



# InfoLEISH

redeLEISH newsletter-4<sup>th</sup> edition

July 2019

## Editorial

In 2018, DNDi's Cutaneous Leishmaniasis (CL) program advanced in its efforts to identify a new treatment for the disease. The phase II combination therapy study, which aims to test the efficacy and safety of thermotherapy (TT) + miltefosine for the treatment of uncomplicated CL in Peru and Colombia, was concluded. Final results are expected by June 2019. Based on these encouraging preliminary results, we are moving to a phase III study which aims to demonstrate the non-inferiority of the combined therapy compared with miltefosine monotherapy and the current recommended treatment of meglumine antimoniate. The study will be conducted in five sites located in Brazil, Bolivia, Peru and Panama. The enrollment is expected to start in 2020.

We have moved up in the Chemistry, Manufacturing and Controls (CMC) and preclinical development of the immunomodulator CpG D35. The first GMP batch of CpG D35 has been successfully manufactured. We presented our strategy regarding the preclinical package and phase I activities to the Health Authorities in the UK (MHRA) during a scientific advice meeting, which took place in London on February 5<sup>th</sup>. The Agency agreed with the overall Active Pharmaceutical Ingredient (API) control strategy approach. They also agreed with the proposal to start the single ascending dose study in healthy volunteers in UK and continuing with the multiple ascending dose study in subjects infected with *L. major*.

The screening and drug discovery efforts on *L. donovani* have expanded since 2015 to include some *Leishmania* strains causing CL. Two compounds showing activity against VL and CL, DNDi 0690 and 6148 have completed their preclinical development and will enter in its clinical development during 2019. If no safety concerns are observed in phase I studies and if there is an indication of its efficacy in VL patients, then these compounds will be tested for CL.

The leishmaniasis team continues to search for opportunities to work in the Old World, given the imminent need to test CpG D35 initially in *L. major* and subsequently in *L. tropica* patients. We are also aiming to tackle other unmet needs such as the infections due to *L. aethiopica* in Ethiopia and the emergent and growing problem of CL in Sri Lanka. •

Byron Arana - DNDi, Geneva



Daniel de Oliveira,  
10 years old,  
affected by  
cutaneous  
leishmaniasis in  
the rural area of  
Teolandia,  
Bahia - Brazil.



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## PHASE III COMBINATION STUDY

MARINA BONI - DNDi - Latin America



**T**ime has come for us to move from a phase II to a phase III trial combining thermotherapy and miltefosine for the treatment of uncomplicated cutaneous leishmaniasis.

DNDi has recently finalized a phase II trial evaluating the safety and efficacy of the combination of thermotherapy (one session) + miltefosine (standard dose of 2.5 mg/kg/day for 21 days, orally) compared to thermotherapy alone (one session) for the treatment of uncomplicated CL in Peru and Colombia. Preliminary results in the ITT analysis, after completing the enrolment of 130 participants, have shown evidence in favor of the combination treatment.

### ADVANTAGES OF USING THE COMBINATION

1. The use of a local plus a systemic treatment would hypothetically have an additive effect, since systemic treatment would eliminate those circulating or remaining parasites located in the periphery of the lesion that local treatment fails to remove and which might be the cause of relapses;
2. It offers the opportunity to increase the current cure rate reported with any other treatment approach available when used alone;
3. The combination reduces the length of treatment with miltefosine. And, if the combined approach renders the expected cure rates, there will be evidence to recommend the replacement of antimonials as first line treatments for non-complicated CL cases.

In view of that, our phase III trial aims to determine whether this same combination treatment is non-inferior in comparison to the standard first line treatment (meglumine antimoniate dose of 20 mg/kg/day for 20 days, parenterally) and to miltefosine monotherapy (standard dose of 2.5 mg/kg/day for 28 days, orally). Hence, there will be three treatment arms in the study and participants will be evaluated for initial cure at D90 and final cure at D180.

Four countries and five sites are selected for this open-label randomized trial: Peru, Panama, Brazil and Bolivia, for their high number of new cases,

and with investigators who we work closely and know of their hard work with their patients. The plan is to have 306 participants enrolled in all five sites.

So, where are we at with it all? We all know the huge amount of work that is involved when initiating a trial, besides getting all the documents checked and re-checked internally, such as protocol and informed consent, there is a whole preparation in terms of getting all sites insured, ensuring every site is able to accommodate the number of participants and the exams required as per protocol, a budget review, preparing the electronic data capture system, getting all the monitors ready and their monitoring plans, developing all the safety management plans, organizing the purchase and shipment of the medications going to site, data management plan as well as the statistical analysis plan.

And that is all before the site enrolls our first participant! Throughout 2019 we will be sending the documents such as protocol and informed consent to Ethics Committees and Regulatory Authorities. Some of these countries take longer to approve than others and we are expecting to start recruitment in 2020. •



# PHASE III, RANDOMIZED, DOUBLE-BLIND STUDY OF PAROMOMYCIN TOPICAL CREAM FOR CUTANEOUS LEISHMANIASIS IN PANAMA

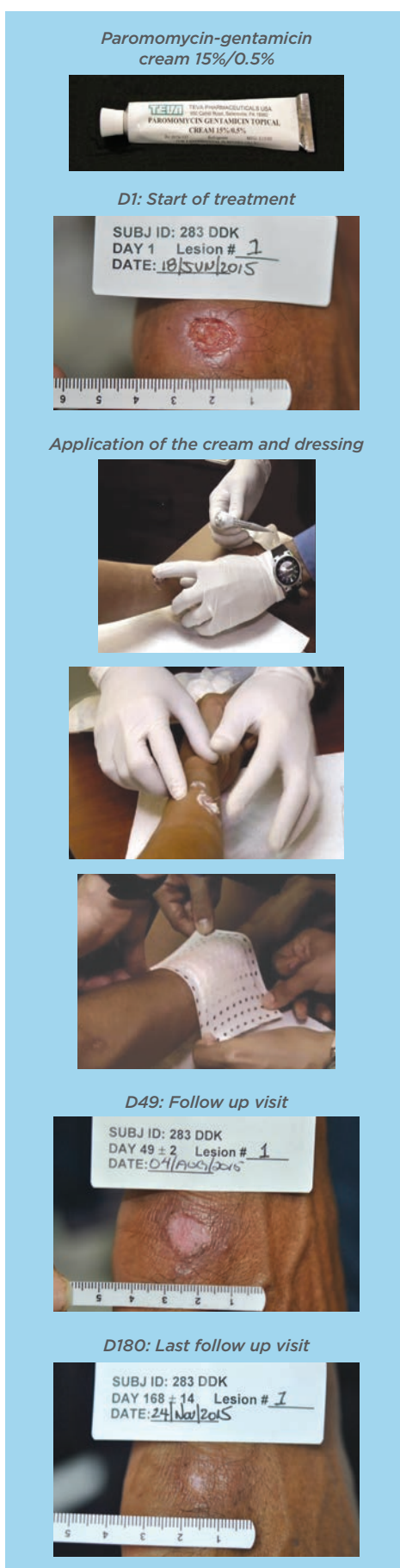
JUAN MIGUEL PASCALE and NESTOR SOSA  
Instituto Conmemorativo Gorgas de Estudios de la Salud, Panama



In Panama, cutaneous leishmaniasis is an important parasitic disease with an average estimate of 2,200 new cases reported per year, although this number is likely a 4-fold underestimate due to underreporting. Among the cases reported in Panama from 2005-2009, the majority were diagnosed as *L. panamensis* which causes typical CL lesions. However, it does have the potential to progress to mucocutaneous leishmaniasis in approximately 5% of cases.

The first line of treatment for CL in Panama is pentavalent antimony, either meglumine antimoniate or sodium stibogluconate, given parenterally for 20 to 28 days. The cure rates for *L. panamensis* CL in adults treated with systemic antimony have been reported in the range from 25-93%. However, these systemic regimens are associated with toxicities that can limit the patient from receiving a full course of treatment. Alternative therapies are needed particularly for patients with mild disease, no mucosal involvement, and who are not immunocompromised, and for patients living in areas with scarce infrastructure (most CL endemic areas).

Looking for new treatments for CL, we carried out a phase III, randomized, double-blind, two-group trial assessing the efficacy and safety of paromomycin-gentamicin and paromomycin alone topical cream in subjects with CL in Panama. A vehicle-control group was not included as it was considered unethical to withhold treatment based on the standard of care in Panama. Study subjects were males or non-pregnant non-lactating females, ages 2 and older, and with 10 or fewer lesions. For each subject, an index lesion was selected with the following characteristics: ulcerative, from 1-5 cm in diameter, and confirmed to contain *Leishmania* parasites via culture or microscopic examination of lesion material.



Subjects were otherwise healthy and without clinical evidence of mucosal involvement.

Three hundred ninety-nine patients with one to ten CL lesions were treated by topical application once daily for 20 days. The primary efficacy endpoint was percentage of subjects with clinical cure of an index lesion confirmed to contain *Leishmania* with no relapse. The clinical cure of the index lesion for paromomycin-gentamicin was 79% (95% CI; 72 to 84) and for paromomycin alone was 78% (95% CI; 74 to 87) ( $p = 0.84$ ). The percentage of subjects under 12 years and 12 to 17 years of age who achieved final clinical cure rate of the index lesion was 84% and 82%, respectively.

Of 399 subjects, 398 were typed using PCR/RFLP. Of those, a total of 312 (78%) subjects were identified as infected with *L. panamensis*, 78 (20%) with *L. guyanensis*, and 8 (2%) with *L. braziliensis*. There was no significance difference in the final clinical cure rate between treatment groups for any of the species identified.

Neither of the two topical creams was associated with any serious or severe systemic toxicity. Specifically, no aminoglycoside-related nephrotoxicity or ototoxicity was observed. Application site reactions associated with the topical therapy and contact dermatitis related to the tape dressing were common.

This trial demonstrates that topical therapy with a paromomycin-based cream offers a potential alternative to the current standard of care for the treatment of CL in Panama. A topical therapy offers possible advantages over systemic treatments, such as pentavalent antimonials, and might be an alternative to treat CL in children or in settings where parenteral therapy is not feasible. Topical treatment could also be studied in future trials as part of combination treatment with oral or parenteral agents. •



## EFFECTIVENESS OF THE COMBINATION THERAPY WITH SODIUM STIBOGLUCONATE PLUS PENTOXIFYLLINE VERSUS SODIUM STIBOGLUCONATE ALONE IN TREATMENT OF MUCOSAL LEISHMANIASIS IN PERU

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**T**egumentary leishmaniasis (TL) continues to be a serious global health problem. Mucosal leishmaniasis (ML) is the most severe and at the same time the most neglected form of TL. ML represents the polar form of TL and usually results from the metastatic spread of a cutaneous infection. In the period 2001-2017 in Latin America an average of 55,317 cases/year of TL have been reported and the proportion of mucosal cases is 3.94% (at about 2,180 cases), a figure that has remained stable in the last decade. Peru is one of the countries with higher ML rates and >98% of cases are caused by *L. (V.) braziliensis* and historically the cure rate with pentavalent antimonials ( $Sb^{5+}$ ) is around 60%.

The severity of ML (mild, moderate and severe) depends on the number of affected mucous membranes and is closely associated with the level of disequilibrium in the host immune response. Severity is the main factor associated with the therapeutic response. The cure rate of the mild form treated with  $Sb^{5+}$  is similar to the classic cutaneous leishmaniasis (CL), while the severe form of the disease the cure rate with  $Sb^{5+}$  is <10%. Pentavalent antimonials continue to be the treatment of choice in Peru and are indicated for all *Leishmania* species. There is evidence in clinical studies (although with a small number of patients) that the combination of meglumine antimonate (anti-leishmania activity) plus pentoxifylline (immunomodulatory activity) has higher efficacy than antimonial monotherapy for the treatment of ML. Based on these findings, we have evaluated the effectiveness of this combination through a retrospective cohort study in which the effectiveness of the combination of sodium stibogluconate (SSG) in standard doses, 20 mg  $Sb^{5+}$ /Kg/day, intravenous, plus pentoxifylline (standard dose of 400mg TID, orally), both for 30 consecutive days was compared with monotherapy of SSG in standard doses. The study

was conducted in the Leishmaniasis Program (2005-2013) of the Cayetano Heredia Hospital/Institute of Tropical Medicine Alexander von Humboldt of the *Universidad Peruana Cayetano Heredia* where the previous combination is being used for several years.

Records of consecutive cases were included by systematic sampling under the inclusion criteria:  $\geq 18$  years old with confirmed ML who received any of the schemes in the doses mentioned and followed-up at day 180. The cure criterion was the complete re-epithelization of the lesions and absence of inflammation at day 180. The evaluation was performed by a physician with experience in leishmaniasis. We selected 234 patients with the inclusion criteria and 205 (87.6%) of them had a 180-day evaluation after treatment. Study groups differed only in the proportion of women (18% versus 82% men,  $p = 0.02$ ). The effectiveness of combined therapy was higher (78.8%, 52/66) in comparison to SSG alone (61.2%, 85/139,  $p = 0.01$ ). The difference remained significant (RR: 1.36, 95% CI 1.13-1.64,  $p = 0.001$ ) after adjusting for severity, previous mucocutaneous leishmaniasis and sex. The severity of ML influences both treatment regimens. The cure rate in patients with moderate ML severity was 63% with the combination SSG plus pentoxifylline versus 37% with SSG alone.

In summary, the combined sodium stibogluconate plus pentoxifylline therapy was more effective than sodium stibogluconate alone for mucocutaneous leishmaniasis, increasing the cure rate by approximately 18 points. This finding corroborates the previously published results on the efficacy of this combination in the clinical practice of a national reference center of the Ministry of Health in Peru. •



**"I've suffered for 10 years without being able to speak or eat properly, and with no money to see a doctor"**

Eusebio Laine Alvarado,  
68 years old,  
mucocutaneous  
leishmaniasis patient,  
Cayetano Heredia  
Hospital - Lima, Peru.



# POOLING DATA RESOURCES ON THE EFFECTIVENESS OF AMERICAN CUTANEOUS LEISHMANIASIS TREATMENT IN UNDER-EVALUATED AGE GROUPS

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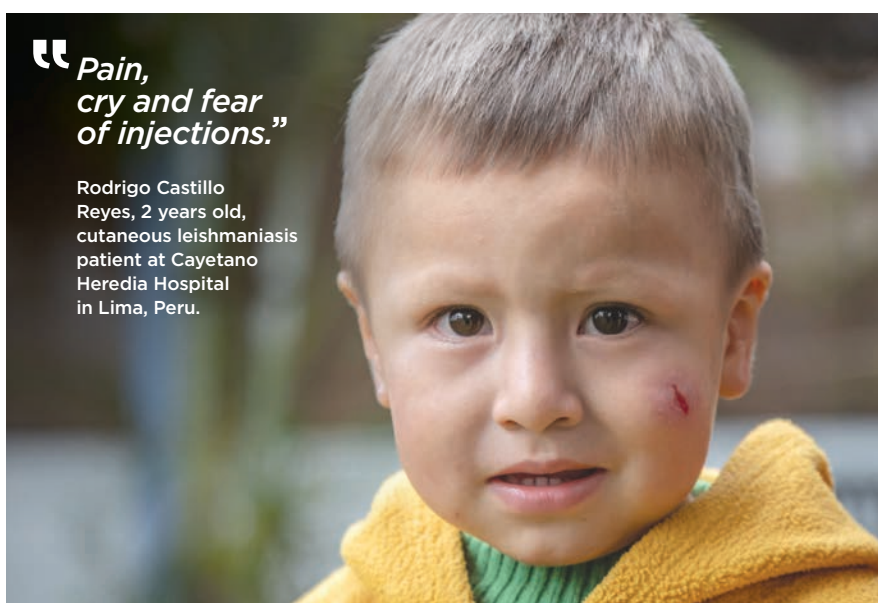


*A data-sharing project aims to gather the available evidence on the effectiveness of leishmaniasis treatments in children and older adults; groups which have tended to be under-represented in published trials.*

**D**uring the 5<sup>th</sup> redeLEISH meeting, held in Rio de Janeiro in July 2018, the participants identified the need to generate evidence to improve the management of cutaneous leishmaniasis in special populations who are not usually included in clinical trials and for whom current national guidelines do not give clear directions. Children 10 years of age or less and patients of 60 years of age and older were selected as priority population for a pilot collaborative data sharing project.

## Inclusivity in Clinical Trials

Randomized controlled clinical trials are considered the gold standard of medical research, in particular for evaluating new treatments. However, one criticism of such trials, for leishmaniasis and other conditions, is that the people included are not always sufficiently representative of all those who might benefit. This limitation affects their generalizability or 'external validity'. One of the main factors which determines inclusion or exclusion from trials is age. At one time, it was thought preferable to exclude children and older adults from clinical trials because they were vulnerable populations. Currently, it is considered unethical to exclude them unless there is good reason, because the possible risks and benefits to them will otherwise not be well evaluated or available to guide their treatment. For this reason, the National Institutes of Health of the USA, for example, requires any age-based exclusions to be justified: this is called the 'Inclusion Across the Lifespan' policy.



## Changing exposure to leishmaniasis

There are concerns that environmental changes such as deforestation and the growth of intensive agriculture are shifting the balance of the transmission of leishmaniasis, from forest to domestic environments. This would tend to increase the frequency of cases among older adults and children, because forest transmission is usually associated with adult workers. The 2019 PAHO Epidemiological Report of the Americas on Leishmaniasis shows that, in a band of Andean countries comprising Bolivia, Peru, Ecuador, Colombia and Venezuela, the proportion of cutaneous leishmaniasis cases in those aged less than ten years is between 7.2 and 15.9 percent with even higher proportions among children in several countries of Central America surpassing 40% in El Salvador.

## Children respond differently to drug treatment

From the few trials of leishmaniasis drugs in children, there is evidence that they respond to treatment differently than adults. One explanation for this lies in allometry, which means the way that different body parts grow at different rates, resulting in changing body proportions. One consequence is that defining drug doses in the usual way, per kilogramme, leads to lower concentrations in smaller people, in particular children. However, the applicability of this idea needs to be tested more extensively, including for a wider range of leishmaniasis drugs.

## A redeLEISH data-sharing project to address this gap in knowledge

WHO-TDR (Special Programme for Research and Training in Tropical Diseases) has funded a project, led by DNDi, and *Centro Internacional de Entrenamiento e Investigaciones Médicas* (CIDEIM) in Colombia, to support data-sharing among centres of cutaneous leishmaniasis treatment in Bolivia, Brazil, Colombia and Peru. This project will collect, in a standardized format, results of drug treatment in children aged 10 years or less, and in adults aged 60 years or older, with the aim of measuring, for different drug regimens, the rates of cure and adverse events. The results will inform drug choices for these age groups and quantify the extent, if any, to which the available drugs are less effective than in other age groups that have been better evaluated to date.

Beyond providing evidence and recommendations to the national leishmaniasis programs for management of special cases, this project will strengthen collaboration between institutions and integrate the redeLEISH community paving the way for the creation of a regional data base on cutaneous leishmaniasis. •



## ATYPICAL VARIANT OF *L. DONOVANI*-INDUCED CUTANEOUS LEISHMANIASIS IN SRI LANKA: A THREAT TO THE REGIONAL DISEASE ELIMINATION DRIVE?

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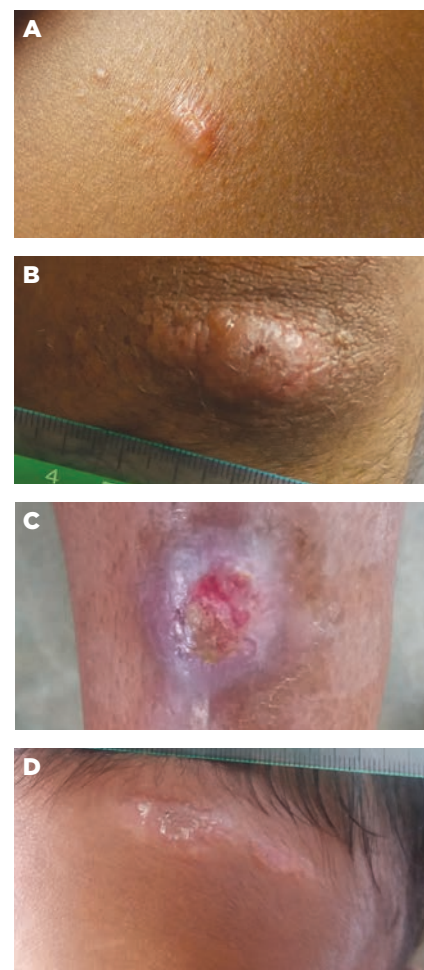


**L**eishmaniasis was considered as an exotic disease in Sri Lanka in the pre-21<sup>st</sup> century era. The disease was linked with foreign travel at that time and was seen mostly among returnees from the Middle East or African region. The first autochthonous case of cutaneous leishmaniasis (CL) was reported in 1992. Leishmaniasis became an established disease in this island nation, since the outbreak of CL reported in the North-Central Province in year 2001. A steady increase was observed thereafter, both in the incidence and spatial spread across the country. The numbers reported to the national healthcare system, however, are likely to portray an under representation with the true disease burden likely to be much higher.

Majority of patients continue to present as CL with only a few cases of visceral and mucosal leishmaniasis. The classical presentations of Sri Lankan CL are non-tender, non-itchy papules, scaling nodules or ulcers affecting exposed areas of body, mainly on the extensor surfaces of limbs and the face (see Figure). Most clinicians now tend to resort to clinical diagnosis due to many factors that include inadequate laboratory facilities for confirmatory diagnosis, high patient loads in busy clinics etc. First line of treatment is intralesional inoculation of sodium stibogluconate (SSG), which is administered in outpatient clinics in hospitals with functional dermatology units. Cryotherapy (which was the original treatment mode as practiced in Sri Lanka) is still used by some clinicians, which is available in most district-level hospitals. Both these forms of treatment require repeated doses hence, multiple hospital visits (usually on a weekly basis) and resultant burden both on the patient and the healthcare system. Poor responsiveness of CL lesions to multiple doses of intra-lesional SSG is widely recognized in the country at present and remains as a cause for concern. Newer forms of treatment e.g. thermotherapy using radio frequency heat has been successfully tested in the local setting through clinical trials with encouraging results. Hence, such cost-effective treatment options are likely to be considered as viable alternatives for the future.

The causative agent of CL in Sri Lanka is *L. donovani*, MON-37. This specie is an established agent of human VL in many countries, including the neighbouring country India. However, dermatropism of *L. donovani*, as seen in Sri Lanka has indeed been reported occasionally from elsewhere as well. This has led to investigations on the existence of apparently more attenuated forms of *L. donovani*, a possible role for host genetics and vector factors that may determine the disease phenotype in *L. donovani* infections with the debate continuing. While the local clinical evidence through long-term follow up of CL patients points towards the essentially dermatropic nature of the local variant of *L. donovani* (with no signs or symptoms of visceralization following apparent cure of CL), the *ex vivo* experimental evidence has confirmed the visceralizing potential of this parasite variant despite its attenuated features. Whole genome sequencing of *L. donovani* isolates from local patients with CL and genotyping experiments have revealed interesting information, including the unique genetic identity of the local isolates that form a distinct cluster in a phylogenetic tree, away from but close to the other regional *L. donovani* strains. This points towards the historical presence of these parasites in the local setting for much longer periods albeit hidden from the national health care system. Early evidence also point towards the presence of a genetic basis for the 'SSG non-responsiveness' in local parasites that is currently being further pursued.

The likely vector of leishmaniasis in Sri Lanka was identified as *Phlebotomus argentipes*, the same species that is found elsewhere in the region. The studies carried out so far support the anthropophagic nature of the local vector and the environmental conditions that exist in most parts of the country favour outdoor breeding (although some studies imply peri-domestic transmission and indoor breeding habits of this insect as well). Entomological studies are continuing to elucidate vector behavioural



Common types of cutaneous leishmaniasis lesions in Sri Lanka  
A: Papule. B: Nodule. C: Ulcer. D: Plaque.

habits, feeding preferences and insecticide-susceptibility pattern that are considered as operationally important biological properties that will aid future strategies for disease control.

Information regarding reservoir hosts still remains inconclusive. Though it is traditionally believed that the only reservoirs of infection of *L. donovani* are human patients, this view has been challenged on many occasions (the nature of the origin of the Sri Lankan leishmaniasis outbreak being a case in point) and therefore, further studies are warranted in this area too. Overall, there are many questions that still remain unanswered on leishmaniasis situation in Sri Lanka and in this backdrop no organized efforts are in place for the control of this disease at national level.

There are obviously many advantages of moving towards elimination of leishmaniasis from the South Asian region. However, it might be timely to take stock of the current situation in the region and outcomes of the elimination program that was put in place as far back as 2005. The lapses thus identified should be addressed with gaps in knowledge bridged using properly designed studies and futuristic ideas. The elimination program needs to be revamped with the necessary monitoring mechanisms in place and also with due considerations made in to the more recent developments in the region, such as the presence of atypical variants of *L.donovani*, which might have the potential to act as reservoirs of infection for the region. Such new and improved strategies would no doubt ensure a more successful outcome of the regional drive towards elimination of *L.donovani*-induced leishmaniasis. •

## PREFERENCES FOR TREATMENT AND EVALUATION OF SCARS IN PATIENTS WITH CUTANEOUS LEISHMANIASIS RECEIVING LOCAL, SYSTEMIC AND COMBINED TREATMENTS

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In 2010, following one of the recommendations of the World Health Assembly, the second committee of leishmaniasis experts was held with the aim of updating the technical report on the control of leishmaniasis published in 1990. The revised and updated version of the guidelines includes, among its recommendations, the search for safe, effective and affordable therapeutic alternatives for cutaneous leishmaniasis (CL), with non-invasive administration, short-duration cycles and good safety profiles. In addition, it encourages the evaluation of such treatments in the framework of well-conducted clinical studies whose results allow evidence-based therapeutic decisions.

Although experts in the area are trying to respond to the recommendations made by the WHO in terms of therapeutic research, so far, the assessment of patients' treatment preferences, as well as the visual evaluation of scars, has been a minor component in the studies that were being developed.

For this reason, a nested study was proposed in a clinical trial with two main purposes, as follows:

### From patient's perspective

To determine the treatment preferences of patients who received pentavalent antimonials, thermotherapy or combination therapy of thermotherapy plus miltefosine as a treatment for CL.

### From medical criterion

To evaluate the scars of cutaneous leishmaniasis in patients treated with the aforementioned therapeutic alternatives.

The study is structured in five follow-up visits over six months from the start of treatment. Each visit has a specific purpose: so at visit 1 (start of treatment) an *a priori* evaluation of treatment preferences is made and the characteristics of the lesions are registered; the main goal of visit 2 (end of treatment) is to ask if those preferences have changed after receiving any of the therapeutic alternatives evaluated; finally, visits 3, 4 and 5 focus mainly on evaluating the scars.

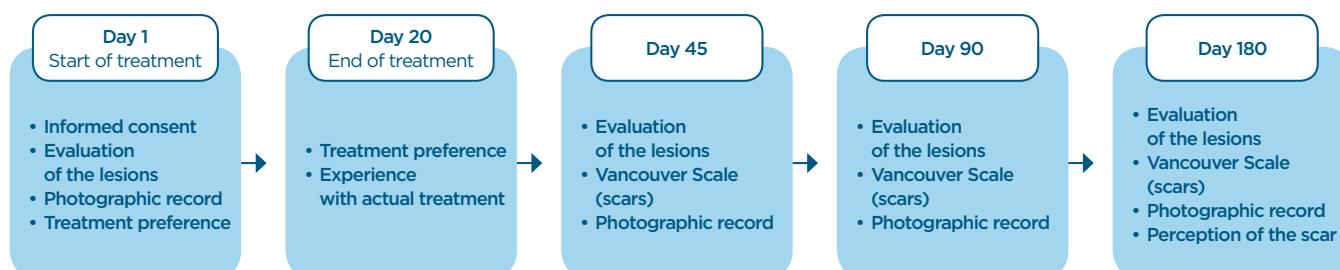
The evaluation of treatment preferences for CL is carried out by ranking therapeutic options and available schemes, where the patient chooses the best therapeutic alternatives for managing his disease. To assess these

preferences, the study physician uses cards that show local, systemic and combined treatment schemes for CL. At the time of the evaluation, the physician presents these cards to the patients and they must choose the three options they prefer. In addition, they must rank their choices, with the first option corresponding to the best treatment.

On the other hand, the evaluation of the characteristics of the scars is carried out by a dermatologist, who does not know which treatment the patient received. For this assessment, the Vancouver scale (VSS) is used. It is a validated instrument for scar evaluation that takes into account the following aspects: pigmentation, vascularity, flexibility and height. Assigning a score of 0-15, with zero being the best score possible, the use of this instrument allows an effective evaluation of CL scars.

Knowing patients' preference regarding treatments for CL, as well as determining whether different therapeutic alternatives may or may not affect the appearance of the scar, will provide information that will be very useful when designing protocols for the disease management. •

### TRIAL EVALUATIONS OUTLINE:







## LEISHMANIACS IN LAB COATS AND CAMOUFLAGE UNIFORMS

LINA BEATRIZ PINTO GARCÍA - Department of Science & Technology Studies, York University - Toronto, Canada



**T**hose who investigate leishmaniasis like to call themselves *leishmaniacs*. The word highlights the sense of belonging to a community interested in a fascinating, biologically diverse disease, which still remains little known. However, few leishmaniacs know about the existence of another group of people who, albeit for very different reasons, also feel identified with this term: the soldiers of the Colombian Army affected by cutaneous leishmaniasis.

Colombia has had an armed conflict for over 50 years. This long and bloody war has taken place in multiple settings, but the jungle is the main conflict space. Different armies have historically confronted each other, from soldiers of the military forces, to far-right paramilitaries and far-left guerrillas such as the FARC (Revolutionary Armed Forces of Colombia) or the ELN (National Liberation Army). Therefore, fighters from all groups are one of the most affected populations by leishmaniasis in Colombia. In particular, it is often said that soldiers of the National Army make up 50% of reported cases.

This figure, however, corresponds to the epidemiological situation of the disease in the mid-2000s, when Álvaro Uribe's administration decided to adopt an offensive military strategy and increase the force by 31.6%.<sup>1</sup> At that time, thousands of soldiers entered the jungle and stayed there for months to maintain constant harassment over guerrilla groups, primarily the FARC. With the subsequent de-escalation of the war, between 2012 and 2016, during peace negotiations between the government of Juan Manuel Santos and the FARC, the presence of soldiers in the jungle decreased. According to an official of the Ministry of Health,<sup>2</sup> in 2016, the members of the Army would no longer represent 50%, but instead 36% of the national leishmaniasis figures.

To address the historical peak of 9,682 cases of leishmaniasis in Army ranks in 2005,<sup>3</sup> the institution adopted drastic measures to alleviate a problem that had



A trash can full of empty Glucantime ampoules after a single day of treatment at CRL.

become strategic to waging war. It established an institutional program that included the implementation of preventive measures and the creation of the Leishmaniasis Recovery Center (*Centro de Recuperación de la Leishmaniasis*, CRL), a center dedicated to active military personnel only, specializing in the clinical management of the disease. Even today, all soldiers who come to this facility receive 20 mg/kg/day of Glucantime® for 20 consecutive days.<sup>4</sup> Although most go through this painful and toxic treatment only once during their military lives, many others endure Glucantime® two, three, four, five and even six times.

Rafael Gómez<sup>5</sup> is a professional soldier with 12 years within the Army who, in 2007, had leishmaniasis for the first time. When he was removed from the operations area, the ulcer was very large, which is why treatment with Glucantime® did not work for him. He was given another complete cycle of Glucantime®. The lesion healed this time. However, ten days after returning to his military unit, he had to go back into the jungle and leishmaniasis reappeared in other areas of his body. He was given Glucantime® again. He returned to the jungle, and soon the initial lesion was open again. As it was an "old" lesion, he was treated with Pentamidine. He returned to his work, but, after a few months, leishmaniasis appeared again, this time on his face. When I met him at the CRL in 2016, Rafael was recovering from his fifth treatment. Worried, and still in pain from the Glucantime®, he told me that, when he was discharged, he would go for several exams on his own, because he wanted to know the state of his liver, pancreas, and kidneys. He also wanted to understand why he had not been able to have children yet, something that — he sensed — had to do with the treatment.

“

*I liked to jog a lot. I can no longer stand a physical test of 2 miles, I can't stand it: halfway through it . . . I have to walk because I feel breathless . . . In the operations area, when I'm walking, it's the same. If I carry a lot of weight, and I am, say, going up a slope or a hill, I have to take several breaks because I just can't do it all at once, as I used to . . . Not anymore. Now I need several breaks of 1, 2, 3 minutes before I can resume walking.”<sup>6</sup>*



The cumulative effects of the toxicity of Glucantime® and other antileishmania drugs on the bodies of soldiers like Rafael have become incalculable. Throughout over 50 years of armed conflict, no one in Colombia has documented them. We do not know what happens to the body after going through so many cycles of such a harmful treatment. We do not know why a body, for example, never regains its weight, its physical condition or its ability to reproduce even after a single treatment. We do not know the effects of Glucantime® 10, 20 or 30 years after receiving it. In fact, we have no answer to a number of questions posed by these camouflaged leishmaniacs — young men from poor and commonly rural families, who usually join the Army out of necessity.

Although cases like Rafael's are not frequent outside the Army, they do occur often within the institution. In a country where armed conflict is part of everyday life, we cannot neglect the many men — thousands of soldiers — who have gone through repeated cycles of toxicity and deterioration due to leishmaniasis. The violence faced by these leishmaniacs does not end in the operations area; it goes on when the only alternative that biomedicine and public health have to offer is highly toxic drugs to treat a disease that is not even deadly. Many choose to leave the Army, not because of the armed confrontation, but because they cannot stand another treatment of leishmaniasis.

Would we, as researchers, be willing to undergo a 20-day Glucantime® treatment if we were ever to get leishmaniasis? If the answer is no, is it worthwhile to continue recommending and using systemically (in terms of the body and of a country's health system) a drug that does not ensure parasitological cure? Is it acceptable to do so when there are alternatives such as thermotherapy or intralesional application of Glucantime® itself for a large number of cases? What else do we need to know to stop the damage? How much longer should we wait? How should we act — we who have the knowledge and much more



*Corporal Rodriguez,<sup>6</sup> nervous, looking at the Glucantime® injections which were about to be administered to him at CRL.*

power than a soldier to influence public policy?

These are some of the reflections and questions that emerge from a social research study rooted in the fields of Critical Medical Anthropology and Social Studies of Science and Technology.<sup>7</sup> Although there are research works in the health field that employ qualitative methods, their approach tends to be limited to KAP studies — the evaluation of Knowledge, Attitudes, and Practices. Without denying their merit, these studies are usually short-term, pragmatic, and typically seek to facilitate or assess the adoption of certain technology by a specific community. However, our work as social scientists is much broader and more ambitious than that. Our objects of study, our theories, and our methodologies do complex analysis of and unravel a world that, in my case, is inhabited not only by leishmaniasis and the wide variety of people affected by this disease, as well as by war. In fact, I am equally interested in the lab coat leishmaniacs and the camouflaged leishmaniacs. The reality of both tells us a lot about the entanglement of health and war in Colombia. Following closely their personal histories — and those

of many others — my work tries to broaden our horizons of knowledge about this tragedy that is not only experienced in Colombia, but also in other contexts decimated as well by violence and infectious diseases. I seek to promote dialogue and generate different type of reflections. Ultimately, I am interested in breaking ground for interdisciplinary collaborations that make our understanding of the problem more complex and that enrich our ability to imagine solutions. •

#### References

- <sup>1</sup>Francisco Leal Buitrago, "Una Visión de la Seguridad Democrática en Colombia" (a view of democratic security in Colombia, roughly translated), *Análisis Político* 24, no. 73 (September 1, 2011): 3–36.
- <sup>2</sup>Interview in April 2017.
- <sup>3</sup>Figures provided by the Army Health Administration in July 2017.
- <sup>4</sup>High-weight soldiers receive Glucantime for more than 20 days. The treatment of soldiers with mucocutaneous leishmaniasis lasts 28 days.
- <sup>5</sup>This is a pseudonym.
- <sup>6</sup>Interview in October 2016.
- <sup>7</sup>Social Studies of Science and Technology (better known as Science and Technology Studies (STS)) constitute an interdisciplinary field that brings together social scientists—mainly anthropologists, sociologists, historians and philosophers—and their methodologies in studying topics marked by the production of scientific knowledge and the development of technologies.



## LEISHMANIASIS AND QUALITY OF LIFE

GLÁUCIA COTA and ENDI LANZA  
Instituto René Rachou – Fiocruz Minas, Brazil



**“Counting the days to heal and resume a normal life.”**

Patrícia Campos,  
cutaneous  
leishmaniasis patient  
at Júlio Müller  
Hospital, Cuiabá,  
Mato Grosso - Brazil.



**T**he valuation of clinical outcomes and the treatment preference according to patients' point of view represent a major current shift in the approach to disease management. In leishmaniasis, the recent initiative of TDR-WHO<sup>1</sup> has shed light on this issue with the prospect of valuing health as a state of well-being and quality of life.

Some issues are acknowledged to be important in understanding the impact of leishmaniasis, such as the toxicity of available treatments, the responsibility to finance treatment, as well as issues regarding the access to diagnosis, which tend to lead to delayed initiation of proper therapy. To consider these aspects means to assess not only the clinical aspects crystallized

in the classic efficacy-accuracy and safety outcomes, but also to consider the biopsychosocial dimensions involved in the choice of interventions and technologies to be implemented, especially in public health programs.

Grounded in this perspective, a questionnaire covering several areas related to localized cutaneous leishmaniasis (CL) has recently been developed and validated as a tool to determine the impact of this disease on the Brazilian population<sup>2</sup>. Through the qualitative and psychometric evaluations of questions involving several aspects of life, such as social life, family life, feelings, income and work, a questionnaire with 25 questions was proposed as an instrument to measure the impact of LC. In short, the application of the questionnaire

generates a final score between 0 and 100 — the higher the score, the greater the impact.

In a first application of the instrument, relevant observations were made, highlighting the statistically significant difference in the average score in the item “Perception of treatment and health services” among patients treated with meglumine antimoniate intravenously, as compared to patients treated by intralesional infiltration. Likewise, with the questionnaire, it was identified that the occurrence of adverse events during treatment, working days lost and the need to bear the cost of treatment are significantly associated with the perception of greater impact on the quality of patients' life.

These are observations with direct and significant implications



for health decisions, bringing a new element to the decision-making process that can no longer be ignored. This and other tools for evaluating patients' perceptions ultimately represent effective means for promoting social participation in public policies. Therefore, the routine use of such strategies for inclusion of patients in health decisions would be a definitive path towards humanization and legitimation of such policies. Let this be only the beginning! •

## DIFFUSE CUTANEOUS LEISHMANIASIS: STIGMA AND PAIN FROM AN UNRESOLVED DISEASE

MARCIA HUEB - Hospital Universitário Júlio Müller  
- Universidade Federal do Mato Grosso, Brazil



No. Tegumentary leishmaniasis (TL) is not a chronic disease. Nor are there many people who suffer irreversible sequelae, but even those few are too many, since people are unique. Each one who had its mucosa and its sense of smell destroyed represents an entire universe of negligence, marked by the absence or the scarcity of treatments, as well as unsatisfactory results. In total, they correspond to 5% of the thousands of people with TL. There are others, in much smaller numbers, but who can easily deny the concept of a "non-chronic disease". There are a handful of people who suffer from a chronic, untreatable disease with irreversible sequelae — in fact, disease and sequelae that are always present. They are those who suffer from diffuse cutaneous leishmaniasis, a form of disease in which the defense system is inactive to fight leishmaniasis: the patient does not respond to treatment or does only

for very short periods. A simple story can give us the dimension of this never-ending disease.

Adriana, 18, has been living for the past 13 years with a disease that is expressed in her skin, which has scars and deformities that make her lead life differently from other girls of her age. She comes to us from another state, with an established diagnosis and after many treatments. Her face is full of scars, but has also a hopeful smile that moves me, as I do not have the good words and medicines to what she needs. The first treatment, known as the best among the worst for this disease (and that had never been offered to her), brings relief for a while. A little improvement brings her an even bigger smile but knowing that the treatment is temporary leaves a trace of sadness in the air that is impossible to miss.

Now I know a little more about



this girl that has been living without a mother since her early childhood, with a father, many siblings and many needs, with her history on the outskirts under poor conditions, her treatments interrupted by life. And I know her current life, living with a family of "brothers and sisters of the church". Even with the precarious circumstances, every week or two, she manages to cover the 300 km that separate us. Adriana comes to collect the medicine that does not give back the life she is entitled to but does bring her a little bit of hope for better times. So, we keep going, me with my anguish and she with her smile and scars. •



Adriana Miranda, 18 years old, living with diffuse cutaneous leishmaniasis since the age of 5. Recently, being followed by Dr. Marcia Hueb's team at Julio Müller University hospital.

### References

<sup>1</sup> An international qualitative study exploring patients' experiences of cutaneous leishmaniasis: study set-up and protocol. *BMJ Open*. 2018; 8(6): e021372. This is an international qualitative study, coordinated and supported by TDR in collaboration with DNDi.

<sup>2</sup> How cutaneous leishmaniasis and treatment impacts in the patients' lives: A cross-sectional study. *PLoS ONE* 14(1): e0211374.





## ABRAPLEISH

**A**BRAPleish is a non-profit association designed to support patients with leishmaniasis, especially those with the tegumentary form of the disease. Considered a neglected disease for many years, leishmaniasis has affected numerous people in several regions of Brazil — not only in the rural or more removed regions such as forest areas, but also in urban centers, where the disease has been expanding.

The ceremony that marked the creation of ABRAPleish took place on Sept 12, 2018 at 7pm in the town of Ipiranga do Norte, state of Mato Grosso, in the City Council. Leishmaniasis is endemic in Ipiranga do Norte, where lots of locals suffer from the disease, Moacir Zini is one of them. He has diffuse cutaneous leishmaniasis, a rare and incurable presentation of the disease. However, just receiving treatment was not enough for him. Alongside other volunteers, Zini worked to create the first Brazilian Association of Individuals living with Leishmaniasis (ABRAPleish), currently based in Ipiranga do Norte. One of the goals of the association is to welcome people with leishmaniasis, in order to

discuss the stigma of the disease and to warmly support them in difficult times. Thus, we seek a way to share and document the very diverse experiences among members. The association also offers assistance, collaborates in outbreak investigation, attracts resources, and raise awareness on the disease.

Recently, the president of the association, Zini has moved to Cuiabá. Therefore, ABRAPleish's headquarters will soon be transferred to Cuiabá, the capital city of Mato Grosso, facilitating access to the Júlio Müller University Hospital, one of the reference centers for the treatment of the disease in Brazil. •



Moacir Zini (center), ABRAPleish president, the association's inception ceremony - Ipiranga do Norte, Mato Grosso, Brazil.



**ABRAPLEISH**  
Associação Brasileira de Portadores de Leishmaniose

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