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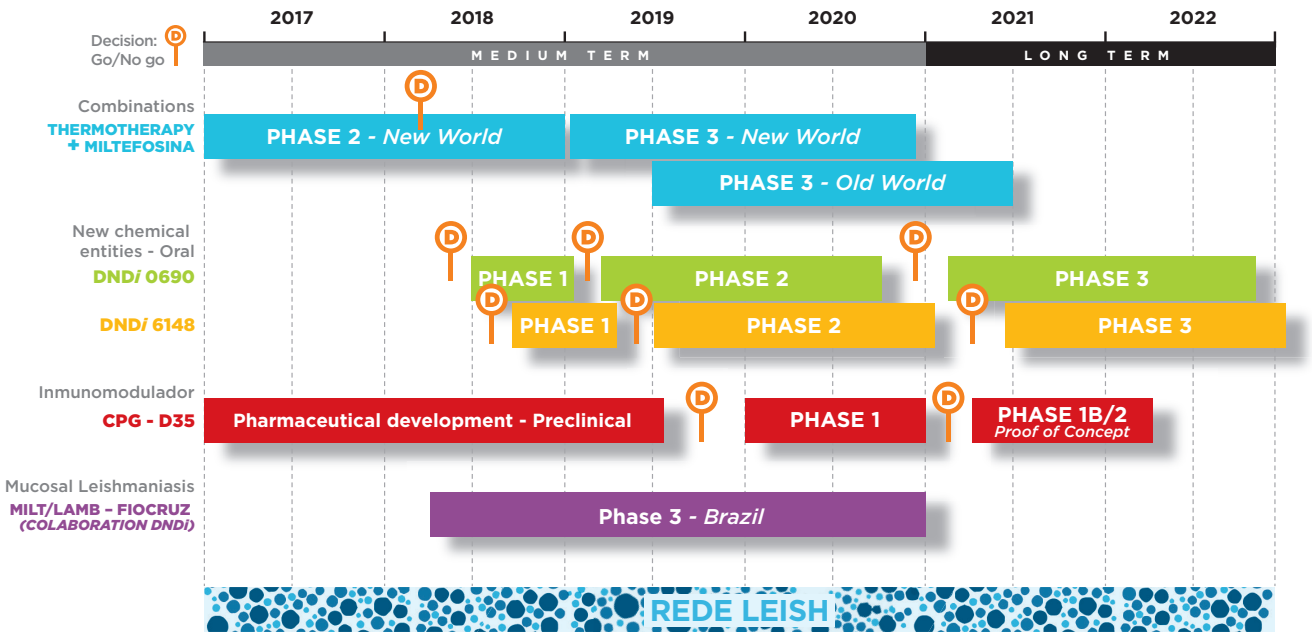
DNDi PLANNING ACTIVITIES IN CUTANEOUS LEISHMANIASIS



Editorial

SUMMARY OF 2017 ACTIVITIES AND PERSPECTIVES FOR 2018

During 2017, the cutaneous leishmaniasis (CL) team was able to advance in the development of different activities as outlined in the CL plans and strategy as follows:

COMBINATION STUDY

This study aims to determine the efficacy and safety of a combined therapy using thermotherapy (TT) (one application, 50°C for 30") + miltefosine (2.5 mg/kg/day for 21 days) for the treatment of uncomplicated CL in Peru and Colombia. In 2017, 72 subjects (47 from Peru and 25 from Colombia) were enrolled into the study.

An interim analysis conducted by the Data Safety Monitoring Board (DSMB) on March 2018, allowed us to continue with the study and start planning a phase III in both New and Old World

IMMUNOMODULATOR (CPG-D35)

Results of the animal model study to investigate whether CpG-D35, either alone or in combination with chemotherapy, would lead to an improved *Leishmania* infection outcome compared with chemotherapy alone became available in 2017. Results suggested that the systemic administration of CpG-D35 in combination with antimonials does not modify the activity of CpG-D35.

ORAL DRUGS

The screening and drug discovery efforts on visceral leishmaniasis (VL) have expanded since 2015 to include some *Leishmania* strains causing CL. Two compounds showing activity against VL and CL, DND*i* 0690 and 6148, were nominated in 2016 for preclinical development. DND*i* 0690 completed its preclinical development in 2017 and was nominated for clinical development by the end 2017, while DND*i* 6148 on March 2018. Phase I studies for both NCEs will be conducted throughout 2018. Results will serve for both VL and CL. Other compounds, such as DND*i* 5561, are expected to be nominated as preclinical candidates in late 2018 or early 2019. We continue monitoring the development of oral compounds by other groups, *i.e.* 18-Methoxycoronaridine (18-MC) developed by Hebron Pharmaceutical, in Brazil and D-121 by Oblita Therapeutic, in Belgium. 18-MC has completed its preclinical development and is currently in Phase II.

OTHER ACTIVITIES

DND*i* together with The Insituto de Salud Carlos III, Madrid, Spain, organized the 6th World Leish (WL6) which was held in Toledo, Spain from 16th to 20th May, 2017. In terms of numbers, 1526 abstracts were submitted, 1473 participants from 70 countries attended the WL6.

The scientific programme included 36 parallel session, 4 plenary sessions, 10 symposia, 2 consensus symposia, 27 oral communications sessions and 4 poster sessions where more than 250 speakers participated.

BYRON ARANA - DND*i*, Geneva

Summary

MULTICENTRIC STUDY TO EVALUATE THE TREATMENT OF MUCOSAL LEISHMANIASIS IN BRAZIL

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With increased incidence and management recommendations still supported by fragile scientific evidence, mucosal leishmaniasis (ML) is the most neglected condition among leishmaniases, whether in relation to public policies of prevention and treatment or to investment in the generation of new knowledge; easily observed by the small number of publications addressing the disease. Many are the unresolved questions regarding ML that make clinical management difficult, among them: the distinction between the various clinical manifestations of the disease; the best diagnostic and therapeutic strategy; the identification of prognostic factors and the definition of the adequate follow-up time after treatment.

ML is also the most morbid manifestation of tegumentary leishmaniasis. Resulting from a hematogenous and lymphatic parasite dissemination, from the cutaneous tissue to the mucosa, this form is able to cause functional alterations and facial deformities, which explains much of the disease morbidity with specific repercussions on psychological and social dimensions of the patients´ life. In the Americas, ML represents approximately 4% of the cases of tegumentary leishmaniasis and, in Brazil, according to data from the Ministry of Health / SVS - National Disease Notification System - SINAN Net, in 2015, 1.195 cases of the disease were reported.

In addition to the significant incidence, epidemiological data have also been revealing unexpected mortality rates among reported cases of tegumentary leishmaniasis in recent years. A phenomenon especially related to the mucosal manifestation of the disease, this observation points to the urgent need to reassess its current approach. The main focus of ML lethality investigation is the current treatment strategy, still based on pentavalent antimonials, despite its known toxicity.

Although liposomal formulation of amphotericin B has been emerging as an efficacious and less toxic alternative, its use lacks robust evidence to support assertive recommendations. Even less consolidated is the place of miltefosine among the therapeutic options for ML, with variable results among the few studies available in the Americas. In view of this scenario and the urgent need to reassess the therapeutic approach of ML, the Brazilian research group, with the support from DND*i* Latin America (Drugs for Neglected Diseases *initiative*) and the Brazilian Ministry of Health proposed, and is organizing to start in June 2018, an open-label, randomized, controlled, phase III non-inferiority clinical trial to assess the efficacy and safety of ML treatment using miltefosine compared to liposomal amphotericin B. René Rachou Institute -Fiocruz (Belo Horizonte, MG), Júlio Muller University Hospital (Cuiabá, MS), Infectology Institute Emilio Ribas and the Hospital das Clínicas of the University of São Paulo will be involved in this trial. The project (*Universal Trial Number* U1111-1205-2372 and CAAE 76644517.4.1001.5091), registered under the number RBR-5r93wn in ReBEC (Brazilian Clinical Trial Register), was contemplated by the Call for Research CNPq / Fiocruz - PROEP/PEC Nº 16/2017 and will be monitored by the Fiocruz Clinical Research Platform.

The choice of miltefosine as the drug to be evaluated was based on its availability as an oral presentation, possibility of use by elderly patients or patients with comorbidities and evidence already gathered for cutaneous leishmaniasis. The choice of liposomal amphotericin B as treatment of the control group is justified by its favorable safety profile when compared to meglumine antimoniate and efficacy data already available in literature. With the intention of exploring a liposomal amphotericin B treatment regimen with only 3 administrations over 3 weeks, in this study a small group of patients under this intermittent treatment regimen will also be evaluated for an initial safety and efficacy assessment.

Adverse events will be monitored by clinical examination, complete blood count, and biochemical tests. Using previously defined parameters for outcomes of interest, patients will be evaluated weekly during the treatment period and, considering D1 the first day of drug administration, the primary endpoint of "cure" will be defined by the disappearance of signs of inflammatory activity in the mucosa and will be assessed at two moments: D90 ± 7 days (initial cure) and D180 ± 14 days (definitive cure). Relapse rates within 1 year of follow up will also be evaluated.

The results of this study are expected to guide potential changes in treatment recommendations and provide improvement in the management of patients affected by ML in Brazil.

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BARRIERS AND OPPORTUNITIES IN THE DIAGNOSIS OF MUCOSAL LEISHMANIASIS

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Tegumentary leishmaniasis is a condition which is in global expansion[1]. The disease alters the skin and mucosal membranes, resulting in serious morbidity and social hardships. The mucosal manifestation of leishmaniasis (ML) often results from a previous untreated or inadequately treated cutaneous leishmaniasis case[2]. ML is mainly described in the Americas due to the association of this clinical manifestation with *Leishmania Viannia braziliensis*. This species holds an important mucosal tropism, however this may be a clinical manifestation found in virtually all pathogenic species of *Leishmania*. ML presents long periods of disease progression, which may result in deformities such as facial disfigurement. The treatment is done with the use of drugs with high toxicity profile, similar to other forms of leishmaniasis[3].

The factors explained above justify the need for an accurate diagnosis for a prompt therapeutic intervention in ML[4]. In the classical form, caused by *L. (V.) braziliensis*, this can be an extremely difficult task since mucosal infection results in a high cellular immunological response and lately in a low parasite load. This intense cellular immune response profile and granuloma development at the affected site, helps to understand the performance of the most classical and the newest diagnostic techniques[5].

Tests evaluating cellular immunity such as Montenegro intradermal reaction (leishmanin) tend to show a pronounced positivity in these cases[6]. This fact can be explained by the cellular immune profile presented by ML patients. Serological techniques present conflicting results in the ML diagnosis. In addition, immunological techniques created for the diagnosis of leishmaniasis have low specificity and the rate of cross-reactions limits their use in clinical practice.

Parasitological techniques such as direct examination and culture on solid or liquid media are highly specific. The finding of the parasite confirms the infection and can be given immediately in the case of direct examination. However, these are techniques with limited sensitivity, mainly in ML caused by *L. V. braziliensis*.[5] The long disease progression period and the high immunological response is accompanied by parasitic scarcity, thus reducing the sensitivity of parasitological methods. It must also be noted that the sample collection (fragments of mucosa) to perform these tests can be difficult. Deep mucosal lesions, affecting the pharynx and oropharynx, may require invasive sampling techniques. This is extremely limiting for a disease that affects vulnerable populations.

Histopathological examination is an important tool for skin and mucosal diseases investigation. It is a test with good specificity (the finding of the parasite confirms the diagnosis), but with limited sensitivity for the same reasons referred in parasitological tests. However, additional information such as the inflammatory infiltrate characteristics assists in the diagnosis of the disease or differential diagnoses. Special staining or immunohistochemistry may be used to increase test sensitivity. Histopathology sampling also has the drawback of requiring invasive techniques.

Molecular techniques seem to present a satisfactory specificity, since it is possible to generate specific genetic targets, with increased diagnostic sensitivity. The genetic characteristics of *Leishmania* can be used in favor of the diagnostic process. The kinetoplast, a specific mitochondrial region, is composed of a network of circular and interconnected DNAs that form the kDNA and corresponds to 30% of the cellular DNA of *Leishmania*. This kDNA is arranged in circular copies, the maxicircles and the minicircles. Minicircles represent up to 5,000 to 10,000 copies. This repetition of genetic load copies explains the high sensitivity in detection of this target, since even fragmented parasites will be detected in polymerase chain reaction (PCR) techniques[7]. PCR amplification of miniexon gene followed by restriction fragment length polymorphism (RFLP) has been used for the diagnosis of mucosal leishmaniasis and has the advantage of allowing the identification of some *Leishmania* species[8,9]. Other techniques that increase the sensitivity of PCR such as forensic extraction kits and technical variations (real-time PCR and digital PCR for example) can be used.

Current scientific and technological efforts focus on molecular biology as a fundamental tool for the diagnosis of ML. The relative complexity of these tests and the cost involved are the main limiting factors. However, one must consider that PCR is becoming increasingly accessible to affected patients. It is a technique that allows the use of a non-invasive sampling such as swabs and scrapings. Sample shipment to referral centers is already a reality and a challenge that aims to reduce the need for complex laboratory centers in remote areas where ML is endemic. Despite this progress, sensitivity limitation still exists and in a considerable portion of patients with ML (5 to 20%) molecular tests will not detect the parasite[10].

The development of a gold standard test for the diagnosis of ML seems an unachievable task for the current scientific evolution. Technical and social challenges need to be overcome and the need for investment in more accurate strategies is imperative. Despite the difficulties, the diagnosis of ML has evolved considerably in the last 20 years, which has made the therapy safer and more precise.

It is necessary to join efforts of research groups from different countries to validate a diagnostic test from non-invasive samples.

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AN OVERVIEW OF THE USE OF IMMUNOMODULATORS IN THE TREATMENT OF AMERICAN TEGUMENTARY LEISHMANIASIS

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Cutaneous leishmaniasis (CL) and mucosal leishmaniasis (ML) represent important forms of American tegumentary leishmaniasis (ATL) caused by *L. braziliensis*, either because of elevated frequency (CL - above 90% of cases in an endemic area) or because of clinical aggressiveness as in the case of ML. Treatment of these forms of ATL has been done for decades using pentavalent antimonial monotherapy (Sb^v), and is associated with increasing rates of therapeutic failure. Currently in the endemic area of Corte de Pedra in Bahia State, cure with a series of high dose Sb^v occurs only in 55% and 45% of cases of CL and ML, respectively. In addition, Sb^v is a drug that presents a high degree of toxicity and many side effects, and can only be administered parenterally, which increases the socioeconomic impact of ATL in endemic areas.

In recent years progresses in the understanding of the immunopathogenesis of CL and ML have shown that besides the parasitic factor, the exaggerated and ineffective host inflammatory immune response has an important role in tissue damage and consequently in clinical expression and therapeutic difficulty of ATL. The agents implicated and identified so far are inflammatory cytokines such as TNF e IFN-y, produced by cells of the immune system after contact with the parasite. Although these cytokines are important for the defense mechanisms against *Leishmania*, their production at high levels has a deleterious impact for the host by contributing to the intense inflammatory infiltrate. Therefore, the use of drugs having such cytokines as a target may contribute to decrease inflammation and tissue damage, thereby facilitating the destruction of the parasitic agent by the host and associated anti-leshmania drug.

In CL, the use of GM-CSF associated with Sb^v is based on the knowledge of 3 mechanisms of action of this cytokine: (1) activation of macrophages, increasing their ability to destroy *Leishmania*; (2) modulation of the tissue immune response with increased production of IL-10-cytokine that is able to inhibit the inflammatory response by decreasing (without abolishing) local production of IFNy e TNF; (3) skin healing stimulation by increasing the proliferative activity of epidermal cells. In two randomized controlled trials we had the opportunity to demonstrate that the topical intralesional use or dressing use of GM-CSF associated with conventional Sb^v treatment increased the cure rate from 50% (Sb^v + placebo group) to 80% (intralesional) to 100% (dressing). In addition, the association Sb^v + GM-CSF significantly accelerated the ulcer healing time in both studies. Another study in five patients with refractory CL (no cure after at least 3 Sb^v series) demonstrated that the topical use of a 10 µg / ml solution of GM-CSF applied to the ulcerated lesion three times a week, and in combination with a new Sb^v treatment series was able to cure all cases. The fact that GM-CSF was removed from the market when it was replaced by G-CSF temporarily prevented further studies.

In ML the use of pentoxifylline is based on the inhibition of the production of TNF, an inflammatory cytokine produced on a high scale in this disease and largely responsible for the dense inflammatory infiltrate found in the mucosal tissue. ML is a disease with a very aggressive profile, which in more advanced cases can lead to complete destruction of the nasal septum, important deformities in the structure of the nasal pyramid, including upper respiratory obstruction and death. Oral pentoxifylline in combination with Sb^v was initially used in 10 refractory cases of ML (absence of cure after at least 3 series of Sb^v), obtaining cure in 90% of patients. A subsequent randomized controlled trial in patients with treatment-naive ML showed cure rate of 100% in the group that used the combination compared to the control group that used Sb^v and placebo and whose cure rate was 58%. In a recent and not yet published study, a larger number of patients from Corte de Pedra has been confirming the benefit of the association with pentoxifylline in the cure of ML. Currently, the Brazilian Ministry of Health recommends the association of pentoxifylline to the conventional treatment with Sb^v in ML.

At present, therapeutic trials with the association of immunomodulators and newer and less toxic leishmanicidal drugs, such as miltefosine, are far from being a priority. The socioeconomic and psychological impact of ATL in the low-income population has been underestimated and neglected over the years. There is a need for greater awareness of the development agencies and municipal, state and federal governments to reverse this scenario with policies of greater investment in controlling this important endemic. There is no doubt that multidrug therapy combining immunomodulators with substances with better efficacy against *Leishmania* will increase the cure rates of ATL, reducing its morbidity and impact on endemic areas.

CLINICAL TRIALS WITH IMMUNOTHERAPY PERFORMED IN CL AND ML

Study, Year, Drug tested	Type of Study	Leishmaniasis clinical form (nº of patients)	Tested arm (% of cure)	Arm Sb^v (% of cure)
Almeida *et. al.*, 1999, Intralesional GM-CSF+ Sb^v	Randomized, controlled, double blind	Cutaneous (20)	8/10 (80)	6/10 (60)
Lessa *et.al.*, 2001, Pentoxifylline + Sb^v	Open	Mucosal - relapsed (10)	9/10 (90)	Not applicable
Santos *et. al.*, 2004, Topical GM-CSF + Sb^v	Randomized, controlled, double blind	Cutaneous (20)	10/10 (100)	5/10 (50)
Almeida *et. al.*, 2005, Topical GM-CSF + Sb^v	Open	Cutaneous - relapsed (5)	5/5 (100)	Not applicable
Machado *et. al.*, 2007, Pentoxi-fylline + Sb^v	Randomized, controlled, double blind	Mucosal (23)	11/11 (100)	7/12 (58)

CPG-D35: HOPE FOR COMPLICATED CASES OF CUTANEOUS LEISHMANIASIS

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The purpose of cutaneous leishmaniasis (CL) treatment is to increase the speed to final cure, to reduce scarring, and to prevent relapse. One approach to treatment is to eliminate most organisms by chemotherapy, after which host immune mechanisms would control the remaining parasites. Another approach to treatment is to boost clearance by enhancing the immune mechanisms through immunotherapy. A combined approach offers the best opportunity for treatment.

The use of an immune response modifier (IRM) to be used in combination with chemotherapy to improve CL treatment, for the complicated forms of CL *i.e.* leishmaniasis recidivans, diffuse, disseminated and other special forms such as Post kala-azar dermal leishmaniasis (PKDL) is one of the four pillars of DND*i*'s CL strategy.

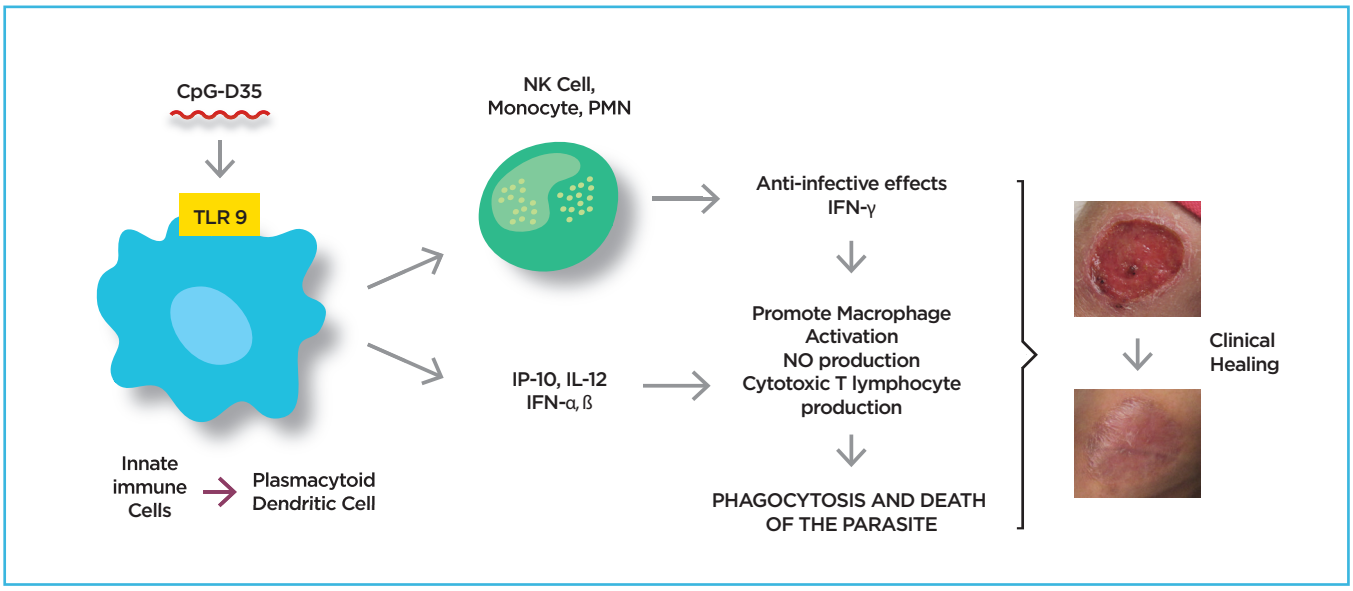
However, the use of a defined IRM is a new approach for leishmaniasis treatment and, unlike anti-parasitic drugs that target the parasite directly, the IRMs involve the host's immune machinery and its intricate regulations. Therefore, besides the usual challenges of producing the IRM and conducting classical drug toxicity studies, IRMs must be tested for safety with respect to the type, extent and duration of immune responses they induce/modify to ensure there is no risk of uncontrolled immune stimulation and autoimmune diseases.

CpG-D35 oligodeoxynucleotide (ODN) is a D-type CpG TLR9 agonist, which has been optimized for humans. It leads to the activation of the cells initiating pro-inflammatory reactions which result in the production of cytokines such as type-I interferon and IL-12. These are the backbone of the response that promotes clearance of intracellular parasites such as *Leishmania spp.* CpG-D35 is the only D-type CpG which promotes the exact type of immune response required for the control of *Leishmania* infection, eliciting plasmacytoid dendritic cells to mature and secrete IFN-γ & α, but having no effect on B cells with the resulting Th2 response associated with most of the K-type CpGs tested for other conditions.

The proposed combination approach for CL treatment provides a major step forward over existing monotherapies or combination therapies using antiparasitic treatments only. We hypothesize that the addition of innate immune response modulators to chemotherapy, ideally an oral drug such as Miltefosine or any other experimental orally available drug, if one becomes available during the following years, will result in the accelerated healing of skin lesions. Accelerated healing would result in reduced super-infection and scaring of CL lesions, and prevent disseminated or mucosal leishmaniasis. Other hypothetical benefits include reduction of the duration of therapy, better treatment outcomes, lower risk of developing further drug resistance and decrease chances of relapse or re-infection.

Several studies conducted during 2017 demonstrated that the systemic administration of CpG-D35 in combination with antimonials did not modify the activity of CpG-D35 nor triggered any toxicity nor resulted in any unexpected adverse events in healthy monkeys exposed to both CpG-D35 and antimonials. These studies also showed that the systemic administration of CpG-D35 administrated alone or in combination with antimonials improves the clinical outcome of monkeys with CL lesions due to *L. major*.

During the next 18 months, DND*i* will continue its work aiming to complete the preclinical and toxicological studies required to demonstrate the safety of CpG-D35 and hopefully obtain approvals to move to human studies by the end of 2019. Efforts to complete the Clinical Development Plan and the Regulatory Strategy Plan are also on going.



There is extensive evidence that a Th1-mediated immune response plays an important role in the control of *Leishmania* infection. Toll-like receptors (TLRs) have a central role in this response and have attracted much interest to the development of drugs for controlling infectious diseases, autoimmune diseases, cancer as well as a vaccine efficacy enhancement.

D-type CpG oligonucleotides are highly specific agonists of TLR9 and have been shown to elicit the desired immune response in mice and primates infected with *Leishmania*.

In the past BCG and first generation vaccines (killed parasites) have been used with some encouraging results for PKDL.

REPURPOSING ORAL DRUGS FOR THE TREATMENT OF CUTANEOUS LEISHMANIASIS: A LITERATURE REVIEW TO GUIDE *IN VITRO* ASSESSMENT OF COMPOUNDS

JOELLE RODE - DND*i* Latin America

In 2010, DND*i* incorporated cutaneous leishmaniasis (CL) in its portfolio and started a program aiming to deliver short duration, safe, non-invasive, efficacious, affordable and field-friendly treatments for CL or at least for those lesions caused by *L.tropica* or *L.braziliensis*. As a short-term strategy, a low-hanging fruit approach was selected in order to identify drugs used in other indications with possible applications for the treatment of different forms of CL. During 2010/2011 a literature review was performed to gather published evidence on antileishmanial activity of oral drugs already in use or in late stage of preclinical development. This review was done to identify potential candidates for further *in vitro* testing against *L. tropica* and/or *L. braziliensis* using a validated assay, in order to conduct possible explorative clinical trial(s) with the selected candidate(s).

Literature search was performed in Pubmed and Lilacs databases, resulting in a final selection of 206 references, out of 6,225, for full text reading and data extraction. For 10 references no abstract was available or full text was in Russian or German. An update performed in 2012 included 9 additional publications. Clinical, *in vivo* and *in vitro* retrieved data for drugs that had already been tested for CL in humans was gathered and quality of evidence was assessed to base the selection of drugs for further *in vitro* assessment. **Table 1** summarizes the findings of the literature review and the level of evidence. Clinical evidence was ranked according to the following criteria: Strong: efficacy > 60%, or > to standard treatment; Controversial: efficacy range variable according to clinical trials and methodological issues; Weak: efficacy < 60% and/or < standard treatment, or efficacy range variable but < 60% and/or < standard treatment in randomized controlled trials.

Results of the literature review were somewhat discouraging, as no evident candidate nor consistently outstanding drug(s) arouse. Furthermore, evaluating clinical evidence was difficult due to the

TABLE 1 - SUMMARY OF LITERATURE REVIEW AND EVIDENCE CLASSIFICATION

Name of Drug	Clinicals Trials		*In vivo* Studies		*In vitro* Studies	
	Evidence clincial trials	#Trials	Evidence *in vivo*	#Studies	Evidence *in vitro*	#Studies
Azithromycin	WEAK (OW AND NW)	8	WEAK (La, Lb, Lm)	3	STRONG (Lm, La, Lb)	3
Chloroquine	WEAK	1	No evidence	0	No evidence	0
Chlorproma-zine	WEAK (Case report)	1	WEAK (Lm, Lmex, Laeth)	2	STRONG (Lt, Lm, Lmex, Laeth)	3
Cimetidine	WEAK	1	STRONG (La, Lmex)	2	No evidence	0
Ciprofloxacine	WEAK	1	No evidence	0	STRONG (Lp)	2
Clofazimine	WEAK	1	WEAK (La, Lm)	1	STRONG (Lb, Lmex, Lt, Lm, La)	2
Clotrimazole	WEAK	2	WEAK (La, Lm)	1	WEAK (Lt)	1
Dapsone	STRONG to WEAK	5	L.sp ?	1*	STRONG (Lm)	1
Doxycycline	WEAK	3	No evidence	0	WEAK (Lm)	1
Furazolidone	WEAK	1	No evidence	1*	STRONG (Lchag, Lb, Lm, La)	3
Isoniazid	WEAK (combination + rifampicin)	5	WEAK (La, Lm)	1	WEAK (La, Lm, Lt)	2
Itraconazol	STRONG - Controversial	10	STRONG	1	WEAK (Lm)	1
Mefloquine	WEAK - Controversial	7	WEAK (La)	1	No evidence	0
Metronidazole	WEAK	6	WEAK (Lm)	1	WEAK (Lt)	1
Miconazole	WEAK	3	WEAK (La, Lm)	1	WEAK (Lt)	1
Omeprazole	STRONG (in combination)	2	WEAK (Lb)	1	No evidence	0
Rifampicin	STRONG to WEAK	13	WEAK (Lm)	3	WEAK - Controversial (La,Lm, Lt)	4
Terbinafine	WEAK	1	WEAK (La, Lm)	2	La, Lb, Lmex, Lm - Sinergistic effect w Ketoconazol	4
Fluconazol	STRONG (but methodo-logical issue)	2	Not included		Not included	
Posaconazole	Case report (strong)	1	STRONG (La)	1	WEAK (La, Lm, Lb, Lp, Lmex)	1
Zinc Sulphate	WEAK	1	Not included		WEAK (Lm)	1

Legend: *full text not available. Laeth = *L. aethiopica*; Lb = *L. braziliensis*; Lchag = *L. chagasi*; Lm = *L. major*; Lmex = *L. mexicana*; Lp = *L. panamensis*; Lt = *L. tropica*; OW= Old World; NW= New World.

high variability in the settings where the studies were conducted as well as to the heterogeneity of key parameters such as treatment schemes, outcome measures, time until cure and others.

A panel of external experts reviewed all the data and selected 43 drugs/compounds showing strong or controversial evidence, either clinical or preclinical, for further analysis. Some compounds from DND*i*´s discovery pipeline developed for other diseases were also included in this list.

Standardized *in vitro* assays were performed at the Imperial College, London, using strains recently isolated of *L. tropica* from Iran (MHOM/IR/09/UTEH101) and *L. braziliensis* strain PER 104/0, isolated from Peru, as reference. In summary, antileishmanial activity of the compounds on intracellular amastigotes were tested using *in vitro* differentiated bone-marrow-derived macrophages (8 days), that were infected overnight with *Leishmania* promastigotes (either *L. tropica* or *L. braziliensis*) at a ratio of 10 parasites to 1 macrophage. Cultures were washed extensively to remove non-phagocytosed promastigotes before adding the drugs to be tested. After 48h of incubation, infected (control), and infected and treated macrophages were lysed with 0.008% SDS, lysis was neutralized and the surviving amastigotes were allowed to transform back into promastigotes. After control cultures reached sufficient density, the effect of the drugs was quantified using the MTT assay. Fungizone was used as positive control. Toxicity of the drugs/compounds on the host cells was measured by evaluating the impact of different concentrations of the drugs/compounds on macrophages using proliferation inhibition of the macrophage cell line RAW 264.7 and the MTT assay.

Results showed that 29 compounds displayed no measurable activity against intracellular *L. tropica* or *L. braziliensis* or were toxic to macrophages, whilst 14 compounds affected the intracellular survival of both parasites to a variable degree (**Table 2**). The most effective compounds against both *Leishmania* species were ravuconazole, itraconazole, HOC and EPL-BS967. HOC and EPL-BS967 were not toxic to macrophages; ravuconazole was only toxic to macrophages at the highest concentration tested (30 µM) and itraconazole showed toxicity at concentration range 30 – 0.04 µM.

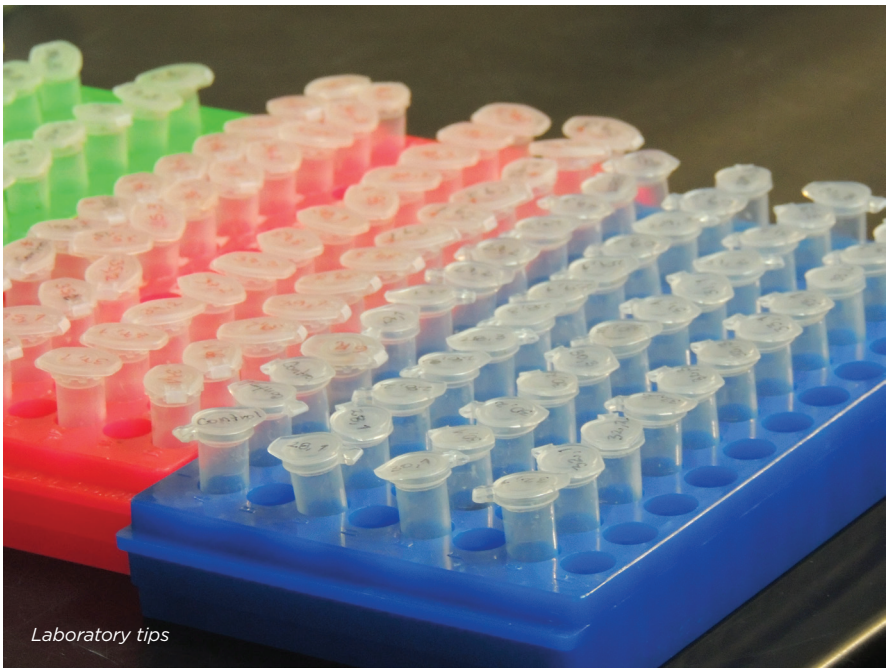

Laboratory tips

TABLE 2 – IC50 (µM) OF COMPOUNDS THAT SHOWED ANTILEISHMANIAL ACTIVITY AND LIST OF INEFFICIENT COMPOUNDS

L. tropica		*L. braziliensis*	
Drug	IC50 (µM)	Drug	IC50 (µM)
Ravuconazole	0.006543	Ravuconazole	0.004242
Itraconazole	0.009452	Itraconazole	0.03391
EPL-BS967	0.05981	HOC	0.443
HOC	0.5303	EPL-BS968	1.283
Clotrimazol	1.673	EPL-BS1247	5.194
Fex-sulfone	1.729	Butenafine hydrochloride	6.108
Clofazimine	1.792	Mefloquine	6.376
Mefloquine	3.849	Fex-sulfone	6.72
EPL-BS1246	4.041	Clofazimine	8.409
Miconazole	4.676	Clotrimazol	8.875
Butenafine hydro-chloride	5.344	Miconazole	13.33
Terbinafine	9.241	Terbinafine	14.71
Chloroquine	9.544	Chloroquine	27.41
Fex-sulfoxide	13.1	Fex-sulfoxide	29.6

Inefficient compounds: Artesunate, Econazole, Naftidine hydrochloride, Bacitracin, Enoxacin, Nitazoxanide, Cetrizine dihydrochloride, Erythromycin, Omeprazole, Ciclopirox olamine, Fex-inidazole, Pyrazinamide, Cimetidine, Glybenclamide, Rifamycin, Ciprofloxacin, Griseofulvin, Silver Sulfadiazine, Clindamycine hydrochloride, Isoniazide, Tioconazole, Dapson, Linezolide, Tolnafate, DND*i* 160412, Loratidine, Variconazole, Doxycycline, Metronidazol.

Further *in vivo* studies in animal models infected with *L. tropica L. infantum, L. major, L.braziliensis* and *L.amazonensis* performed with ravuconazole showed variable activity.

Overall, the R&D team determined that the results obtained in the above mentioned studies did not support the use in clinical studies of any of the screened oral drugs already tested in humans. Ravuconazole for example showed the best IC50 and IC90, however in animal model, its efficacy was below expected. Itraconazole, the second most potent drug in the *in vitro* study has been tested extensively in humans and its efficacy is questionable. Given these results, the low-hanging fruit approach of repurposing drugs for CL was abandoned, and the screening of compounds for some *Leishmania* strains causing CL was incorporated within the drug discovery efforts on visceral leishmaniasis.

PERSPECTIVES OFFERED BY NEW ORALLY ACTIVE CHEMICAL ENTITIES TOWARDS LEISHMANIASIS TREATMENT

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Leishmaniasis is a complex disease that results in diverse manifestations, ranging from localised skin ulcers (cutaneous leishmaniasis) to fatal systemic disease if left untreated (visceral leishmaniasis, also known as kala-azar). The World Health Organization (WHO) estimates that 1 in 7 people worldwide live in leishmaniasis endemic areas, with 600,000 to one million new cases every year[1].

Until recently, antimonial monotherapy for 20-30 days has been the mainstay of treatment. In the last 15 years however, the development of a liposomal formulation of amphotericin B (AmBisome®), of paromomycin and of miltefosine for leishmaniasis treatment (all re-purposed drugs from other therapeutic indications), have significantly contributed to improve treatment in some geographical locations. As an example, the roll-out of single dose Ambisome® for the treatment of visceral leishmaniasis in South Asia was an important tool in the context of the elimination campaign in this region.

The DND*i* short-term objective focused on combination of drugs to shorten treatment duration, maintaining good efficacy and improving safety profile. The combination of paromomycin with miltefosine has proven to be highly efficacious in Asia, while sodium stibogluconate combined with paromomycin is currently first line treatment in Eastern Africa. Nonetheless, attempts to develop short course AmBisome® therapy and combination therapies with AmBisome® in Eastern Africa have been unsuccessful due to poor and variable efficacy. In addition, despite their utility, all these drugs have limitations, including toxicity, sub-optimal tolerability, high cost and, except miltefosine that is orally active, all require parenteral administration. Leishmaniasis patients are still in need of more effective, safer and convenient therapeutic options.

Unprecedented efforts and investments have been made in the recent years to apply modern Drug Discovery methods, tools and technologies and find orally active, safe and affordable new drugs for leishmaniasis. Screening of compound libraries based on *in vitro* assays resulted in identification of selective leishmanicidal compounds. Medicinal chemistry has then led to further improvement of drug-like properties by specific modifications of their chemical structure, while keeping their leishmanicidal activity. Today, with the engagement of various research groups, including pharmaceutical companies all over the world, six new drug candidates with innovative mechanism of action are or will become available very soon and others from four different chemical classes are expected in a near future. This is potentially opening a new era in leishmaniasis Research and Development (R&D), as accumulated knowledge helps finding optimised and differentiated drug candidates. This is expected to successfully deliver new effective, safe, oral, short-course treatments to patients.

In addition, with the perspective of new oral drugs with innovative mode of action being developed, drug combinations will be a feasible achievement. Combination therapy against *Leishmania* is expected to maximise treatment outcomes, while minimizing the potential for development of drug resistance. Combinations of two drugs look most feasible in terms of R&D efforts, costs, safety and formulation. To be further developed, two partner drugs associated for a treatment course of 14 days or less should demonstrate an overall advantage in risk/benefit profile relative to standard of care. This risk/benefit should translate into efficacy, with a better safety and tolerability, including in children, low potential for resistance development or cross-resistance between them and with existing treatments, dosing convenience, better acceptance by patients and by health care providers and affordability.

Combination therapy based on emerging New Chemical Entities is expected to improve and simplify current case management in leishmaniasis. Key points need to be taken into consideration when selecting the pair of drugs to combine. Combination partner drugs should have a low potential for cross-resistance development. This can arise when drugs have common biological targets or common mechanisms of drug-uptake, and combination should in that case be avoided. *In vitro* resistance development and cross-screening should therefore be used early in the selection process, as potential combinations should elicit different pathogen resistance mechanisms and be active against strains resistant to the other potential partners.

To what concerns efficacy, *in vitro* models used for the screening and identification of leishmanicidal compounds can provide evidences for synergy, additivity of activity or antagonism of the drugs, when assessed by pairs. However, preclinical animal models can be even more informative. Although no preclinical model fully captures the complexity of disease states in human and these models all have drawbacks, they have largely contributed to a better understanding of the physio-pathological processes underlying *Leishmania* infection and host response to the disease. They also have played a paramount role for the selection of preclinical candidates, based

on reduction of macrophageal parasite burden in the spleen, liver and bone marrow. Integrating pharmacokinetics parameters in preclinical models also supports establishing the pharmacokinetics/pharmacodynamics relationship for activity and safety outcomes and gives rationale for desired exposure in humans. Data generated in these preclinical models should however be carefully interpreted as they may vary between species and may also differ in humans. Translational science is anticipated to provide better understanding of the possible gaps between animal models and clinical application in man.

In parallel, development of the new drugs and combinations will depend on results of Phase I studies that will provide safety, tolerability and drug pharmacokinetics data in healthy volunteers. Analysis of all preclinical and Phase I clinical data will guide the development of the selected combination to be tested for efficacy and dose-optimisation in patients.

Checkerboard assay determines the interaction (synergy, additivity or antagonism) and in vitro potency of two drugs when used concurrently.

With the expectation of at least 10 new drug candidates from different chemical classes progressing toward clinical development, the availability of a new oral, safe and field-adapted therapy for leishmaniasis is likely achievable in the coming decade.

Reference

[1]WHO | Leishmaniasis. http://www.who.int/mediacentre/factsheets/fs375/en/. (Accessed March 2018)

PERSPECTIVES ON THE ACCESS FOR MILTEFOSINE

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Miltefosine as an anti-leishmania drug was originally developed in partnership with Aeterna Zentaris and TDR (WHO Special Programme for Research and Training in Tropical Diseases). In 2002 it was registered in India for the treatment of visceral leishmaniasis (VL). The fact that miltefosine is the sole oral drug available for VL treatment and relatively easy to implement in public health systems, have drawn the scientific community´s attention to extend its recommendation to other forms of leishmaniasis. In 2013 the Pan-American Health Organization (PAHO/WHO) also recommended miltefosine for cutaneous leishmaniasis (CL) treatment, particularly for *L. guyanensis* and *L. panamensis*. Based on recent and ongoing clinical trials, experts have recognized miltefosine´s potential to be used in combination with other currently available treatments or in cases of antimonial resistance. However, the increase in price, lack of registration in endemic countries and the fact that this drug has only one good quality supplier, have limited the access to miltefosine in the last few years.

Miltefosine was developed by Aeterna Zentaris, and subsequently transferred through various acquisitions. Under the name of Impavido®, miltefosine was registered in the *Food and Drugs Administration* (FDA) for cutaneous and visceral leishmaniasis treatment in 2014. Currently, the trademark rights on Impavido® are under a company named Knight Therapeutics, a Canadian biotech. Prior to being transferred to Knight Therapeutics, Impavido® was marketed by Paladin Labs which had entered into a supply agreement at a preferential price with WHO. It is necessary to identify alternative sources of Miltefosine since Knight Therapeutics selling price is much higher than Paladin's.

While WHO, Médecins Sans Frontières (MSF) and DND*i* are attempting to negotiate a preferential price with Knight Therapeutics, WHO issued a call for Miltefosine manufacturing. In parallel, DND*i* has deployed efforts to identify pharma companies in Asia that could be interested in manufacturing and supplying a generic form of Miltefosine. The benefit of this exercise was positive as several companies showed interest in manufacturing Miltefosine despite the lack of clear visibility of the forecast.

Generic companies usually accept to invest in the manufacturing of a new product when they can expect a return in investment however, this is difficult to evaluate in the case of Miltefosine. The issue of Miltefosine lies on its real sales potential, since the VL patient population is small and the use of Miltefosine for CL treatment is not widely spread. Despite this uncertainty, DND*i* has been able to arise interest of several companies that are committed to deliver the first batches of the product for registration in their respective countries by the end of 2018. At least two companies are willing to submit their Miltefosine to WHO prequalification procedure and register it widely, in CL and VL endemic countries.

In addition, DND*i* will attempt to develop a potential sales forecast modelling for Miltefosine.

CUTANEOUS LEISHMANIASIS IN ETHIOPIA: A UNIQUE SPECIES, VECTOR AND RESERVOIR

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Ethiopia is located in the horn of Africa and has a high central plateau that ranges from 1200 to 2700 meters. At the border regions, hot lowland areas can be found. The population currently stands at 100 million. Ethiopia is endemic to both visceral (VL) and cutaneous leishmaniasis (CL). While VL is found in the lowlands, CL is restricted to the highlands. Published reports of CL date back to the early twentieth century, with Italian soldiers suffering from oriental sore. Later on, extensive forms of CL were described, initially misdiagnosed as lepromatous leprosy. Probably, the disease exists since much longer, as there is a specific name in various native languages in most endemic areas. In Amharic it is called *Qunchr*.

Close to 30 million people are at risk for CL in Ethiopia, with an estimated 20-50,000 cases/year. CL in Ethiopia is caused by a unique species, *L. aethiopica*. Except for a small pocket in Kenya, this species has only been found in the Ethiopian highlands. Exceptionally, CL in Ethiopia can be caused by other species (*L. major, L. tropica, L. donovani*). The disease is zoonotic, with hyraxes as reservoir. Two types of hyraxes are thought to be involved: the rock hyrax (Procavia habessinica) and the tree hyrax (Heterohyrax brucei) [**Figure 1**]. These animals typically reside in rocky cliffs and are often seen close to villages in CL endemic areas. Whether other animals act as reservoir is currently unknown. Two vectors have been implicated: *P. longipes* and *P. pedifer*. These sandflies have been commonly found in caves and around steep cliffs, bringing them in close contact with hyraxes. It is currently unknown where humans mostly get infected. Some studies have indicated it is most likely to occur at the rocky cliffs during outdoor activities, other studies have suggested there could be peri-domestic transmission as well. This information is vital for disease control activities. Importantly, there are suggestions that CL is spreading to new areas. For instance, an outbreak with a prevalence of 5% was reported in 2005 in an area 150 km from the capital city Addis Ababa. Whether this relates to the spread of the reservoir or vector is currently unknown.

Three clinical forms of CL exist in Ethiopia: localized CL (LCL), mucocutaneous CL (MCL) and diffuse CL (DCL). LCL is the most frequent manifestation. In most areas, children and young adults are the most affected. Interestingly, more than half of the lesions occur on the face, contributing to the substantial stigmatization of affected individuals. In turn, this can lead to drop-out of kids from school. In health facility-based reports, MCL was also relatively common, accounting for > 40% of the CL cases. However, the often dramatic clinical presentation might be related to that, besides the fact that the relatively scarce treatment available is often reserved for the more severe cases. In population surveys lower numbers have been reported. Mucosal lesions are typically present together with the skin lesion(s) and most often mucosal lesions expand to the skin [**Figure 2**]. Possibly, some of the MCL cases are due to sandfly bites on or close to the mucosal barrier (for instance on the lips), or with an initial skin lesion expanding to the mucosa. This is different from the situation in Latin America, where MCL is thought to result from hematogenous spread from the skin lesion, and mucosal lesions typically occur after the primary skin lesion. Compared to LCL, MCL is reportedly less responsive to treatment. DCL is the most severe form as it is notorious for its chronic and progressive course. Patients with DCL fail to mount an effective specific immune response against the parasite and have highly parasitized nodular lesions spread throughout the body [**Figure 3**]. Response to treatment is often limited. Even if after prolonged treatment parasitological clearance can be obtained, patients will typically relapse. Only a few studies have aimed to understand what determines the clinical manifestations. While immunological responses clearly differ between LCL and DCL, it is unclear to what extent parasite, genetic or other host-related factors contribute. Available parasitological studies did not find clear differences in parasite features across the clinical spectrum. However, as these were typically conducted many years ago, these should be repeated with the newer, more powerful technologies, aiming for more refined parasite characterization.

Figure 1: *Hyraxes are considered the reservoir for CL in Ethiopia*

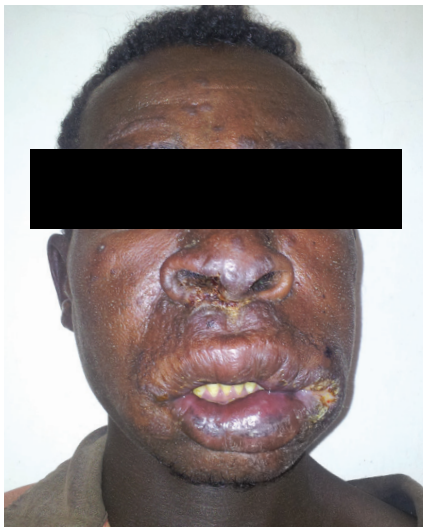

Figure 2: *A case of mucocutaneous leishmaniasis (MCL).*

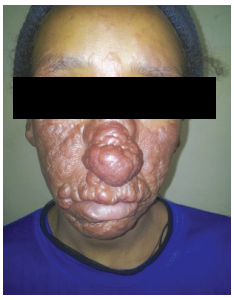

Figure 3: *A case of diffuse cutaneous leishmaniasis (DCL).*

While there is currently a national VL program in Ethiopia, a national CL program providing CL treatment is lacking. However, national leishmaniasis treatment guidelines have been developed, recommending a range of treatment options. Importantly, as clinical trials on CL due to *L. aethiopica* are lacking, the guidelines clearly state that developing the evidence-base for CL treatment in Ethiopia via clinical trials is a priority. Current treatment practices for LCL are cryotherapy, heat therapy and intralesions injections of antimonials. For patients needing systemic treatment, intramuscular antimonials are given. Experience with miltefosine is limited to compassionate use via VL programs. While expert advice suggests this to be effective, it remains to be properly evaluated.

Overall and despite the substantial burden, CL due to *L. aethiopica* has been largely ignored by the scientific community and health policy makers. Research is now needed to provide the necessary knowledge and tools for an effective disease control program. Besides a better knowledge on the vector, reservoir and transmission, field-adapted tools for diagnosis and treatment should be developed.

LETTER OF CUIABÁ: TOWARDS THE CREATION OF THE FIRST ASSOCIATION OF LEISHMANIASIS PATIENTS?

MADY BARBEITAS - DNDi Latin America

On August 27th, 2017, the opening of the 53rd Congress of the Brazilian Society of Tropical Medicine (MedTrop) in Cuiabá brought together students, teachers, managers, health professionals and a small group that listened closely to the ceremony: patients affected by the diseases to be discussed therein.

Opening space for the patients' voice, in a primarily scientific event, is an initiative that comes from the Annual Meeting of the Clinical Research Platforms on Chagas Disease and Leishmaniasis (RedeLEISH) and the 52nd MedTrop in 2016. Aware that in order to deal with tropical diseases it is necessary to include the patient´s needs in the definition of the agenda to establish priorities to address these diseases, the coordinators of the 53rd MedTrop again granted a space at the opening ceremony. Moacir Antonio Zini was the one to speak, representing more than 50 patients. He has been on treatment for over 20 years for diffuse leishmaniasis one of the most aggressive manifestations of cutaneous leishmaniasis.

More than patients, they became protagonists and members of the Brazilian Social Forum for Confronting Infectious and Neglected Diseases (Forum) that includes representatives of associations and entities organized by people living with leishmaniasis, Chagas disease, leprosy, viral hepatitis, HIV/AIDS, helminthiasis and other infectious and neglected diseases. In a context of social remobilization and resistance to the progressive under-funding of the Unified Health System (SUS), the Forum was created in an attempt to join forces to fight against the invisibility and the stigma of "diseases that could have already been eliminated", as stated in the Letter of Cuiabá - manifesto drafted by the Forum and conveyed at the opening of the Congress by Moacir.

One of the main goals of the Forum is to promote education, communication, empowerment and inclusive development of people affected by neglected diseases in order to guide them to fight for their rights by putting pressure on the leaders to increase the budget dedicated to public health policies. However, the challenges to achieving this goal are many and varied. The first of these is related to the Forum organization and formalization. How to effectively involve people who are dispersed in various regions of Brazil? How to draw the Forum´s common goals if each disease has its specificities and priorities? With several dilemmas and the lack of an organizing committee to direct actions, Moacir Zini decided to take advantage of the repercussion of the Forum to articulate the creation of an association of people living with leishmaniasis in the State of Mato Grosso, the second state in the country (Brazil) with the highest incidence of cutaneous leishmaniasis cases.

Opening of the 53rd Congress of the Brazilian Society of Tropical Medicine (MedTrop): reading of the Letter of Cuiabá by diffuse leishmaniasis patient, Moacir Antônio Zini

"Our main claim is for new treatments, for research and innovation in medicines" – said Moacir, who also complained that the anti-leishmaniasis drugs are old and have many side effects, and reported that he now takes a more "adequate" medication, miltefosine, but that is not yet available in the country.

> *"My dream is that everyone can have better treatment opportunities."*
>
> *Moacir Zini*

Moacir joined forces with the Movement for the Reintegration of People Affected by Leprosy (Morhan) and the Federation of Agricultural Workers of the State of Mato Grosso (FETAGRI-MT) and began to raise awareness in rural settlements to share his knowledge and mobilize more people for the cause. In Campo Verde/MT, he met with the mayor and health secretary, was interviewed on the radio and television and spoke to more than 600 families, including doctors and health workers.

Together with his wife Thalita, Moacir attended the First Conference of Health Surveillance that happened in Palmas/TO. The conference mobilized all spheres of health management, from the World Health Organization (WHO) to the Municipal Secretariats (CONASEMS), to deliberate together with civil society about the guidelines for the creation of the national health surveillance policy and to strengthen actions to promote and protect health. According to Thalita, the great learning of the conference was to realize the importance of working together with the health secretariats. ***"Patient associations must walk along with the municipal secretariats, participating and accompanying social projects and the secretariat must also assist in the creation of the association."***

Health Secretary Rogério Noro from the municipality of Ipiranga do Norte/MT tells how he met Moacir and how he became involved with leishmaniasis: ***"Mr. Zini is one of the militants on this matter in our region and has been helping us to articulate several actions in partnerships with our municipal health units, such as his participation in the Municipal Hepatitis Prevention Campaign. I emphasize the importance of Mr. Zini in such an event, aiming to disseminate all the actions carried out by the Secretariat and the importance of preventing against leishmaniasis."***

Even with all the efforts made by Moacir and Thalita, one of the greatest challenges in leishmaniasis is to sensitize people who present with the least complicated forms. In the words of Moacir: ***"They have a small lesion, treat for 20-30 days and are cured, that is, after a while, they don´t even remember they had the disease."*** However, the most severe cases that present relapses, extensive scars or deformities on the face, usually remain on patient´s memories, due to the enormous stigma and suffering they bring to people's lives.

However, these cases - diffuse, disseminated or mucousal leishmaniasis - are rarer and are spread throughout the entire country. For this reason, Moacir and Thalita preferred to start with the process of formalizing the association. They obtained the support of a lawyer, set up a board and are working on the charter. Once the association is created, they may have privileged access to other health secretariats in the state and may be able to more easily identify the municipalities with the highest number of cases in order to promote awareness and recruit more members.

References

[1] Data of 2016 - SVS, Brazilian Ministry of Health.

1º MANIFESTO LETTER TO SUPPORT RESEARCH IN MUCOSAL LEISHMANIASIS

Context:

Launched during World Leish 6 by redeLEISH members.

Goals:

- Raise awareness of policy makers and scientific communities about the seriousness of mucosal leishmaniasis, hoping that more resources are devoted to research for this clinical manifestation.
- Seek support for the development of clinical projects to generate robust evidence.

Release:

- Scientific events (WorldLeish 6, MedTrop 2017, Patient´s forum)
- Online via Webforum (https://www.abaixoassinado.org/abaixoassinados/37330)
- Scientific publication (Journal of the Brazilian Society of Tropical Medicine - Jan/feb 2018 edition) - http://www.scielo.br/

Achievements:

- 143 signatures.
- Prioritization of mucosal leishmaniasis in the redeLEISH and incentive to conduct a multicenter clinical trial in Brazil.

redeLEISH webforum

Virtual network of investigators in leishmaniases

SIGN IN:

http://platforms.dndi.org/redeleish

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