Twelve months outcome in kala-azar patients treated with 3 novel regimens, at public health care facilities in Bihar

Provide evidence based recommendations for policy makers

ICID 5th March 2016 Vishal Goyal
Introduction

New treatment regimens developed 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)*

There was need to generate data to make evidence-based recommendations for replacing miltefosine monotherapy with AmBisome and combination therapies in the National Kala-azar Elimination Program

Rationale:
Reducing the duration of therapy will improve compliance, reduce side effects and also prevent the emergence of resistant parasites and thus increase the duration of effectiveness of available drugs.
Objectives

• Determine effectiveness (including 12 month outcome) and safety profile of 3 new treatment regimens under real field conditions

• Provide evidence based recommendations for policy makers
Open label, prospective, non-randomised, non-comparative, multicentre study in public health sector 2012-2015

**Regimens:**

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

**Pilot Implementation Study - India**

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PHC

<table>
<thead>
<tr>
<th>4+ PHC</th>
<th>5+ PHC</th>
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<tbody>
<tr>
<td>Milt + PM for 10 d</td>
<td>AmB (5mg/kg) + Milt for 7d</td>
</tr>
</tbody>
</table>

District Hospital/ Referral centre

| 1-2 sites eg. RMRIMS, Sadar Hospital, Medical colleges |
| Referral Centres (special cases) |
| SDA (10mg/kg) |
| Other VL treatments if SDA contraindicated or unavailable |

**PROJECT DESIGN**

- Treatment by Government doctors/staff except Hajipur
- Training: GCP + KA case management
- Upgradation of health centers e.g. lab, ILR, drugs, diagnostic kits
- IEC team: training of ASHA

**ETHICAL CLEARANCE:**

RMRIEC, MSF-ERB, LSHTM

**ASSSESSMENT:**

Assessment at 6 months and 12 months
Enrolment (n=1761)
Study Duration Aug 2012-Sep 2015

District Hospital: 1430
PHC: 235

Saran District n= 498
Chapra District n= 378
Children n=181
Adults n=197

RMRI n= 96
PHCs (Adults) n=120
Baniyapur PHC n=61
Dariyapur PHC n=42
Marourha PHC n=17

Vaishali District n= 1167
PHC (Adults) n= 115
Vaishali PHC n=33
Raghopur PHC n=41
Mahua PHC n=25
Mahnar PHC n=10
Goroul PHC n=6

Adults ≥ 12 (n=1250, 71%)
Children <12 (n=511, 29%)
## Results – Initial Outcome (n = 1761)

<table>
<thead>
<tr>
<th></th>
<th>SD AmB</th>
<th>AmB+MF</th>
<th>MF + PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients started on treatment (n=1761)</td>
<td>891</td>
<td>358</td>
<td>512</td>
</tr>
<tr>
<td>Initial cure at day 10 (%) (95% CI)</td>
<td>884 (99.2%) (95%CI-98.6-99.8)</td>
<td>354 (99.0%) (CI-98.3 – 100.0)</td>
<td>508 (99.2 %) (CI-98.4- 99.9)</td>
</tr>
</tbody>
</table>
## Results - Final Outcome (Worst Case Analysis)

<table>
<thead>
<tr>
<th></th>
<th>SD AmB</th>
<th>AmB+MF</th>
<th>MF + PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients followed up at 6 mnth (n=1761)</td>
<td>891</td>
<td>358</td>
<td>512</td>
</tr>
<tr>
<td>Cure at 6 month</td>
<td>810 (90.9%) (95%CI-89.0-92.8)</td>
<td>314 (88.0%) (95%CI-85.5-92.1)</td>
<td>496 (97.0%) (95%CI-95.6-98.5)</td>
</tr>
<tr>
<td>Relapse rate (n=64) Defaulter</td>
<td>43 (4.8%)</td>
<td>19 (5.3%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>Lost to Follow Up (n=66)</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Treatment stopped by doctor for side effects</td>
<td>34</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Number of patients followed up at 12 months (n=1457)</td>
<td>755</td>
<td>314</td>
<td>388</td>
</tr>
<tr>
<td>Relapse Rate (n =11) PKDL(n=15)</td>
<td>2 (0.3%)</td>
<td>6 (2%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td></td>
<td>02 (0.2%)</td>
<td>01 (0.3%)</td>
<td>12 (3.0%)</td>
</tr>
<tr>
<td>Lost To Follow Up (n= 96)</td>
<td>50</td>
<td>21</td>
<td>25</td>
</tr>
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## Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>SD AmB N=891</th>
<th>LAmB + MF N=358</th>
<th>MF + PM N=512</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Adverse Events Reported</td>
<td>174 (19.5%)</td>
<td>137 (38.4%)</td>
<td>123 (24%)</td>
</tr>
<tr>
<td>No. of subjects with at least one AE n(%)</td>
<td>133 (14.9%)</td>
<td>90 (25.2%)</td>
<td>92 (18%)</td>
</tr>
<tr>
<td>Drug Related Serious Adverse Events n(%)</td>
<td>2* (0.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Non-Drug Related Serious Adverse Events n(%)</td>
<td>3** (0.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

AE captured during start of treatment to EOT
All SAE resolved
Limitations of Study

• Children **not** treated at Primary Health Centre level and treated at District Hospital only as per regulatory recommendation
• Patients admitted and provided treatment at Saran District Hospital for MF/PM
• Patients referred from PHC/Saran District Hospital to higher centre for parasitology
• Biochemistry tests done only at District Hospital
Conclusion and Recommendations

• Combination regimens and SDA are safe and effective treatment in public health sector at field level and feasible to implement at large scale to facilitate VL elimination

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

• Combination regimen to be choice of treatment at sites where cold chain cannot be deployed

• Relapses continue to occur after 6 month post treatment, need to Follow up patients for 12 month within national program in region to generate further evidence on relapse

• Cohort Event Monitoring should be strengthened at all sites in India to document long term outcome data and adverse drug reaction to identify relapse, PKDL, treatment failure, ADRs
Acknowledgements

- State Health Society Bihar
- Rajendra Memorial Institute of Medical Sciences
- Médecins Sans Frontières
- National Vector Borne Disease Control Programme
- All Government Doctors, staff involved in study
Thank you