Visceral Leishmaniasis, a study case of collaboration

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Drugs for Neglected Diseases initiative
Leishmaniasis

- VL & CL (MCL, DCL, PKDL, LR, HIV/VL)
- 98 endemic countries
- Incidence: 40,000 VL, 1 M CL cases/yr
- VL is fatal if untreated

90% in just 7 countries: Brazil, Ethiopia, Kenya, India, Somalia, South Sudan, Sudan

PKDL
10% Bangladesh
25% Sudan
Current drugs for leishmaniasis

- Variable efficacy, serious toxicities, only one is oral & rest are painful IV/IM
- Urgent need for new effective, safe, and convenient treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular Weight</th>
<th>pKa</th>
<th>Efficacy / Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meglumine antimoniate</td>
<td>MW 525, clogP -3.8</td>
<td></td>
<td>Painful injections, cardiotoxicity</td>
</tr>
<tr>
<td>Sodium Stibogluconate (SSG)</td>
<td>MW 664, clogP -4.2</td>
<td></td>
<td>Painful injections, cardiotoxicity</td>
</tr>
<tr>
<td>Liposomal Amphotericin B</td>
<td>MW 924, clogP -2.3</td>
<td></td>
<td>Painful injections, cardiotoxicity</td>
</tr>
<tr>
<td>Paromomycin sulfate</td>
<td>MW 616, clogP -6.1</td>
<td></td>
<td>Painful injections, cardiotoxicity</td>
</tr>
<tr>
<td>Miltefosine</td>
<td>MW 409, clogP +1.3</td>
<td></td>
<td>Painful injections, cardiotoxicity</td>
</tr>
</tbody>
</table>

- 20mg/kg/day, 30 days
- 35-95% depending on area, resistance in India
- >95% efficacy in India, variable response in Africa
- 93-95% India 64-85% Africa
- 94-97% India 60-80% Africa

- Painful injections
- Cardiotoxicity
- Hepatotoxicity
- Pancreatitis

- Rigor & chills
- Nephrotoxicity
- Hypokalemia
- Anaphylaxis

- Painful injections
- Nephrotoxicity
- Ototoxicity

- Teratogenic
- Gastrointestinal toxicity
- Hepatotoxicity
Utilizing and Strengthening Research Capacities in Disease-Endemic Countries

Major Role of LEAP:
- Defining patients’ needs and target product profile (TPP)
- Strengthening local capacities
- Conducting clinical trials (Phase II/III studies)
- Facilitating registration
- Accelerating implementation (Phase IV & pharmacovigilance studies)
Operations in East Africa

Short term:
• improve existing treatments through combination therapies in terms of safety, efficacy & acceptability
• Overcome barriers to affordability

Long term:
• Develop new, field-appropriate oral combination therapies with NCEs in partnership

Capacity building initiatives:
- **GCLP** to improve standards
- **GCP**, Study Files, Auditing
- **Safety and Pharmacovigilance** trainings
The LEAP Numbers

- 10 Clinical Trials
- 13 Scientific Publications
- From 2010-Q2 2019: **31,218 suspected cases ↔ 14,604 VL patients treated (3500 in Sudan) ↔ 1,856 patients in clinical trials (325 in Sudan)**
- Over 700 staff - Short-term trainings
- Over 20 Long-term trainings
- Total cumulative cost (2006-2015): **€18.7million** (OR, Capacity building)
- LEAP Platform hosting various clinical trainings and scientific meetings and publishing research news (since 2003)

The 3 most important achievements

- New treatment delivered (SSG/PM) and increased access to treatment
- Overall better efficacy miltefosine treatment in paediatric population
- Improved treatment for HIV-VL co-infected patients
Pathway of medical studies of K-A in East Africa

• Rehabilitation Tx centers: LEAP
• Data Center, Kenya

LEAP-0714 Miltefosine PK (Kenya & Uganda; n=30)
Dg urine study (Kenya, n=55)

LEAP-0511 HIV-VL (Ethiopia; n=60)

2016

LEAP-2080 AmB/SSG/Miltefosine (Kenya, Sudan; n=151)
LEAP-0106 AmBisome single dose (Sudan & Ethiopia; Ph-II n=124)
Pharmacovigilance study (4 LEAP countries; Ph-IV; n=3126)
Fexinazole (Sudan; n=14)

2013

2014

2012

2011

2010

2008

2004

LEAP-0104 SSG/PM (Ph-III n=1149)
WHO Expert Committee (TRS949)

MIL/PM phase III (4 LEAP countries; Ph-III n=440)
PKDL(Ph-II, Sudan, n=110)

Doka
UmElKhair
Kassab
SSG-PM: an improvement, but with limitations

- Efficacy of 91% at 6 months
- 17 days of 2 injections
- Toxicity related to SSG
- Lower efficacy (81% EOT) and higher mortality (9%) in > 50y
- Not recommended for HIV-VL

Replacement of SSG by miltefosine have the potential of a safer treatment with shorter hospitalization, suitable for children and more field-adapted
To develop a safe, efficacious and field-adapted combination therapy for VL in Eastern Africa by 2021

Phase III MF/PM clinical trial:
An Open Label, Phase III, Randomized Controlled, Multicentre Non-Inferiority Trial to Compare Efficacy & Safety of Miltefosine/Paromomycin with SSG/PM Combination for Treatment of Primary Visceral Leishmaniasis (VL) Patients in Eastern Africa

- Countries: Ethiopia (2), Kenya (1), Sudan (3) and Uganda (1)
- Patient population: confirmed primary VL patients 4-50y old, HIV neg, signed ICF
- Sample size: 192/arm, total of 576 VL patients

348 pts enrolled out of 440
PKDL Clinical Trial in Sudan (phase II)

An Open-label, Randomized, Parallel arm Clinical Trial of Two Regimens to Assess the Safety and Efficacy for Treatment of Post Kala-azar Dermal Leishmaniasis (PKDL) Patients in Sudan

Primary objective:
To assess the safety and efficacy of Paromomycin (PM) combined with miltefosine (MF) and AmBisome® (AmB) combined with miltefosine for the treatment of PKDL in Sudan

- 1 study site: Doka
- Patient population: 6 to 60 years old with stable (i.e. > 6 months) or grade 3 PKDL cases who signed ICF
- Study Arms:
  Arm 1. PM 20 mg/kg/d IM 14 days + MF allometric BID PO 42 days
  Arm 2. AmB 5mg/kg/d IV D1, D3, D5, D7 (20 mg/kg total dose) + MF allometric BID PO 28 days
- Sample size: 55/arm, total of 110 PKDL patients

64 pts enrolled out of 110
TPP is focused on IMPACT for leishmaniasis patients

**Current treatments**
- Largely injectable
- Some toxicity
- Variable efficacy
- Limited spectrum
- Hospitalization, cold chain
- Expensive

**New combination(s)**
- Oral
- Well tolerated
- Improved efficacy
- Wide spectrum
- Lower level health systems
- Affordable

**New oral short-course combination treatment**
Challenges

- Political instability in Sudan and Ethiopia impacting the local operations
- Natural oscillation of cases impacting the study progressions
- Administrative managerial difficulties
- Monolithic scientific structures with lack of younger scientists
- Transparency
- MSF-Swiss leaving Attabarakallah hospital overloading DNDi possibilities
- No regional program in East Africa discouraging donors
Thank you to all our Partners, donors and colleagues of the IED