

### EFFICACY OF MILTEFOSINE IN THE TREATMENT OF AMERICAN CUTANEOUS LEISHMANIASIS CAUSED BY *LEISHMANIA BRAZILIENSIS* IN BRAZIL

Paulo R.L. Machado<sup>1</sup>, Julia Ampuero<sup>1</sup>, Luiz Henrique S. Guimaraes<sup>1</sup>, Albert Schriefer<sup>1</sup>, Edgar M. Carvalho<sup>1</sup>, Sinésio Talhari<sup>2</sup>, Gerson O. Penna<sup>3</sup>

<sup>1</sup>Serviço de Imunologia, HUPES, Universidade Federal da Bahia, Salvador - BA, Brazil, <sup>2</sup>Fundação de Medicina Tropical, Amazonas, Brazil, <sup>3</sup>Universidade de Brasília - Núcleo de Medicina Tropical, Brasília - DF, Brazil

Miltefosine has been used in the treatment of visceral leishmaniasis in India. Recently, miltefosine has been tested in New World cutaneous leishmaniasis (CL) and Old World CL. The cure rate from the studies in New World CL in Colombia and Guatemala ranged from 91% (*Leishmania panamensis*) to 33% (*L. braziliensis*). There are no data regarding miltefosine use in CL caused by *L. braziliensis* in Brazil. This is a phase II randomized trial with 90 CL patients from the endemic area of Corte de Pedra in Bahia, Brazil. Patients included presented 1 to 3 months of untreated CL, with 1 to 5 ulcerative lesions. Diagnosis was confirmed by a positive culture or polymerase chain reaction methods and by intradermal leishmania skin test. After randomization 30 participants were treated with parenteral meglumine antimoniate (20mg/kg/day x 20 days) and 60 with miltefosine administered orally (2.5mg/kg/day x 28 days). Outcome measures were cure rate or complete cicatrization of the ulcer 2 and 6 months after the end of the treatment. Cure rate at 2 months for the antimony group was 65% and for the miltefosine group 75%. The final cure rate at 6 months was 58% in the antimony group and 62% in the miltefosine arm. Intent to treat analysis showed no difference regarding the primary and final cure rate in both groups. Adverse events occurred in 80% of antimony patients compared to 77% in miltefosine patients. In the antimony group the most common side effects were headache (43%), fever (23%), arthralgia (22%) and myalgia (22%). In the miltefosine group, vomiting and nausea (39%), headache (29%) and dizziness (13%). CL caused by *L. braziliensis* in Brazil has a similar cure rate when treated with antimony or miltefosine. Considering that the oral administration of miltefosine is an advantage compared with the parenteral route used for antimony standard treatment in the rural area, our data suggests that miltefosine may be considered for the treatment of CL caused by *L. braziliensis* in Brazil.

### EVALUATION OF COMPOUNDS FOR CUTANEOUS LEISHMANIAL ACTIVITY IN BALB/C MICE INFECTED WITH *LEISHMANIA MAJOR*

Arba Ager<sup>1</sup>, Bill Ellis<sup>2</sup>, Bill Ellis<sup>2</sup>, Juan Mendez<sup>2</sup>, Alan Magill<sup>2</sup>, Richard Boodoo<sup>1</sup>, Jenbon Lui<sup>1</sup>, Max Grogil<sup>2</sup>

<sup>1</sup>University of Miami, Miami, FL, United States, <sup>2</sup>Walter Reed Army Institute of Research, Silver Spring, MD, United States

Cutaneous leishmaniasis (CL) is probably the most neglected disease of all the neglected diseases; a new case of CL happens every 4 seconds. In the United States CL is treated with IV Pentostam (SbV) under IND or Ambisome off-label. A FDA approved topical or oral drug that is safe and easy to use is urgently needed. For this reason, two Cutaneous models of *Leishmania major* in BALB/c mice are being used to evaluate chemicals for antileishmanial activity as part of the US Army. In one model, the metacyclic forms are injected into the footpads (FP) of mice. In the other model they are injected intradermally in the skin at the base of the tail (BT). Test chemicals are administered starting on the 3<sup>rd</sup> day after infection for 14 days. Lesions are measured weekly for 4 weeks and expressed as a mean effect of the chemical on footpad thickness or skin lesion size in relation to control infected non-treated mice. AmBisome is used as a positive control. The chemicals are administered either intraperitoneally (IP) or orally (PO) in the footpad test and either IP, SC, transdermally (TD), or PO in the tail base test. Antibiotics, antifungal compounds and

8-aminoquinolines have been evaluated. The most active chemical entities and classes will be presented and discussed.

### A NEW PEDIATRIC TABLET STRENGTH OF BENZNIDAZOLE FOR THE TREATMENT OF CHAGAS DISEASE

Dianne J. Terlouw<sup>1</sup>, Fabiana P. Alves<sup>2</sup>, Sergio Sosa-Estani<sup>3</sup>, Hector Freilij<sup>4</sup>, Jaime Altcheh<sup>4</sup>, Laurent Brutus<sup>5</sup>, Jean-René Kiechel<sup>2</sup>, Isabela Ribeiro<sup>2</sup>

<sup>1</sup>Liverpool School of Tropical Medicine (LSTM), Liverpool, United Kingdom, <sup>2</sup>Drugs for Neglected Diseases initiative (DNDi), Geneva, Switzerland, <sup>3</sup>Centro Nacional de Diagnóstico e Investigación de Endemo-epidemias (CeNDIE) ANLIS Dr. Carlos G. Malbrán, Ministry of Health, Buenos Aires, Argentina, <sup>4</sup>Hospital de Niños Ricardo Gutierrez, Buenos Aires, Argentina, <sup>5</sup>IRD-UR010 Santé de la mère et de l'enfant en milieu tropical, Université Paris Descartes, Paris, France

Successful Chagas vector control substantially reduced vector-borne transmission as well as new childhood infections in Latin America in the 1990s. Congenital *T. cruzi* infections have become a key route of transmission and control issue, as vertical transmission remains relatively unaffected by progress in vector control. The main drug for acute Chagas disease, benznidazole (Bz), is only available as an 'adult' tablet formulation, and a pediatric formulation is urgently needed. Bz dose recommendations, dosing practices and patient age and weight profiles were reviewed from 10 centers involved in the treatment of children with *T. cruzi* infections. The priority pediatric target patient population, therapeutic dose range and identified programmatic needs were used to guide a pragmatic decision-making process to determine an appropriate pediatric tablet formulation, strength and associated dosing regimen. In absence of pediatric pharmacokinetic studies, but based on substantial clinical experience, 5-10mg/kg/day Bz split over two doses was considered the appropriate therapeutic intake dose range in children <12 years. Data from 2424 patient records, over 99% from children <18 years and 317 infants, highlighted the challenge for accurate dosing in infants as compared with older children. Prioritizing treatment of congenital Chagas, a dispersible tablet of 12.5mg is proposed to complement the available 100mg tablet and improve dosing accuracy in newborn infants most at risk of over and under-dosing. Use of the proposed pediatric tablet (p) would focus on children <10 kg and consist of 1p tablet (12.5mg) for 2.5-5kg, and 2p (25mg) for 5-10kg per intake dose. In conclusion, a pragmatic review and decision-making process helped to determine an appropriate pediatric tablet strength of Bz, for development as a dispersible tablet by DNDi in partnership with LAFEPE. Such work will help to improve dosing accuracy for infants, an increasingly important patient group.

### EVALUATION OF NEW TESTS FOR EARLY DIAGNOSIS OF VISCERAL LEISHMANIASIS AND ITS COMPLICATIONS AT THE 'POINT-OF-CARE'

Kazi M. Jamil<sup>1</sup>, Abu Toha Bhuiyan<sup>1</sup>, Gulam M. Khan<sup>1</sup>, Mohammad S. Alam<sup>1</sup>, Rashidul Haque<sup>1</sup>, Makoto Itoh<sup>2</sup>, Eisei Noiri<sup>3</sup>, Stephen P. Luby<sup>1</sup>

<sup>1</sup>International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh, <sup>2</sup>Aichi Medical University, Nagakute, Aichi-ken, Japan, <sup>3</sup>University of Tokyo, Tokyo, Japan

Bangladesh is one of the endemic countries for visceral leishmaniasis (VL) with reported incidence of 10,000 cases annually with 20 million people considered to be at risk for VL. We conducted a clinical study to assess the cure rate in 200 VL patients treated with 28 intramuscular injections of sodium stibogluconate (20 mg/kg body wt given once daily). The diagnosis of VL in all the subjects with clinical features of the disease was confirmed by splenic aspiration followed by parasitological examination. We evaluated several diagnostic tests for VL including PCR and Loop-Mediated Isothermal Amplification (LAMP) in blood, KATEX and another