Simposio
Innovación y desarrollo de productos

Susceptibility of clinical strains of *Leishmania* to pentavalent antimony and miltefosine: challenges and opportunities

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Introduction

Passive case detection and treatment constitute the principal and often the sole measure of control for dermal leishmaniasis in Central and South America yet pentavalent antimonials, the first line therapy, are often ineffective. Treatment failure is frequent and concerning in the management of cutaneous leishmaniasis in South America. Overall non-response is of the order of 24% based on a recent metaanalysis (Tuon, *et al.,* 2008). Although therapeutic response is multifactorial, treatment with Glucantime® has been shown to select antimony (Sb^v)-tolerant/resistant parasites and drug resistance to contribute to treatment failure in some patients (Rojas, *et al.,* 2006).

Methods

In order to determine the susceptibility of the most prevalent *Leishmania* species affecting human populations in Colombia to currently used anti-leishmanial drugs, we evaluated *in vitro* susceptibility of 150 clinical strains of *Leishmania braziliensis, Leishmania panamensis* and *Leishmania guyanensis* from the major endemic regions of the country, to Glucantime® and miltefosine. Susceptibility was determined based on reduction of intracellular parasite burden in human U-937 macrophages by screening at single drug concentrations and ED_{50} determination. Experimentally selected antimony and miltefosine resistant lines and the corresponding wild type strains provided internal standards. Low susceptibility was defined as <50% reduction of parasite burden at the screening concentration of 32 µg Sb^v/ml, based on the C_{max} of antimony in plasma during treatment, and 16 µM for miltefosine considering the susceptibility profile of experimentally selected resistant lines and toxicity of higher concentrations for U-937 host cells.

Results

Susceptibility to miltefosine and Glucantime® differed among species and by geographic origin. Between 20 to 50% of *L. panamensis,* and 40 to 53% of *L. braziliensis* strains presented low susceptibility for Sb, depending upon the geographic origin of the infection. Low susceptibility to miltefosine was evident in 14 to 80% of *L. panamensis,* and 58 to 79% for *L. braziliensis*. In contrast, all *L. guyanensis* strains were highly susceptible to both antimony and miltefosine. *Leishmania* from the Orinoco and Amazon River basin regions were less sensitive to both drugs than strains from other high transmission areas.

Leishmania braziliensis presented low sensitivity to both drugs more frequently than other species of the *(Viannia)* subgenus. No significant difference in susceptibility to Sb was detected among strain cohorts (N=85) isolated between 1980-1989 and 2000-2009 in the municipality of Tumaco. However during the 1980-1989 period, a higher proportion of strains from the Rosario river focus presented low susceptibility to antimony than strains from the Mira river focus (50% vs. 27%, p=0.032).

Discussion

The results of this large scale evaluation of clinical strains support both intrinsic and acquired differences in drug susceptibility of *Leishmania (Viannia)* species. Although *L. braziliensis* and *L. panamensis* strains frequently presented low susceptibility to antimony or miltefosine, many strains of both species were highly susceptible to one or both, demonstrating that the species are not intrinsically less susceptible to these drugs, rather individual strains may be intrinsically less susceptible.

Because *L. panamensis* and *L. braziliensis* are the most prevalent species among human cases

of cutaneous leishmaniasis and infection is not eliminated by treatment (Schubach, *et al.,* 1998; Vergel, *et al.,* 2006), decades of monotherapeutic use of antimonial drugs is likely to have selected tolerant and even resistant populations of these species that could have been disseminated in circumstances of anthroponotic transmission.

Leishmania guyanensis is of low prevalence, and until recently has been confined to sylvatic transmission in the Amazon river basin (Rodríguez-Barraquer, *et al.,* 2008). The uniform, high susceptibility of *L. guyanensis* strains to antimony concurs with limited exposure to large scale treatment with this drug.

Miltefosine was approved as an alternative treatment by the Ministry of Social Protection in 2006 and has had limited availability and use. Differences in susceptibility to miltefosine among species and strains are therefore likely to reflect intrinsic variability rather than acquired loss of susceptibility.

Conclusion

The high frequency of clinical strains of *Leishmania* with evidence of low susceptibility to antimonial drugs or miltefosine underscores the risk of treatment failure and the need to develop alternative therapies including combined and local treatments.

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É possível o desenvolvimento de novos medicamentos para as doenças negligenciadas?

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Segundo a Organização Mundial da Saúde, as doenças negligenciadas afetam mais de um bilhão de pessoas no mundo, principalmente em áreas rurais, periferias metropolitanas pobres e zonas de conflito, contribuindo para a manutenção do ciclo da pobreza. Por atingirem populações com pouca visibilidade, pouca representatividade política e, principalmente pouco ou nenhum poder de compra, esses números não se traduzem em investimentos adequados em pesquisa e desenvolvimento. Por isto, os desequilíbrios resultantes exigem respostas alternativas do mundo da ciência, mercado e sistemas públicos de saúde para atenderem às demandas mais urgentes de saúde global.

Nos últimos anos houve uma tendência em nível mundial de buscar alternativas para esta situação com modelos de colaboração e articulação entre diversos setores, explicitada por Carlos M. Morel e Richard T. Mahoney no artigo "A Global Health Innovation System (GHIS)" como a "era das parcerias". Entre os modelos de parcerias existentes se encontram as parcerias para desenvolvimento de produtos. As parcerias para desenvolvimento de produtos concentram-se em uma ou mais doença negligenciada e visam o desenvolvimento de produtos apropriados para estas. Apesar de constituírem um modelo relativamente recente, o número de parcerias para desenvolvimento de produtos tem aumentado desde o final da década de 90. Com um modelo virtual de organização, estas trabalham com expertos, e providenciam financiamento, supervisão técnica e a gestão do portfólio, enquanto as atividades são delegadas a parceiros de diversos setores (Cheri, p. 7). As parcerias para desenvolvimento de produtos conseguem abranger múltiplos parceiros no setor privado, público, acadêmico e filantrópico, assim como, muitas vezes, conduzir ações de *advocacy* de maneira a conscientizar diferentes públicos acerca das doenças negligenciadas em alvo (Moran, *et al.*, p. 68).

Ao canalizarem suas diversas contribuições, e providenciarem investimentos diretos em pesquisas, as parcerias para desenvolvimento de produtos

com freqüência têm custos de operações mais baixos, assim como alto grau de efetividade. Em recente pesquisa financiada por *Wellcome Trust*, foi demonstrada as vantagens comparativas das parcerias público-privadas para desenvolvimento de produtos. Além de terem alcançado resultados positivos, tais como a disponibilização de 10 novas tecnologias e a existência de 143 novos candidatos no seu *"pipeline"* de desenvolvimento, as parcerias para desenvolvimento de produtos ainda se mostram mais eficazes em termos de tempo de desenvolvimento, custo-eficiência, valor para a saúde e níveis de inovação dos produtos. Em termos de vantagens externas, as parcerias para desenvolvimento de produtos se destacaram pelo seu conhecimento profundo de mercado e necessidades, seu envolvimento público significativo no local de trabalho, sua capacidade de definição de parâmetros regulatórios, de desenvolvimento de estratégias sustentáveis de distribuição e acesso, e de aumento da visibilidade das doenças negligenciadas.

A Iniciativa Medicamentos para Doenças Negligenciadas (*Drugs for Neglected Diseases initiative*, DNDi) é uma das pioneiras entre as parcerias para desenvolvimento de produtos. Desde sua criação em 2003, a DNDi concentrou-se principalmente no desenvolvimento de novos tratamentos para doenças extremamente negligenciadas, tais como a doença do sono, a leishmaniose visceral e a doença de Chagas.

O principal objetivo da DNDi é fornecer até 2014 de 6 a 8 novos tratamentos para a leishmaniose, a doença do sono, a doença de Chagas e a malária, e também estabelecer um portfólio sólido de projetos de pesquisa e desenvolvimento para desenvolver tratamentos que atendam as necessidades dos pacientes. Houve estabelecimento de estratégia e objetivos de curto, médio e longo prazo, com priorização de acordo com sua possibilidade de disponibilização e necessidades existentes.

Grandes avanços foram alcançados desde sua criação com disponibilização de duas combinações em dose-fixa para malária falciparum; uma nova combinação de nifurtimox e eflornitina para o tratamento de primeira linha da doença do sono, assim como uma nova combinação para leishmaniose visceral. No campo da doença de Chagas, a DNDi em colaboração com o laboratório LAFEPE, submeteu para registro uma nova apresentação pediátrica para o benznidazol. O estudo clínico de farmacocinética populacional foi iniciado em vários centros na Argentina, tendo como investigador principal a Jaime Altcheh. Também como projeto em fase de desenvolvimento clínico em parceria com a empresa Eisai, avalia-se a segurança e eficácia do E1224, uma pró-droga do ravuconazol, para o tratamento dos pacientes na fase crônica indeterminada da doença.

Um projeto em colaboração com Médicos Sem Fronteiras avalia novas técnicas para otimização de procedimentos da PCR em tempo real, em especial o número e volume de amostras necessárias para aumento de sensibilidade. Em fase pré-clínica, implementase a triagem de compostos de alto rendimento (*High-Throughput Screening*). Em colaboração com o Instituto Pasteur-Coréia, DNDi desenvolveu tecnologia para triagem de compostos em escala, permitindo a avaliação exploratória de grandes bibliotecas de compostos. Por último, temos ainda as atividades do Consórcio para a Otimização de Compostos Líderes. Este projeto iniciado em 2008, em parceria com o Centro de Otimização de Candidatos a Medicamentos (*Centre for Drug Candidate Optimisation,* CDCO), Epichem, a Universidade de Murdoch na Austrália e a Universidade Federal de Ouro Preto, no Brasil, tem hoje algumas moléculas e classes promissoras identificadas.

Certamente é importante lembrar as necessidades de políticas de incentivo à pesquisa e desenvolvimento em medicamentos para doenças negligenciadas que venham a viabilizar a sustentabilidade de iniciativas, assim como resolver os desafios e hiatos burocráticos e restritivos à inovação. No entanto, o progresso destes últimos anos nos aponta para um futuro de contínua articulação em prol de parcerias e de melhor resposta às necessidades das populações negligenciadas.

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Development of new drugs for visceral leishmaniasis

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During the last 15 years, several new drugs have been made available for the treatment of visceral leishmaniasis, most of them through highly relevant public-private partnerships. One of the first efforts was the validation of a cheap generic pentavalent antimonial, called sodium antimony gluconate and produced in India. However, appearance of resistance quickly limited its use in India.

The traditional amphotericin B deoxycholate (Fungizone®), in use for more than 50 years, remains a highly effective drug with an efficacy rate of at least 97%. Its main limitations are: the need for a close monitoring of the prolonged infusions, the frequent, although controllable, adverse events and the relatively high cost. However, the acceptability of amphotericin B remains high.

Miltefosine, developed through a partnership between Zentaris/Aeterna and WHO/TDR, is the first oral drug for visceral leishmaniasis. It is an alkyl phospholipid analogue, initially used as anti-neoplastic drug. It has been adopted by India, Nepal and Bangladesh as the first-line drug for the visceral leishmaniasis elimination program. However, it is contraindicated in pregnant women, and child-bearing age women have to use contraception up to two months after the end of treatment due to the potential risk of teratogenicity of the drug and its long half-life. DOT-like surveillance system has to be urgently put in place as lack of compliance is common and risk of resistance is increasing.

Although antileishmanial activity of intramuscular paromomycin was discovered in the 1960's, its development has been slow. Fortunately, with commitment to support the visceral leishmaniasis elimination program in India, Nepal and Bangladesh, OneWorld Health, together with WHO/TDR, secured a grant from the BMGF, to carry out phase III and IV clinical trials in Bihar State of India. Following its development, intramuscular paromomycin is now included among the WHO essential drug list and has been granted the status of orphan drug by EMEA and the Food and Drug Administration. Intramuscular paromomycin is safe, effective, and affordable. It has also been registered with the Drug Controller General of India in 2006. Main limitations are the duration of treatment (21 days) and injection site pain, the most frequent adverse event.

Among the lipid formulations of amphotericin B, Ambisome® (a liposomal formulation from Gilead) is the most extensively used and several regimens have been tested successfully. The drug has a high safety profile. Side-effects are limited. So far, no resistance has been reported. Even a single dose of Ambisome® has proved to be highly effective (5 mg/kg: 91% cure, 10 mg/kg: 96% cure). WHO has been able to negotiate a preferential price of US$ 20 per vial of 50 mg, making Ambisome® more accessible for visceral leishmaniasis patients living in endemic countries.

As there is no new compound expected to be developed in the next 5 years, any effort should be made to preserve the efficacy of currently available drugs. There is an urgent need to set up pharmaco-vigilance and drug-resistance surveillance systems. Indiscriminate use by inexperienced health care providers should be prevented.

Another option is to promote the use of combo therapies and evaluate their respective efficacy, safety and practicality in different regions. In India, an evaluation of the different options for combo therapy has been recently achieved by Drug for Neglected Diseases Initiative (DNDi). It has shown that the 3 main options (Ambisome® + miltefosine, Ambisome® + intramuscular paromomycin and intramuscular paromomycin + miltefosine) have, in India, a similar high efficacy (98%) and all were well tolerated.

A consortium project, which includes three partners: the Drug for Neglected Diseases Initiative (DNDi), OneWorld Health and WHO/TDR, has just started. Its goal is to evaluate the feasibility to use a single-dose Ambisome® in combination with either intramuscular paromomycin or miltefosine, and the use of intramuscular paromomycin plus miltefosine at the district hospital and primary health care levels. The rationale to use combo therapies is to reduce the duration of treatment, improve the compliance, reduce the risk of resistance, reduce the cost and enhance efficacy.

In South-Asia, the main goal of all these studies is to contribute to the visceral leishmaniasis elimination program by reducing the burden of the disease in endemic rural communities of India, Bangladesh, and Nepal in coordination with the partners and respective governments. In East Africa other combo therapies are currently under evaluation. In South America, studies on combo therapies are already planned to start soon.

Two clinical entities: post kala-azar dermal leishmaniasis, a cutaneous complication of visceral leishmaniasis, and the leishmania/HIV coinfection entity which is becoming more frequent, deserve more attention. Current treatments are long and toxic. New schemes of treatment have to be evaluated urgently.

Any new drug has to be, not only safe and efficient, but also available, accessible and affordable.

Visceral leishmaniasis remains a highly neglected disease, but the recent availability of new tools for control makes it more promising.

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Program update on a topical paromomycin plus gentamicin formulation (WR279,396) for the treatment of cutaneous leishmaniasis

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Global incidence of symptomatic leishmaniasis (all forms combined) is estimated at 2 million cases per year. Annual mortality is approximately 70,000. Disease burden is 2.4 million disability-adjusted life years (DALY).

Of the 2 million patients suffering from leishmaniasis each year, approximately 1.0-1.5 million have cutaneous leishmaniasis. Cutaneous leishmaniasis is among the most neglected of neglected diseases due to the fact that it affects the poorest of the poor and does not result in death. However, the true socioeconomic impact of cutaneous leishmaniasis cannot be quantified. Severe disfigurement, disability, and social/psychological stigma often result. Cutaneous leishmaniasis is primarily an endemic disease, with epidemic outbreaks happening in both sedentary and mobile (military personnel, refugees, travelers) populations. Prevention is limited to personal protective measures such as insect repellent, bed nets, portable tent air conditioners, and control of disease reservoirs such as rodents and dogs. There are no vaccines or chemoprophylactic drugs to prevent leishmaniasis and there are no drugs approved by the Food and Drug Administration (FDA) for treatment of cutaneous leishmaniasis.

Cutaneous leishmaniasis has a significant impact on military populations serving in Iraq, Afghanistan, and other endemic areas. It is a chronic, disfiguring disease without a simple, safe, and widely effective treatment. Topical therapy of cutaneous leishmaniasis is both practical and desirable, yet such a product has not yet been developed for worldwide use.

The aminoglycoside paromomycin is the most studied compound for topical treatment of cutaneous leishmaniasis, but testing of different formulations worldwide has led to mixed results. WR279,396 is a third generation topical antileishmanial cream, which contains 15% paromomycin and 0.5%

gentamicin. WR279,396 was formulated in a hydrophilic base that facilitates penetration and delivery of the active ingredients to sites containing *Leishmania* amastigotes.

In a Balb/c mouse cutaneous leishmaniasis model, WR 279,396 cured lesions caused by multiple *Leishmania* strains in 100% of the mice without subsequent relapse. Significant progress has been made in the development program for WR279,396 in the last 4 years. WR279,396 was scaled-up and manufactured by TEVA Pharmaceuticals USA, and has received orphan drug designation by the US FDA.

In the first phase 2, randomized, double blinded, placebo-controlled, multicenter study of Old World cutaneous leishmaniasis, 47 of the 50 (94%) subjects treated twice daily for 20 days with WR279,396 met the definition of complete clinical response, compared with 30 of the 42 vehicle subjects (71%).

In a second phase 2 study in which WR 279,396 was administered once-a-day for 20 days, the complete clinical response rate was 91.7% in the gauze-and-tape group. Additionally, at day 10, there was a statistically significant reduction in the parasite load in both the superficial dermis (52.8-fold) and the deep dermis (76.8-fold). WR279,396 was found to have a favorable safety profile with no deaths or serious adverse effects. All adverse effects were rated as mild to moderate in severity. There was no laboratory evidence of renal toxicity, no reports of vertigo, and no abnormal Romberg test results or audiometric evidence of clinical decreased hearing in patients who received WR279,396.

Currently, a phase 3 pivotal clinical trial is underway in Tunisia, a second phase 3 trial is planned for the New World, and phase 2 studies are ongoing or planned in Washington, D.C., Peru, Panama, France, and Guatemala. The WR279,396 development strategy, FDA approved clinical plan, and clinical results will be discussed.

In summary, treatment optimization and final therapeutic decision in cutaneous leishmaniasis can be more complex than in visceral leishmaniasis, despite the greater severity of the later. Paradoxically, drugs used to treat visceral leishmaniasis are not necessarily efficacious in cutaneous leishmaniasis. The therapeutic decision is complicated by the numerous forms of the disease and the lack of a single drug that is efficacious against all of them.

The efficacy of a new third generation paromomycin cream has been demonstrated in phase 2 studies, and further phase 2 and phase 3 studies are ongoing. Additionally, current development efforts at the Walter Reed Army Institute of Research (WRAIR) are concentrated on finding a safe, oral drug that is effective against all forms of cutaneous leishmaniasis, has superior cosmetic results, and is affordable and adaptable for use in rural areas.

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Current business models to address research and development for products for neglected diseases

Implications for developing countries: the good, the bad and the ugly

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The 1990 Commission on Health Research for Development made the first estimates of worldwide spending on health research and development (US$ 30 billion) and in analysing the flows of resources described what became known as the “10/90 gap” – capturing the inequality revealed in their estimate that less than 10% of the global budget for health research and development was being spent on 90% of the world’s health problems.

To address the 10/90 gap different initiatives to enhance product research and development for neglected health problems were established. These initiatives are based on business models that promote partnerships and collaborations between the private and the public sector, with financing to a large extent from the philanthropic and international cooperation initiatives. Today the preponderant model is the so called product development partnerships that are non-for profit organizations with mandates to research, develop and support accessibility of new health technologies that target diseases disproportionately affecting developing countries.

Product development partnerships typically employ a portfolio approach to research and development to accelerate product development working in close partnership with academia, large pharmaceutical companies, the biotechnology

industry and governments in developed and developing countries. Product development partnerships typically use private industry approaches to portfolio and project management choosing and funding partners that offer the highest possibilities for successful outcomes.

On the other hand, the pharmaceutical sector (private or public) has also responded to the "10/90 gap" by establishing fully funded and dedicated facilities to address research and development for neglected tropical diseases. While recognizing the impact of the above initiatives, the World Health Organization (WHO) member states after a thorough and lengthy process agreed in 2008 on a World Health Assembly resolution (WHA 62.16. Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property) calling for:

i) strengthening the innovative capacity of developing countries, to support local researchers in driving research efforts required to respond to the local public health needs, and
ii) promoting research aimed at ethically developing health products that are available in sufficient quantities, are effective, safe and of good quality, are affordable and accessible, and are used in a rational way.

As a follow-up of this resolution an action plan and budget proposal was developed by the WHO and endorsed by the World Health Assembly. It is anticipated that this will lead to a significant scale-up of resources for research in developing countries. The key question that still remains to be answered is how to best use these political instruments and the available global resources to on one hand sustain the current initiatives (e.g., product development partnerships) and on the other to address the need of many developing countries to develop and strengthen local research and development initiatives that respond to local health priorities (even if those may not stand high among the global health agenda) while contributing to their socioeconomic development.

The presentation will attempt to examine the existing global neglected tropical diseases product research and development models and frameworks and particularly address how they interface with institutions/organizations in developing countries highlighting issues, gaps and opportunities.

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