Safety and Effectiveness of new treatment regimens for visceral leishmaniasis in Bangladesh and India

DNDi
Drugs for Neglected Diseases initiative

RMRIMS - Patna

Vishal Goyal

State Health Society Bihar

DNDi
Drugs for Neglected Diseases initiative
Introduction

New treatment regimens developed only in the last few years from already existing drugs for VL, specifically - AmBisome®, paromomycin and miltefosine

*These new treatment modalities have now been recommended by WHO Expert Committee on the control of leishmaniasis (March 2010) and RTAG (WHO SEARO)*

DNDi conducted 2 studies on combination treatments and Ambisome monotherapy:
- Phase 3 clinical trial in Bangladesh (safety and efficacy)
- Pilot implementation study in India (safety and effectiveness)

Objectives:
Provide data for authorities to make evidence-based recommendations for replacing Miltefosine monotherapy with ambisome and combination therapies in the National kala-azar Elimination Program

Rationale:
Reduce duration & side effects, improve compliance and also prevent emergence of resistant parasites (increase duration of effectiveness of available drugs)

Vishal Goyal, Drugs for Neglected Diseases initiative
VL Bangladesh combination trial

A Phase III, open label, randomized, non inferiority study conducted (2010-2014)
Milt (2.5mg/Kg/d) + PM (11mg/Kg/d) for 10 days
Amb (5mg/kg SD) + Milt (2.5mg/Kg/d) for 8 days
Amb (5mg/Kg SD) + PM (11mg/Kg/d) for 11 days,

**compared to:** Amb (5mg/Kg on Days 1,3 and 5, total dose of 15mg/kg)

**PROJECT DESIGN**

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community Based Medical College, Mymensingh</td>
<td>3 Upazila Health Centres n=482</td>
</tr>
<tr>
<td>120 patients enrolled</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trishal 218</td>
</tr>
<tr>
<td></td>
<td>Bhaluka 67</td>
</tr>
<tr>
<td></td>
<td>Gafargaon 197</td>
</tr>
</tbody>
</table>

Vishal Goyal, Drugs for Neglected Diseases initiative

**Ethical Clearance:** ICDDR,B BMRC
## Results – Bangladesh study (n=601)

<table>
<thead>
<tr>
<th></th>
<th>Ambisome</th>
<th>AmB+PM</th>
<th>AmB+Milt</th>
<th>PM+Milt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n=601)</td>
<td>158</td>
<td>159</td>
<td>142</td>
<td>142</td>
</tr>
<tr>
<td>Initial cure at D45 – n(%)</td>
<td>155 (98.1)</td>
<td>158 (99.4)</td>
<td>134 (94.4)</td>
<td>139 (97.9)</td>
</tr>
<tr>
<td>Final Cure at 6 month n(%)</td>
<td>155 (98.1)</td>
<td>158 (99.4)</td>
<td>134 (94.4)</td>
<td>139 (97.9)</td>
</tr>
</tbody>
</table>
Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>AmBisome (158)</th>
<th>AmB+PM (159)</th>
<th>AmB+Milt (142)</th>
<th>PM+Milt (142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total adverse events reported</td>
<td>310</td>
<td>320</td>
<td>329</td>
<td>318</td>
</tr>
<tr>
<td>Total no of subjects with adverse events n(%)</td>
<td>95 (60.1)</td>
<td>97 (61)</td>
<td>86 (60.6)</td>
<td>90 (63.4)</td>
</tr>
<tr>
<td>Drug Related Serious Adverse Events (n=4)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Non-Drug Related Serious Adverse Events (n=8)</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Death: 03- All not related to study drug
All other SAEs (Related and Non Related) were resolved

Vishal Goyal, Drugs for Neglected Diseases initiative
Conclusion

• All treatments showed excellent safety and efficacy

• These new treatments can be safely administered at Upazhala level
  o Shorter treatment duration
  o Better compliance
  o Less side effects

• Combination regimen to be choice of treatment at sites where cold chain cannot be deployed as in case of Ambisome treatment.

Vishal Goyal, Drugs for Neglected Diseases initiative
Pilot Implementation Study - India

Objectives
- Determine under field conditions - effectiveness, - safety profile
- Provide evidence based recommendations for policy makers

Open label, prospective, non randomised, non comparative, multicentre study in public health sector 2012-2015

Single Dose Liposomal Amphotericin B (Ambisome) 10mg/kg
Milt (2.5mg/Kg/d) + PM (11mg/Kg/d) for 10 days
AmB (5mg/kg SD) + Milt (2.5mg/Kg/d) for 8 days

Project Design

<table>
<thead>
<tr>
<th>PHC</th>
<th>District Hospital/ Referral centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-15 PHCs in 2-3 districts in Bihar eg Vaishali, Saran</td>
<td>1-2 sites eg. RMRIMS, Sadar Hospital, Medical colleges</td>
</tr>
</tbody>
</table>

4+ PHC

Milt + PM for 10 d

5+ PHC

AmB (5mg/kg) + Milt for 7d

Referral Centres (special cases)

SDA (10mg/kg)

Other VL treatments if SDA contraindicated or unavailable

Vishal Goyal, Drugs for Neglected Diseases initiative

Ethical clearance: RMRIEC, MSF-ERB, LSHTM
# Results – India study

(n = 1761)

<table>
<thead>
<tr>
<th></th>
<th>SD AmB</th>
<th>AmB+MF</th>
<th>MF + PM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients started on treatment (n=1761)</strong></td>
<td>892</td>
<td>357</td>
<td>512</td>
</tr>
<tr>
<td><strong>Initial cure at day 10 (%) (95% CI)</strong></td>
<td>885 (99.2%) (95%CI-98.6-99.8)</td>
<td>354 (99.2%) (CI-98.3 – 100.0)</td>
<td>508 (99.2 %) (CI-98.4- 99.9)</td>
</tr>
<tr>
<td><strong>Number of patients completed 06 Month FU (n=1591)</strong></td>
<td>828</td>
<td>331</td>
<td>432</td>
</tr>
<tr>
<td><strong>Final Cure at 06 Month n (%)</strong></td>
<td>768 (93%) (CI-91.3-94.8)</td>
<td>296 (89.4 %) (CI-86.1-92.7)</td>
<td>421 (97.4 %) (CI-95.9-98.9)</td>
</tr>
<tr>
<td><strong>Number of Relapse (n)</strong></td>
<td>37 (4.5%)</td>
<td>16 (4.8%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td><strong>Number of patients completed 12 Month FU (n=788)</strong></td>
<td>349</td>
<td>183</td>
<td>256</td>
</tr>
</tbody>
</table>

12 month follow up yielded additional 6 relapse in SDA, 6 relapse in A+M and 5 PKDL cases in M+P arm

Vishal Goyal, Drugs for Neglected Diseases initiative
## Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>SD AmB</th>
<th>LAmB + MF</th>
<th>MF + PM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Adverse Events Reported</strong></td>
<td>159</td>
<td>137</td>
<td>121</td>
</tr>
<tr>
<td><strong>Total no of subjects with adverse events n(%)</strong></td>
<td>120 (13.5)</td>
<td>90 (25.2)</td>
<td>90 (22.4)</td>
</tr>
<tr>
<td><strong>Drug Related Serious Adverse Events n(%)</strong></td>
<td>2* (0.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Non-Drug Related Serious Adverse Events n(%)</strong></td>
<td>3** (0.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* Allergic reaction + Atrial ectopic. Both resolved
** Pneumonia, Empyema, Urinary Tract Infection. All resolved

Vishal Goyal, Drugs for Neglected Diseases initiative
Limitations

- Children **not** treated at Primary Health Centre level and treated at District Hospital only as per regulatory recommendation

- Higher number of severely complicated patients treated in one arm, that is single dose Ambisome arm
Conclusion and recommendations

• All treatments (except Amb + MF) showed excellent safety and effectiveness within public health sector

• Indian National program revised policy in Sep 2014
  – Single Dose Ambisome as first option
  – Combination as second option

• Combination regimen to be choice of treatment at sites where cold chain cannot be deployed
• Establishment of Active Pharmacovigilance at sentinel site is recommended
Lessons learnt

• 3 Combination regimens and SDA are safe and effective treatment in public health sector at field level and feasible to implement at large scale in both countries

• Relapses continue to occur after 6 month post treatment, need to Follow up patients for 12 month to generate evidence on relapse

• Cohort Event Monitoring should be strengthened at all sites in India and Bangladesh to document long term outcome data

• Committed field workers for follow up activity ensuring minimal LTFU
Acknowledgement

• State Health Society Bihar
• Rajendra Memorial Institute of Medical Sciences
• Médecins Sans Frontières
• National Vector Borne Disease Control Programme
• International Centre for Diarrhoeal Disease Research, Bangladesh
• Shaheed Suhrawardy Medical College, Dhaka
• All Government Doctors, staff involved in study
THANK YOU

www.dndi.org

Vishal Goyal, Drugs for Neglected Diseases initiative