiological and Sociological Determinants of Chagas Disease, Basic Information to Establish a Surveillance and Control Policy” meeting in Rio de Janeiro, is designed to open the debate on appropriate strategies for continuation of the successful initiatives against Chagas disease.

Key words: access to diagnostics treatment - Chagas disease - endemic countries

Chagas disease – caused by infection with Trypanosoma cruzi – is endemic to the Americas, over a region roughly from the Great Lakes of North America (~ 42ºN) to southern Patagonia (~ 46ºS), although it is also spreading to other areas due to migration of infected people. Peak estimates of prevalence in the 1980s suggested that up to 24 million people were infected (Walsh 1984), and the World Bank ranked Chagas disease as the most serious parasitic disease of the Americas in terms of its social and economic impact (World Bank 1993).

Over the last 15 years however, prevalence estimates have been steadily reduced, largely due to intensive large-scale programmes designed to halt transmission by eliminating domestic populations of the insect vectors (to halt vector-borne transmission) and to improve the screening of blood donors (to reduce the likelihood of transfusional transmission). In many countries, these programmes also included extended screening and monitoring of chagasic mothers, with parasitological diagnosis and treatment of infected new-bornes.

These national and multinational initiatives, coordinated by WHO-PAHO, have been remarkably successful. Transmission of Trypanosoma cruzi has been effectively halted over vast areas of the Southern Cone countries, and parts of Central America and the Andean Pact region, such that current prevalence estimates have been reduced to around 10 million people infected (Remme et al. 2006). This success has been primarily due to concerted action against the vectors, and as part of the ‘safe-blood initiative’. Less attention has been given – so far – to the human aspects of case detection and treatment.

BACKGROUND TO CHAGAS DISEASE TREATMENT

The drugs currently accepted for treatment of Chagas disease are Nifurtimox manufactured by Bayer Health Care as Lampit®, and Benznidazole manufactured by Roche as Rochagan® or Radanil®. Launched in 1967 and 1972, respectively, these drugs were quickly shown to be effective for the treatment of acute infections, but were largely ignored for the treatment of chronic infections because of a high frequency of undesirable side effects, poor indices of apparent cure, and a lack of international consensus about diagnostic criteria and criteria for parasitological cure. Even for treatment of acute and congenital infections, there was a lack of clinical consensus about which was the better drug. By contrast, there was international consensus about the validity of effective vector control and improved screening of blood donors, and these became the main operational foci of national and international control efforts.

Such concepts are being increasingly challenged on several grounds. Large-scale vector control can be highly successful in halting transmission, but still leaves a high proportion of people already with chronic infection. Treatment of chronic infection can be successful – at least in the sense that a proportion of those treated will seroconvert, even though detection of such seroconversion may take several years. Undesirable side-effects of treatment do occur, but their frequency and severity seems much reduced in younger age-groups. Most importantly however, while it is both ethnically and epidemiologically appropriate to eliminate domestic vector populations, and to improve the safety of blood transfusions, the continued sustainability of such large-scale interventions will be progressively questioned in terms of cost-effectiveness, and cannot prevent accidental transmission by adventitious silvatic vectors – what has
been called the “Acapulco Syndrome” (Dias et al. 2002). In other words, even where transmission control has been highly successful, there is a need and ethical requirement to retain and extend capacity to detect and treat accidental new acute cases.

**THE ACCESSIBILITY PROBLEM**

Diagnosis and treatment of acute and chronic Chagas disease depends on several factors, of which the first must be generalized consensus of its importance – at personal, scientific, and political levels. From this stems demand, which in turn stimulates availability.

There seems a general agreement that the earlier a diagnosis can be made – and treatment initiated – then the better the prognosis for the patient. Presumptive treatment immediately following a laboratory accident can be effective with no more than 10-12 days specific therapy (JR Coura, pers. commun.); treatment of a parasitologically-confirmed acute case, before seropositivity, is likely to be successful with a full 60 day course of therapy (AR Prata, pers. commun.); treatment of seropositive acute cases should be successful in over 70% of cases (JCP Dias, pers. commun.); but treatment of seropositive chronic cases may only be successful in some 30% of cases (S Sosa-Estani, pers. commun.). Further research on clinical outcomes following treatment is clearly merited, to help define treatment recommendations. But early diagnosis also presents logistic questions, both for the supply of diagnostic reagents and for the appropriate access to specific therapies. Solving the question of early diagnosis requires definition of a clear process for screening populations according to available facilities and in terms of the level of disease endemicity. But defining diagnostic procedures becomes of little relevance if treatment is unavailable. A comprehensive strategy is needed to improve and increase early diagnosis and provide early treatment.

As yet however, there is no international consensus on the concept of large-scale diagnosis, nor on the tools that would be most effective for different stages of the infection or for the various objectives of parasitological or epidemiological surveillance. Similarly there is little consensus about criteria for treatment, physical framework for treatment, clinical follow-up, or criteria of cure. Without such agreement, it is effectively impossible to predict demand or requirements for different diagnostic kits, or for specific therapeutics, which makes it extremely difficult for the relevant suppliers to plan their production and commitment.

**AVAILABILITY OF SPECIFIC TREATMENT**

*Nifurtimox* - Production of nifurtimox by Bayer (Argentina) was suspended in 1997 due lack of perceived demand. In 2000 however, to fulfill commitments to provide this drug for treatment of Gambiense sleeping sickness in Africa, production was restarted at the modern Ilopango complex of Bayer in El Salvador. Today, through agreements with WHO, production of nifurtimox is guaranteed by Bayer Healthcare for as long as there is a requirement. For Chagas disease, Bayer Healthcare has donated substantial quantities of nifurtimox through WHO, although this will cover projected requirements for a relatively short time. Discussions between WHO and Bayer Healthcare led, 13 April 2007 to a large 5 years donation of the drug, covering needs for Latin America.

*Benznidazole* - Benznidazole is currently manufactured by Roche, although the manufacturing technology is being transferred to Lafepe in Pernambuco, Brazil. The availability of benznidazole is guaranteed by a Roche commitment to ensuring availability of active ingredient until full approval and availability of the Lafepe product. Questions remain however, about the future pricing of benznidazole, and registration of the Brazilian product in other endemic countries.

For both drugs – nifurtimox and benzidazole – future availability, registration, and pricing, depend crucially on an efficient system to forecast demand, in order to avoid any shortage or overproduction of drugs. Such a forecast system must be built on an efficient epidemiological surveillance system. Neither drug is ideal, so that work on improved formulations (especially pediatric presentations) possible combination therapy and other new treatments, would be appropriate.

**CONSENSUS REQUIREMENTS**

It is of immediate concern to establish a consensus for diagnostic procedures and treatment of patients according to the stage of the disease (acute phase, chronic phase, complications). Indications for use of existing tools and procedures must be defined and harmonized, together with specifications for possible new diagnostic tools. Consensus for treatment procedures and schedule must be established, that includes recommendations for compliance and monitoring of side effects, clinical follow-up and counseling, and criteria of cure. Research and development must be promoted to define diagnostic tools able to guide the decision for treatment.

Of considerable importance is the development of pediatric formulations to allow safer and more accurate treatment for children.

Following the proposed policy for control of neglected tropical diseases, WHO (2006) has proposed to continue emphasis on the elimination of domestic Triatominae, and to reinforce all aspects of disease management. The reinforcement of disease management would be made by:

1. Ensuring access to existing drugs for all patients.
2. Ensuring the stability of production, affordability and distribution of the existing drugs.
3. Supporting logistics for regular and emergency supply of drugs.
4. Developing an improved epidemiological surveillance system which could also be used as a drug forecast system.
5. Building a consensus between countries to define precisely the indications, dosage and treatment schedule for nifurtimox and benznidazole – bearing in mind possible parasite strain differences or other factors that may affect local treatment efficacy and tolerance. This consensus would strongly contribute to a rationale use of the drug.
6. Building a consensus between countries to define adequate and practicable procedures to diagnose early infections. The goal is to define populations which should be targeted for early treatment and intensive case finding.

7. Promoting research and development for better diagnostic tools, safer drugs, and improved formulations.

8. Promoting the development of pediatric formulations for available drugs.


REFERENCES


