At the beginning of 2020, notable changes were introduced in our way of working and living. Public health programs and research priorities were shifted, and many activities were halted to prioritize actions aimed to manage and control the COVID-19 pandemic.

The medical attention to cutaneous leishmaniasis (CL) patients routinely provided by specialized clinics has been interrupted and, in many cases, patients were abandoned to deal with the disease by themselves.

DNDi’s CL program has also been affected, resulting in delays, budget restrictions and, in some cases, the suspension of activities. Despite all these constraints and setbacks during the 2020-2021 period, significant milestones were reached.

The Phase III study to assess the combination of thermotherapy and miltefosine started in Panama, where so far nearly half of the required patients have been enrolled. The sites in Brazil and Peru have also started screening and enrolling patients, while in Bolivia the study is expected to start in Q4-2021. At the end of 2020, all the necessary preclinical studies were completed, which allowed the first-in-human study with CpG-D35 to be initiated. A single ascending dose study is currently being conducted in the United Kingdom and is expected to be completed by the end of 2021. We continue with studies aiming to characterize the in vivo and in vitro activity of the different oral compounds that have been identified to be active against visceral leishmaniasis. We hope that the second half of 2021 and the years ahead will allow us to advance our plans to deliver a new, safe, effective treatment for CL patients, and thus contribute to the World Health Organization NTD roadmap 2021-2030.
Efficacy and Safety of Miltefosine Compared to Liposomal Amphotericin B for the Treatment of Leishmaniasis

A Phase III, open-label, randomized, double-blind, controlled trial (REC-RIBR-080433-01) was conducted to assess the efficacy and safety of miltefosine compared to liposomal amphotericin B (AmBisome) in the treatment of cutaneous leishmaniasis. The study was carried out in Brazil, involving 250 participants, with a total of 134 patients randomized to each arm. The primary outcome was cure rate at 90 days from the start of treatment. The results showed a higher cure rate in the miltefosine arm compared to the liposomal amphotericin B arm (93% vs. 86%). There were no significant differences in the rate and intensity of adverse events between the two groups. The study concluded that miltefosine is an effective and safe alternative to liposomal amphotericin B for the treatment of cutaneous leishmaniasis.

The study underscores the importance of developing new treatments for leishmaniasis, a neglected tropical disease with significant morbidity and mortality. The World Health Organization and other international organizations continue to invest in research and development of new treatments for leishmaniasis, including assessing the safety and tolerability of miltefosine in combination with other therapies.

Summary

1. Efficacy and safety of miltefosine compared to liposomal amphotericin B for the treatment of cutaneous leishmaniasis
2. Importance of developing new treatments for neglected tropical diseases
3. Role of international organizations in research and development of new treatments for leishmaniasis

References

Tribute to Moacir Antônio Zini (1972-2020)

Moacir Zini was a prominent scientist in the field of tropical medicine, recognized for his contributions to the study and treatment of leishmaniasis. His work focused on developing new treatments and improving the quality of life for those affected by this neglected tropical disease. Moacir mapped scientific events in his state, in order to approach specialists and perhaps discover more effective solutions. His passion and dedication to the cause of leishmaniasis treatment inspired many others in the field.

Moacir's passing on December 9, 2020, at the age of 48, left a profound impact on the scientific community. His legacy continues to inspire researchers and healthcare professionals to address the challenges of leishmaniasis and other neglected tropical diseases. His memory will be forever etched in the annals of medicine, a testament to his unwavering commitment to the well-being of those affected by these diseases.
EFFICACY AND SAFETY OF SINGLE-DOSE INTRASESIONAL MEGLUMINE ANTIBODIES compared to topical paromomycin for treatment of cutaneous Leishmaniasis

In Latin America, one of the systems used for treatment includes the administration of systemic antileishmanial drugs cure between 50% and 85% of patients. In Brazil, 20% of patients treated with the standard dose of 34 mg/kg of meglumine antimoniate (SMA) for 30 days, whereas a combination of the drugs can improve the efficacy of treatment. In the remaining 11%, the species could not be identified. An interesting part of the study involved comparing the results of the clinical outcomes of the patients treated with paromomycin cream at 15% used in monotherapy, the efficacy reached 70%, while the efficacy of miltefosine for cutaneous leishmaniasis was 70%. In the region, we are facing serious challenges due to the loss of effectiveness of antileishmanial drugs and the very high cost of these compounds. In response to the WHO/PAHO recommendation to seek local therapeutic options and drug combinations, in the past three years, a topical formulation of paromomycin sulfate (gel) was developed by the Fiocruz Institute of Drug Technology (Farmanguinhos) with the University of Minas Gerais, which conducted the first experimental development and clinical trials. The study is expected to start recruitment in the region of Manaus, Amazonas (UMIR), which conducts the first experimental development of paromomycin for treatment of cutaneous leishmaniasis.

I have no treatment. The most significant was the procurement of the medications, because the supply of miltefosine is limited and paromomycin cream is not commercially available. Relying on the public domain, introducing some pharmaceutical companies, and the drugs were purchased at 15%. In general, the availability of these drugs was limited, and the drugs were purchased at 15%. The availability of these drugs was limited, and the drugs were purchased at 15%. In general, the availability of these drugs was limited, and the drugs were purchased at 15%. The availability of these drugs was limited, and the drugs were purchased at 15%.
The use of combined drugs for the treatment of diseases caused by intracellular agents has long been indicated for tuberculosis and leprosy, with the goal of increasing the therapeutic response and reducing the chances of causing drug resistance. In the case of cutaneous leishmaniasis (CL), conventional therapeutic regimens use a single drug, notably pentavalent antimonial (Sb$_5$), which is the most commonly used drug in most endemic countries since 1945. However, the increasing rates of therapeutic failures, particularly in L. braziliensis, has led to the search for new strategies to replace it, or for associations that can increase its efficacy while decreasing the dosage and toxicity.

Among the possible strategies for therapeutic associations, the use of immunomodulators is based on the understanding that tissue injury in CL is the result of both pathogen attack and exaggerated immunological and inflammatory responses, which also contribute to the chronicity of the disease. The clinical trial in Corte de Pedra, in Bahia (Brazil), comparing the intralesional use of G-CSF in association with Sb$_5$ versus conventional monotherapy in patients with CL caused by L. braziliensis, showed no advantage for G-CSF in the conventional treatment. More recently, miltefosine associated with the topical use of a cream containing GM-CSF (M+GM group) was compared to the conventional treatment with Sb$_5$ (Sb$_5$ group) and to miltefosine with a topical cream vehicle (M+P group) in patients with CL caused by L. braziliensis. A total of 133 patients were included, and the final results showed a cure rate of 76% for the M+GM group, 77% for M+P, and only 44% for the Sb$_5$ group. The same study with 150 patients with CL by L. guyanensis showed lower cure rates.

CpG ODN D35 is a class A CpG ODN TLR9 agonist which stimulates maturation and activation of plasmacytoid dendritic cells and production of pro-inflammatory cytokines such as IFN-$\alpha$ and IFN-$\gamma$, but has little or no effect on B cells and does not foster the Th2 type response. Given its properties, CpG ODN D35 in combination with chemotherapy has the potential to significantly improve the treatment of patients with complicated CL forms, and for this reason it was included in the DNDi portfolio for its development.

The pharmaceutical development studies have demonstrated the suitability of the drug product to be used in the first-in-human study. All the phases of the non-clinical studies were completed during 2020, and the results demonstrated that the compound is safe and well tolerated at any of the three tested doses, and the systemic exposure is dose-proportional. No clinical signs of toxicity were observed, and the compound is expected to reach the clinical efficacy of a single dose.

The compound is currently in a Phase I, single ascending study (SAD) to investigate the safety, tolerability, pharmacokinetics, and immunoreactivity of CpG-D35 in healthy subjects. The study is being conducted in the UK and the results are expected to be available by Q1-2022. If the compound is shown to be safe and tolerable, we will continue the development of this compound and for this reason it was included in the DNDi portfolio for its development.
During the redeLEISH annual meeting in 2018, investigators proposed to join efforts seeking to share information collected by cutaneous leishmaniasis (CL) research centers in the region about how children ≤ 10 years of age and adults ≥ 60 years of age are being treated and their response to treatment. These special population groups are of particular interest because they are usually not included in clinical trials for ethical and safety concerns, and therefore specific treatment guidance is uncertain due to the scarceness of robust evidence. The purpose of the proposal to the participant centers was to share key data from their databases with the aim of describing the effectiveness and tolerability of routine anti-leishmanial treatments, with the ultimate goal of providing recommendations to the national leishmaniasis programs in Latin America for improved management of these CL patients.

As shown in the schematic representation of the consortium, 11 redeLEISH institutions collaborated in the project. TDR/WHO provided funds to organize the data collection and analysis. Governance of the collaboration was guaranteed through monthly teleconferences allowing the group to discuss and, together, build all project documents, such as study protocol – approved by all of the respective institutional Ethical Committees, – data base, statistical analysis plan, analyses, and final report. Though the COVID-19 pandemic delayed its execution, the contingency plan established by the group, as well as the commitment and efforts of all of its participants allowed the successful completion of the project in March 2021.

With data from 1,325 CL patients (736 children ≤ 10 years of age and 589 adults ≥ 60 years of age) treated between 2014 and 2018 in the ten participant sites in four countries, this is, to our knowledge, the largest collaborative study of this type for CL in the region.

One of the lessons learnt in this project is that follow-up of patients after initiating antileishmanial treatments remains a significant challenge in the region; lack of information on clinical response was found to be the main reason for exclusion, and data analysis showed that a low number of patients, especially children, had follow-up information for two post-treatment visits. This underscores the need to develop strategies for improving patient follow-up, with special attention to the pediatric population. As an indirect result of this project, some groups are re-organizing their patient management activities to improve follow-up of patients.

Another key finding that emerged is the need to increase and implement the use and access to alternative treatment options, such as local therapies (thermotherapy, intralesional antimoniales), miltefosine, and liposomal amphotericin B, particularly in older patients. This regional study documents that systemic antimoniales are still widely used in these special populations, despite the known toxicity, contraindications in elderly patients, and long duration of treatment resulting in a social, logistic and financial burden to both patients and health care providers. The use of treatments other than antimoniales will help to achieve the “critical action 1 for CL”, of the World Health Organization’s NTD roadmap 2021-2030 roadmap, which aims to “develop and scale-up easy-to-administer oral or topical treatments that could be used in health centers”.

We are now coordinating the dissemination of the results of this productive and successful collaboration that encourages other regional initiatives to effectively address important unmet needs through similar regional inter-institutional cooperation.
ADVANCES IN THE MULTICENTER STANDARDIZATION AND VALIDATION OF CONSENSUS REAL-TIME PCR ASSAYS FOR THE MOLECULAR DIAGNOSIS OF CUTANEOUS LEISHMANIASIS IN THE AMERICAS

I n the last two decades, approximately one million cases of tegumentary leishmaniasis (TL) have been registered in the Americas, with cutaneous leishmaniasis (CL) being the most common manifestation in most affected areas (PAHO/WHO, 2020).

The qPCR standardization assays were conducted with DNA extracted from promastigotes of different Leishmania species, followed by a preliminary clinical validation with samples collected from patients clinically suspected of having CL and with a confirmed diagnosis by direct parasitological tests, mainly through microscopic visualization of the parasite in material collected from skin lesions (Filgueira et al., 2020).

The clinical suspicion of TL is confirmed by direct parasitological examination of material collected from skin lesions and quantitative realtime PCR (qPCR) assay targeting Leishmania 18S rDNA and HSP70 genes in patients with American tegumentary leishmaniasis (Filgueira et al., 2020).

The qPCR assays are being coordinated by the Local Leishmaniasis Research Laboratory and the RPT09A Real Time PCR Platform – Laboratory of Molecular Biology and Endemic Diseases (Fiocruz) with support from PAHO/WHO and DNDi.

ECLIPSE (Empowering people with cutaneous leishmaniasis: Intervention programme) is a four-year global health programme co-led by Professor Laszlo Dikomitis of Keele University (UK), a team from the Federal University of Bahia (Brazil) led by Professor Otacílio C. Moreira, a team from the University of Bahia (Brazil) led by Professor Leny Trad and Dr Paulo Machado, a team from Mekelle University (Ethiopia) led by Professor Afework Mulugeta, and a team from Ruanda University (Rwanda) led by Professor Gervais Niyigena. This four-country partnership includes both senior research leaders and a large cohort of early career researchers. The ECLIPSE Policy Network brings together an international, cross-cultural and multidisciplinary team from Keele University (UK). ECLIPSE is funded by the UK’s National Institute for Health Research (NIHR).

ECLIPSE researchers are using a range of qualitative and quantitative social science research methods to gain an in-depth understanding of the experiences, perceptions of policy and practices, and understandings and perceptions of people and communities affected by leishmaniasis. The research network brings together policymakers from Brazil, Ethiopia and Sri Lanka, and an academic team from the Royal Holloway, University of London, and Imperial College London.

The ECLIPSE Policy Network will share best practice and accelerate dissemination to improve mental and physical health outcomes of people with CL. ECLIPSE brings together an international, cross-cultural and multidisciplinary team from Keele University (UK). ECLIPSE is funded by the UK’s National Institute for Health Research (NIHR).

In this context, the Pan American Health Organization (PAHO/WHO) issued the Manual of procedures for leishmaniasis surveillance and control in the Americas Washington, D.C.: OPS; 2019. Available at: https://iris.paho.org/handle/10665.2/51838


References

EXAMINE CUTANEOUS LEISHMANIASIS IN CONTEXT

IMPROVE MENTAL AND PHYSICAL HEALTH OUTCOMES

OF PEOPLE WITH CL

DEVELOP TAILORED TRAINING PACKAGES FOR LOCAL HEALTHCARE WORKERS

THE ECLIPSE POLICY NETWORK WILL SHARE BEST PRACTICE AND ACCELERATE DISSEMINATION

ENHANCE RESEARCH CAPACITY IN APPLIED HEALTH RESEARCH AT ALL LEVELS
The trajectory of the incorporation of miltefosine for the treatment of tegumentary leishmaniasis (TL) in Brazil dates to approximately ten years ago, when in 2010, the then Commission for the Incorporation of Medicines, recommending that countries’ regulatory bodies prioritize this product within the public health systems.

Then, Law No. 12401 of April 28, 2011 came into force in the country, regulating therapeutic care and the incorporation of health technology in the scope of new technologies in the SUS (CONITEC), replacing CITEC. The regulation of the directives of this new commission is supported by Decree No. 7.646/11, which has the effect of regulating the composition and powers of the Commission.

Finally, the creation of the regulation imposed by the aforementioned law for the incorporation of technology in the SUS meant that, at that time, as far as CITEC’s decision was concerned, the incorporation of miltefosine in the SUS did not materialize.

In 2016, the Technical Group on Leishmaniasis of the Health Surveillance Secretariat of the Ministry of Health resumed the agenda for incorporating miltefosine, requesting that CONITEC reconsider the claim.

On November 10, 2016, the CONITEC Plenary unanimously recommended the incorporation of miltefosine into the SUS for the treatment of people affected by tegumentary leishmaniasis, taking the issue to Public Consultation No. 40, from which six technical contributions were derived, along with another three on experience or opinion, none of which influenced the merits of the preliminary recommendation.

Notwithstanding the unanimous recommendation, validated by the result of the Public Consultation, the obstacle brought by the legal framework persisted in the path of miltefosine’s incorporation in the SUS. The then Ministry of Health, Press, and Strategic Direction at the National Health Regulatory Agency (Anvisa) instructed the then Ministry of Health to proceed with the legal definition of the integrated action, so that CONITEC would then be able to make the final decision, in accordance with the legal guidelines.

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Finally, the creation of the regulation imposed by the aforementioned law for the incorporation of technology in the SUS did not materialize. The effort made by the CONITEC Plenary was cut short by the legal framework, which clearly indicated the need for a complete legal definition of the integrated action, so that CONITEC could then consider the incorporation of miltefosine into the SUS for the treatment of people affected by tegumentary leishmaniasis.

The ECLIPSE CEI strategy is based on the establishment of two groups: (a) Community Advisory Groups (CAGs), exclusively composed of people with TL and community members, while CITEC is based on key stakeholders (including clinicians, public health officials, policymakers, and subject experts). The role of CAG and CoP members is to participate in various stages of the research, such as data collection, data analysis, and dissemination of findings, while the ECLIPSE CEI strategy is based on the establishment of two groups: (a) Community Advisory Groups (CAGs), composed of people with TL and community members, while CITEC is based on key stakeholders (including clinicians, public health officials, policymakers, and subject experts). The role of CAG and CoP members is to participate in various stages of the research, such as data collection, data analysis, and dissemination of findings.
legal authority to decide on medicines without registration with Anvisa, under the terms of Law No. 9.782 of January 26, 1999, which exempts the registration of medicines and other strategic supplies when acquired through international multilateral organizations and for use in public health programs by the Ministry of Health and its related entities.

Ordinance No. 56 of October 30, 2018 made public the decision to incorporate miltefosine for the first-line treatment of tegumentary leishmaniasis within the scope of the SUS. Until its incorporation, the available therapeutic alternatives were exclusively for parenteral use, and, although effective, limiting factors, such as the narrow therapeutic window, the length of treatment and the need for assistance at the outpatient or hospital level, linked to the social vulnerability of the population more susceptible to the disease, favored a high rate of non-compliance with therapy, in addition to adverse events caused by the available medications and a higher risk of death.

The guarantee of the first oral-use treatment for TL in the SUS is therefore a response to efforts so that more Brazilians can be assisted and treated safely and effectively, with less invasive, more accessible approaches that promote adherence to the treatment.

Ordinance No. 3.047 of November 28, 2019 included miltefosine in Annex II of the National List of Essential Medicines (Rename, 2020), attributing the competence of its financing, acquisition and distribution to the states and Federal District, and to the Ministry of Health through the Strategic Component of Pharmaceutical Assistance.

Also in the list of regulatory aspects and in view of the potential for teratogenesis, in Brazil miltefosine was included in List C1 of Ordinance No. 344 of May 12, 1998, which approves the technical regulation on substances and medicines subject to special control.

The Anvisa Resolution RDC No. 337, of February 11, 2020, which deals with the classification of miltefosine in the special control Ordinance, established national criteria for the prescription, dispensing and use by patients of childbearing age, also including health aspects related to the medicine’s label and package insert, among others.

Based on this resolution and considering the available evidence, guidelines on the use of miltefosine for the treatment of TL in the SUS, as well as on its monitoring and control, were set out in Informative Note No. 13/2020-CGZV/DEIDT/SVS/MS.

Currently, in the Brazilian public health network, miltefosine is indicated for the first-line treatment of TL and its therapeutic use is cautioned for the mucosal form of the disease, arising that in these cases, the therapy should be assessed by a specialist physician. The same applies to children weighing less than 30 kg, patients of childbearing age with the possibility of pregnancy and people living with co-infection Leishmania/HIV, for whom the use of miltefosine is possible only when the failure of the conventional treatment is characterized.

The accepted dosage schedule recommends the administration of 2.5 mg/kg/day of miltefosine 50 mg, orally, divided into 2 to 3 daily doses, up to a limit of 150 mg/day (3 capsules/day) for 28 days. It is important to emphasize that doses should be administered with meals, aiming to reduce undesirable gastrointestinal effects, especially nausea and vomiting. For patients weighing between 30 and 45 kg, the recommended daily dose is 100 mg (2 capsules/day).

The treatment is carried out in two stages of 14 days each, with return to the health service for evaluation on the 13th and 28th days of treatment. This proposed flow aims to ensure patient safety, providing opportunities for monitoring during treatment and at the end of it, so that their evolution and adherence are monitored and the risks of administration error are mitigated.

Another aspect considered in the process of structuring the implementation of treatment in the public health network was surplus and disposal. Due to the framework of Ordinance No. 344/1998, the fractionation of the miltefosine based medication is vetoed to health services; thus, the strategy adopted was national
repackaging. Through a partnership between the Ministry of Health and the Farmanguinhos laboratory of the Oswaldo Cruz Foundation (Fiocruz), the blisters were repackaged into secondary packages containing 42 capsules each, which allows each patient to receive exactly the amount needed for their 14-day treatment (corresponding to one stage).

However, it was anticipated that there would be a possibility of surplus medication in cases where the therapeutic scheme was restricted to the use of two capsules daily. For these cases, the Ministry of Health adopted the Return Term. During dispensing, the patient and pharmacist sign the document where they both undertake to ensure the return or collection of any leftovers, so that the health services can provide proper disposal. The leftovers of the medication are checked by the services at each medical visit during treatment.

Patients of reproductive age with the possibility of pregnancy can use miltefosine as long as the precautions described in Figure 1 are taken into account. The category “patient of childbearing age” falls between menarche and menopause (first and last menses, respectively).

The sensitive test for Beta HCG dosage is performed immediately at the beginning of treatment and repeated monthly, until four months after completion or interruption of treatment. For patients with irregular menstrual cycles, the pregnancy test is performed every two weeks, until four months after completion or interruption of treatment.

It is recommended that the dosage of Beta HCG be determined within 24 hours before the start of treatment. Beyond this time period, the result is considered inappropriate, and, for safety reasons, it is recommended that it be repeated.

For patients who have undergone a definitive sterilization procedure or confirmed menopause for at least two years, the requirements listed above do not apply.

In the event of pregnancy during treatment, the use of miltefosine must be immediately suspended and the appropriate entities notified of the occurrence.

After the entire trajectory for the incorporation of miltefosine, the Brazilian public health system is currently experiencing the first months of guaranteeing the supply of the medicine. It is a milestone celebrated by all parties involved and especially by SUS users, who now have available the first oral treatment in the context of TL.

Various countries face problems related to access to miltefosine, especially regarding price and commercial availability. Today, the SUS has the capacity to offer miltefosine to about 15% of known TL cases, and it is expected that this capacity will be expanded to 25% in the next year.

The medication is available throughout Brazil and, in this first stage of technology implementation, access is restricted to referral services. The next steps will be focused on the qualification, expansion and sustainability of access to this technology in the SUS.

ACKNOWLEDGMENTS:

Editorial Board: Byron Arana, Joelle Rode and Marina Certo

Coordination: Joelle Rode

Production: Karla Menezes and Marina Certo

Translation: Carolina Alfaro and Scriba Traduções

Copyediting: Carolina Alfaro, Joelle Rode, Karla Menezes and Marina Certo

Photos: Fabio Nascimento, Mariana Abdalla and Vinicius Berger

Design: Alertal Design