The Future of Global Treatment of Cutaneous Leishmaniasis

B. Arana
# Current treatment recommendations for CL

## Diseases Severity

<table>
<thead>
<tr>
<th>No treatment</th>
<th>Topical</th>
<th>Systemic</th>
<th>Combinations</th>
</tr>
</thead>
</table>
| Small lesion, *L. major* or *L. mexicana*, not in face or joint | ≤ lesions, ≤ 4 cm diameter, not in face or joint | Those who failed with a topical, > 4 lesions, or lesions > 4 cm diameter, any anatomical location. | • Antimonials + allopurinol for *L. recidivans*  
• Antimonials + paromomycin for *L. aethiopica*  
• Antimonials + Pentoxifiline for MCL |
| • Thermotherapy  
• Liquid Nitrogen  
• IL SSG | • Antimonials  
• Miltefosine  
• Pentamidine  
• Amphotericin B deoxycholate  
• AmBisome |
# Current Treatment Options for CL

<table>
<thead>
<tr>
<th>Systemic</th>
<th>Topical</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable efficacy, serious toxicities, only one is oral &amp; rest are painful IV/IM</strong></td>
<td><strong>Variable efficacy, some times lengthily, painful, only for non-complicated cases</strong></td>
</tr>
</tbody>
</table>

## Systemic

<table>
<thead>
<tr>
<th>Medicine</th>
<th>IM or IV or IL</th>
<th>IM or IV or IL</th>
<th>PO</th>
<th>IM or IV</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meglumine antimonate</td>
<td>20 mg / kg / day / 21 days</td>
<td>20 mg / kg / day / 21 days</td>
<td>1.5- 2.0 mg /kg / day / 28 days</td>
<td>4 mg/kg/ 3 doses in 7 days</td>
<td>3.0mg /kg /day /7 doses</td>
</tr>
<tr>
<td>Sodium Stibogluconate</td>
<td>20 mg / kg / day / 21 days</td>
<td>20 mg / kg / day / 21 days</td>
<td>1.5- 2.0 mg /kg / day / 28 days</td>
<td>4 mg/kg/ 3 doses in 7 days</td>
<td>3.0mg /kg /day /7 doses</td>
</tr>
<tr>
<td>Miltefosine</td>
<td>55-90%. Depending on species and region</td>
<td>L. guyanensis ~75-90%. Others 35% - 75%</td>
<td>Painful injections Renal and cardiac toxicity, Hyperglycaemia, B/P alterations</td>
<td>Painful injections Renal and cardiac toxicity, Hyperglycaemia, B/P alterations</td>
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</tr>
<tr>
<td>Pentamidine</td>
<td>OW<del>53%; NW</del>78% Variable depending on species and region</td>
<td>Mainly for complicated forms</td>
<td>Rigors Childs Hypokalaemia Anaphylaxis</td>
<td>Rigors Childs Hypokalaemia Anaphylaxis</td>
<td>Rigors Childs Hypokalaemia Anaphylaxis</td>
</tr>
<tr>
<td>Liposomal Amphotericin B</td>
<td>Painful injections Nephro &amp; Cardio toxicity Hepatotoxicity Pancreatitis</td>
<td>Teratogenic GI toxicity Nephro-Hepatotoxicity</td>
<td>Painful injections Renal and cardiac toxicity, Hyperglycaemia, B/P alterations</td>
<td>Painful injections Renal and cardiac toxicity, Hyperglycaemia, B/P alterations</td>
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## Topical

<table>
<thead>
<tr>
<th>Liquid Nitrogen</th>
<th>Intralesional antimonials</th>
<th>Liquid Nitrogen + IL antimonials</th>
<th>Thermotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 applications per week</td>
<td>3-10 applications</td>
<td>3-10 applications</td>
<td>1-3 applications</td>
</tr>
<tr>
<td>50-85%</td>
<td>~53% OW ~75% NW</td>
<td>75-82% in OW</td>
<td>55-90%</td>
</tr>
</tbody>
</table>

- **Nitrogen supplies, multiple applications**
- **Requires local anesthesia, AE Grade II (2nd grade burns)**

**DNDi: Drugs for Neglected Diseases Initiative**
Room for improvement the treatment for CL

- Improve efficacy from ~53-70% to ≥90%
- Reduce AEs rate from ~40-75% to ≤30%
- Reduce length of Tx from ~21-84 d to 14 -21 d
- Increase compliance from ~50% to ≥90%
- Speed of healing from ~6-17 W to 6-13 W
DNDi’s CL Strategy

To achieve short, safe, non-invasive, efficacious, affordable and field-friendly treatments for CL or at least for lesions caused by *L. tropica* and *L. braziliensis*.

**Disease presentation**

- **1-4 lesion; ≤ 4 cm**
- **Large or multiple lesions**
- **Special Forms (LR, DCL, PKDL)**

**Activity / Project**

- **Immunomodulators**
  - **CpG D35** (Pre-Clinical)

- **NCEs**, Oral, systemic
  - Phase I & Pre-Clinical

- **Topical (Anfoleish)**
  - **Combinations** (Phase III)
Anti-leishmanial efficacy of oral DNDI-0690 (50 mg/kg, once daily for 10 days) in an OW and NW CL model infection of BALB/c mouse

CpG D35

Dendritic Cell

TLR9

CpG D35

Monocytes

Inflammatory cytokines
IFNγ, IL-12
Regulatory cytokines
IL-10

NK Cells (NKC)

PMNs (PMN)

T Cell

Th1

IP-10, IL-12, IFN-γ, IFN β, IFN-α

Th2

Activate macrophages, anti-infective effects

Activated Macrophage

NO production, Cytotoxic T lymphocyte production

Phagocytosis and death of the parasite

Clinical Healing

DNDi
Drugs for Neglected Diseases Initiative
Lesion size in infected Rhesus monkeys by treatment group

* p <0.05; ** p <0.01

Time to re-epithelization (Mean # of days) per treatment group

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>SbV 5mg/kg</th>
<th>CpG D35</th>
<th>CpG D35 + SbV 5mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (# days)</td>
<td>28.5</td>
<td>23.7</td>
<td>17.5</td>
<td>14.3</td>
</tr>
<tr>
<td>SD</td>
<td>7.6</td>
<td>2.3</td>
<td>4.0</td>
<td>7.4</td>
</tr>
<tr>
<td>SEM</td>
<td>3.8</td>
<td>1.3</td>
<td>2.0</td>
<td>3.7</td>
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Combination Study

Rationale
It will take 5-10 more years to develop a new Tx for CL. Our best option right now is to better use the existing approved treatments in combination.

DNDi proposal
To test 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 NW
The ThermoMed™ device, which produces heat utilizing radio-frequency technology remains the most tested local heat modality. Its safety and efficacy have been demonstrated in multiple clinical trials. It is WHO recommended and FDA approved its use for the treatment of CL, among other skin conditions.

- Miltefosine is the only oral treatment currently available for treatment of leishmaniasis.
- In 2014, was registered at FDA for the treatment of infections due to *L. braziliensis, L guyanensis* and *L. panamensis*.
- Included in PAHO treatment guidelines and PAHO strategic fund list of medicines in 2015.
Combination (TT + MLT) Study in Peru and Colombia

- PoC study completed on January, 2019
- The Combination of TT + MLT showed to be significantly better than TT alone for the treatment of uncomplicated CL in NW (PP at D180: TT 64.3%; Combination 84%).
- Subjects with lesions due to *L. braziliensis* and/or *L. peruviana* responded better to the Combination (22 out 27 = 74.1%) than to TT alone (7 out 19 = 36.8%).
- **Next Step:** Conduct a phase III study comparing the non-inferiority of the Combination against the current recommended treatment (SSG) and miltefosine. FV/FP expected by Q2-2020
# Other Potential New Treatments for CL

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<th><strong>Topical</strong></th>
<th><strong>Combinations</strong></th>
</tr>
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<tbody>
<tr>
<td>SinAmpholeish</td>
<td>GM-CSF + Miltefosine</td>
</tr>
<tr>
<td>PMM – WRAIR</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td></td>
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<th><strong>Orals</strong></th>
<th><strong>Immunomodulators</strong></th>
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<tr>
<td>Extend the label of Miltefosine (OW)</td>
<td>GM-CSF</td>
</tr>
<tr>
<td>D-121 (Oblitas)</td>
<td>Canakinumab (Ilaris)</td>
</tr>
<tr>
<td>18-MC (Hebron)</td>
<td></td>
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## Drugs for Cutaneous Leishmaniasis

*Promising new series for a brighter future*

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![Chemical structures](image)

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<tr>
<th>DNDI-0690</th>
<th>DNDI-6148</th>
<th>GNF6702</th>
<th>Aminopyrazoles</th>
<th>CpG D35</th>
</tr>
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*Image credit: *DNDi*