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Deadly Attack against *Trypanosoma cruzi*

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Abstract

Chagas disease (CD) is produced by *Trypanosoma cruzi*, a hemoflagellate of the family Trypanosomatidae whose main route of transmission is through the contamination by fecal of insects kissing bugs from the family Reduviidea subfamily Triatominae. The first empirically developed drugs widely used for their treatment are benznidazole and nifurtimox. Since their introduction, these drugs have shown a very good activity in the acute phase, but their effect has many variations depending on the geographical area of origin and the strain that infects the individuals under treatment. Among the limitations of these compounds are the high incidence of side effects and the poor anti parasitic activity in the chronic phase, since in the great majority of patients subjected to these drugs no radical parasitological cure is observed, an essential requirement to eliminate the effects produced for the disease. All these drawbacks have led to the search for better compounds based on the biochemistry of *T. cruzi*, which has allowed the development of drugs under a rational approach, trying to select action targets in metabolic pathways specific to the parasite that are not found in the mammalian host, in order to minimize side effects; Combinations of drugs that act in different points of the same metabolic pathway have also been used to enhance their activity through synergistic effects, which allows to reduce the amounts of the compounds used and thus decrease toxicity in the treated individuals. A rational strategy has allowed the discovery of the inhibitors of ergosterol biosynthesis (EBI). These compounds show a great antiparasitic activity in acute and chronic phase, with a safe and reliable administration because the side effects are considerably reduced. In recent years, mixtures of benznidazole with EBI have been used to evaluate their activity as a whole. Studies of this type are promising in the search for compounds of excellence for the effective treatment of CD, which must have a very high activity at very low concentration, minimal side effects, that produce cure in acute and chronic *T. cruzi* infections, that are safe so that they can be administered to all chagasic people regardless of their condition and are economically accessible for all people suffering from this silent infection.

Introduction

CD is caused by *T. cruzi*, a parasite of great importance from the epidemiological point of view due to its high mortality and morbidity rates. It is a neglected tropical disease because the populations of low socioeconomic resources for many time have been more susceptible to suffer this scourge and also, because it produces no apparent symptoms (it is silent) and for this reason it passes totally unperceived while the *T. cruzi* multiplies and destroys the host cells, until it invades the heart tissue, in this point it can cause physical disability, chagasic cardiomyopathy, and ultimately death of the patient. Their geographical distribution extends from southern Chile and Argentina, through Central America, into wide areas of the southern USA [1]. In recent years, the epidemiological pattern of this infection has changed, due to the migration of people from rural areas to urban areas, which has led to its appearance in large urban centers and has ended the dogma of the CD association with rural regions; the problem is so serious that cases of chagasic patients have already been detected in non-endemic areas such as the United States and Europe, places where there are around 300,000 and 100,000 people infected, respectively [2]. Despite being responsible for the greater economic burden caused by a parasite in Latin America and an emerging condition throughout the world, it is surprising that even today in the course of the XXI century it remains the most forgotten parasitic disease on the planet. In addition to these important facts, the long-term cost associated with CD in the USA it is already the largest in the globe [3-5].

The great Uruguayan writer Eduardo Galliano has described CD in a brilliant way: "*It neither explodes like bombs nor has the sound of gunfire; like hunger, it kills silently. Like hunger kills those who keep quite: those who are condemned to silence and die condemned to be forgotten. Tragedy that has no sound, ill people who don't pay, disease that doesn't sell. Chagas disease is not an attractive business for the pharmaceutical industry or an interesting topic for politicians or journalists. It chooses its victims amongst the poor. It bites them slowly, gradually, it destroys them. Its victims have neither rights nor the money to buy these rights they are lacking. They are even lacking the right to know what causes their death*". All this overview so devastating makes us wonder how is it possible that there are so many chagasic people and so few specific treatments? CD is the main cause of heart problems in Latin America, for this reason, a series of studies carried out by different research groups from many countries aims to find effective and low cost chemotherapeutic compounds that produce minimal side effects and have a great ant parasitic effect on *T. cruzi* even at low doses [6,7]. The currently recommended ant parasitic drugs to treat *T. cruzi* infection are nifurtimox and benznidazole [8,9] which have been empirically discovered in the 1960s and 1970s. Due to the absence of solid scientific evidence, treatment regimens with these compounds vary between countries and study groups. At present, the efficacy data of nifurtimox between different groups of patients with different strains of *T. cruzi* remain scarce, as well as the profiles of safety and tolerance [10]. Benznidazole produces a variety of side effects that can be classified into three groups; (a) hypersensitivity, such as dermatitis involving skin rashes, arthralgia, myalgias, and lymphadenopathy; (b) polyneuropathy, paresthesias and polyneuritis; and (c) disorders of the bone marrow, such as thrombopenic purpura and agranulocytosis [11].

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The distribution of nifurtimox has been discontinued for your minimal activity in the chronic phase, and the serious effects that it produces on treated individuals as: gastrointestinal disorders, peripheral neuropathy and central nervous system [12]. These drugs are contraindicated in women in gestation period, during lactation, patients with severe liver, kidney or neurological problems. Although treatment with these drugs has been recommended for the acute phase and congenital infection, the effectiveness of both drugs in eradicating *T. cruzi* during the chronic stage does not have convincing results, mainly due to the lack of reliable tests and biomarkers in the assays carried out [13,14]. Despite all the drawbacks presented by these ant parasitic drugs, on August 29 2017, the US Food and Drug Administration (FDA) approved Chemo Research´s New Drug Application (NDA) for benznidazole (https://www.dndi.org/2017/media-centre/press-releases/fda-approves-benznidazole-chagas-children/). This is the first medication certified by this body to treat CD and the most used due to its better safety record. The treatment has been less toxic in children and adolescents, while in the majority of the treated patients mild side effects were observed, that is to say, those that did not interfere with the daily activity of the individuals.

Subsequently, innumerable investigations have been carried out in order to obtain rationally designed compounds with specific targets on *T. cruzi*, which considerably reduces the collateral effects on mammals affected by this parasite. The search for these drugs has been based on the implementation of biochemical tools in order to detect chemotherapeutic targets with significant differences between humans and parasites, which favors the reduction of toxic side effects on humans and can increase the effectiveness of specific treatments that destroy these microorganisms. The synthesis of sterols is one of the metabolic pathways most widely studied by numerous research groups, because in the protozoa the primary steroid is ergosterol, while in mammals it is cholesterol, which indicates that there are significant differences between host and parasite at the level of this potetntial source of chemotherapeutic targets. The ergosterol constitutes a fundamental part of the cellular membrane of the parasites; they form a very important piece in the cell division, besides being an active part of the maintenance of the selective permeability. *T. cruzi* depends on endogenous ergosterol, since these molecules are essential to maintain its cellular viability [15]. One of the strongly tested targets is sterol 14α-demethylase (CYP51), the cytochrome P450 enzyme that is required for the removal of the 14α-methyl groups from the sterol precursors and thus ultimately giving rise to ergosterol production, which in turn serve as essential components of eukaryotic membranes and are regulators of the cell cycle and development. This enzyme used as a chemotherapeutic target has shown such promising results that the inhibitors of *T. cruzi* CYP51 are the only compounds drug candidates with clinical trials for CD chemotherapy, because they are extremely active in *T. cruzi in vitro* and in animal models. The inhibitors of this enzyme (azoles) are the most efficient antifungal agents in clinical medicine and in agriculture, for this reason it has been chosen to be used in *T. cruzi*, because these microorganisms shared the sterol synthesis route. In addition to blocking sterol biosynthesis, the potency of azoles is enhanced by the accumulation of toxic methylated sterols precursors that also promote the arrest of the growth of the microorganism and produce detrimental changes in the permeability of the membrane [16,17]. Recent studies on the clinical treatment of this infection based in azoles are shown to continuation: 1) posaconazole used in the CHAGAZASOL clinical study (Vall d'Hebron Hospital, Barcelona, Spain), was unable to induce suppression sustained parasitaemia [18]. The effectiveness of this compound can be improved with the implementation of certain measures: a) the use of a new formulation (tablets of prolonged release) that provides higher plasma levels of the drug, without security problems, whose presentation is already available for clinical use, b) prolong the course of treatment, since radical parasitological cure of a patient in chronic phase has been demonstrated using Noxafil® 400 mg BID for 90 days, c) using a combination therapy, the mixture of posazonazole and benznidazole produces great synergistic effects [19]. The use of several mixed compounds is done with the purpose of attacking the parasite from several fronts and in this way favoring the lethal effect on this microorganism; 2) E1224 trial was designed to evaluate the efficacy of a ravuconazole prodrug (E1224), in a study where benznidazole was simultaneously evaluated. The drug is being tested in a phase II study conducted by ISGlobal, in conjunction with the Platform for the Integral Care of Patients With Chagas Disease, a collaborative project involving CEADES (a Bolivian NGO), Universidad Mayor de San Simón de Cochabamba, and Universidad Autónoma Juan Misael Saracho (Tarija) (https://www.dndi.org/diseases-projects/portfolio/completed-projects/azoles-e1224/). This phase II proof-of-concept study will analyse the potential of E1224 as an oral, easy-to-use, safe, and affordable treatment for CD. The project is being coordinated by the Drugs for Neglected Diseases Initiative and funded by the Wellcome Trust. E1224 was safe and effective to achieve the elimination of the parasite, but it does not reach effectiveness 1 year after finishing the treatment, instead, with benznidazole was obtained 80% persistent death of the parasite as determined by PCR [20]. The authors conclude that this study opens the possibility of combining E1224 with shorter treatments of benznidazole for administration in adults with chronic CD [http://www.dndi.org/pressreleases/532-eisai-and-dndi-enter-into-a-collaboration.html; [21]. These clinical trials have allowed us to reach the following conclusions: (1) azoles are not effective as monotherapy for the treatment of patients in the indeterminate phase of the disease and (2) benznidazole has been proven to be an effective drug to maintain a sustained clearance of parasite even 1 year later [22]. Diniz [23] evaluated benznidazole combinated with posaconazole in mice infected with *T. cruzi* during acute phase. Treatments of benznidazole to 100 mpk y later posaconazole 20 mpk provide an 80% cure, which originated the elimination of the infection with a greater effectiveness than that observed when the drugs are used separately, which indicates a synergistic effect. It is found that the administration of low doses of benznidazole and posaconazole in combination are beneficial because they reduce the costs and toxicity of the treatment, which translates into greater well-being for the infected patients. Apparently, the benznidazole allows a quick elimination of the parasites, so that afterwards the posaconazole acts that presents a large volume of distribution and a prolonged time of life in the tissues of mammals, a joint action that favors a deadly attack very effective against *T. cruzi* This combination treatment administered on chagasic patients allows to reduce the doses and the time of administration of the drugs used, which produces benefits such as the reduction of toxicity levels and the reduction of costs. Future projects aimed at the discovery of drugs of excellence to be used in the treatment of CD should be based on knowledge of the host-parasitic interactions, deep and extensive knowledge of the parasite's biochemistry to determine differences between therapeutic targets, in addition, the development of biomarkers that allow the rapid and effective detection of the antiparasitic activity of the evaluated compounds. All these methodological advances allow to advance in an approach to obtain a radical parasitological cure during the chronic phase of CD, of great relevance because it is the first cause of chronic myocarditis in Latin America, which generates physical disability and the death of affected patients.

Discussion

Since Carlos Chagas discovered this parasite in 1909, hard battles have been fought in order to discover a chemotherapeutic treatment that produces a radical parasitological cure. Extensive research is crucial because *T. cruzi* triggers the largest parasitic disease burden on the American continent and is a silent killer that generates gigantic morbidity rates associated with multimillion-dollar losses of nations coupled with the severe social problems it causes and more serious, is the first responsible for deaths from heart damage in Latin America. Because this infection causes the death of more than 15,000 people each year it has been listed as a neglected tropical disease. Although it has been called the disease of poverty because of its close association with people of low socioeconomic levels, nowadays it attacks people from any social stratum due to its migration to large urban centers. It has spread throughout Latin America and many countries of the world and has an insidious nature, since it produces apparent symptoms only many years after the initial infection when the damage produced by the parasite is irreversible, that is, it does not generate a state of generalized alarm in the population. The main problems for the development of effective chemotherapeutic compounds are based on the fact that many aspects of the biology of parasite and pathogenesis are not known [24]. In addition to all this, the tools available for testing both *in vitro* and *in vivo* experimental animal models have far to predictive value, which obviously affects our understanding of the pharmacokinetic/pharmacodynamic (PK/PD) relationships for CD, during the drug discovery process [22]. The way to obtain the approval of a compound is too long, begins with *in vitro* studies, then *in vivo* tests in experimental animals such as mice, then evaluations in monkeys because they are more evolutionarily related to humans [25]. For these reasons, these areas of basic and applied research must be developed in order to solve these problems and give health to millions of people suffering from this lethal infection.

Conclusion

CD is a silent and silenced infection that affects people throughout Latin America, regardless of their social status and also, in recent years has crossed the borders and come to the United States and countries of the European continent. At one time it was restricted to rural areas because there were vectors cohabiting with humans, but due to the migration of chagasic individuals to urban areas this epidemiological pattern has changed drastically. It is the first cause of death due to cardiac damage and for this reason it produces disability and sometimes the death of affected individuals. This infection has been included in the group of neglected tropical diseases due to its close association with people of low socio-economic resources and for this reason it is called the disease of poverty, although in recent times cases have been observed in urban areas; its insidious nature which makes it go unnoticed in its initial stages without the possibility of administering drugs that prevent the progression of the disease; It generates health problems that cause physical disability in the long term and can lead to death. The WHO catalogs it as a forgotten disease because it affects a large number of poor people on the planet, of great importance because they are totally and because there are no adequate treatments available to cure it. EBI are the most promising drugs to exert a sufficient antiproliferative and lethal effect to generate a radical parasitological cure on chagasic patients, in very recent studies EBI has been used together with benznidazole to benefit from the benefits of both compounds, and thus enhance their Trypanocidal effects and decrease the amount of drugs to use. The combined use of chemotherapeutic compounds favors the appearance of minimal side effects, guarantees that the patient suffers as little as possible during the period of time required to administer the treatment and improve the antiparasitic effects, which increases the possibility of a general radical parasitological cure . The optimal drug for CD treatment must meet certain characteristics: minimal adverse effects; safe administration on all chagasic patients including women in gestation period, during lactation, patients with severe liver, kidney or neurological problems; maximum activity using the minimum concentration. Advances in drug development have also been slow because CD is silenced because the big pharmaceutical companies that have a very important capital are not interested in developing and manufacturing drugs to treat it, since it is not a lucrative business because it is very associated to poverty. The search, development and improvement of chemotherapeutic treatments continues to achieve an effective deadly attack against *T. cruzi*.

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