Challenges in the treatment of Kala-azar in the Indian sub-continent

Dr Suman Rijal, MRCP (UK), FRCP (Edin.), PhD
Head, DNDi India Regional Office
New Delhi, India
Kala-azar reported cases (average 2004-08) and estimates

<table>
<thead>
<tr>
<th>Region</th>
<th>Cases reported/year</th>
<th>Estimated annual cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>America</td>
<td>3,661</td>
<td>5,000 to 7,000</td>
</tr>
<tr>
<td>West Africa</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>East Africa</td>
<td>8,569</td>
<td>30,000 to 40,000</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>875</td>
<td>1,500 to 2,000</td>
</tr>
<tr>
<td>Middle East &amp; Central Asia</td>
<td>2,496</td>
<td>5,000 to 7,500</td>
</tr>
<tr>
<td>Indian Subcontinent</td>
<td>42,619</td>
<td>160,000 to 320,000</td>
</tr>
<tr>
<td></td>
<td>58,220</td>
<td>201,500 to 376,500</td>
</tr>
</tbody>
</table>
Challenges in the treatment in kala-azar

- Access to care
- Efficacy and tolerability of current anti VL treatment
- Cost of anti VL treatment
- Emergence of parasite drug resistance
- Others: HIV-VL co-infections
Kala-azar: access to clinical care

PCA of asset index (Boelaert, 2009)

83% HH from the 2 lowest quintiles

Women high CFR in Bangladesh (Ahluwalia, 2003)

- CFR 19% among adult women, compared with 6-8% among other demographic groups
- Female patients were ill longer than males before they received treatment

High VL CFR in tribal populations in Bangladesh (Huda, 2014)

- 51 094 population from Godagari (16% tribals) and Trishal upazilla: screened for VL deaths
- Mean VL CFR 6.12% (12/196); 75% (9/12) occurred at home
- CFR in the tribal ethnic 17 times higher. OR 18 (95% CI 3.6, 90.6)
Delay in treatment and outcome in kala-azar

- Anaemia, severe malnutrition and long duration of illness: increased risk for mortality (Collin 2004)

- Increased failure to SSG was significantly associated with fever for ≥12 weeks [odds ratio (OR) = 7.4] (Rijal 2009)

- Low patient satisfaction with public health services for ease of access or time provider spent with patient (Banjara 2012)

Choice of health care provider (Mondal et al 2009)

![Choice of health care provider chart]

- Bangladesh/Rajshahi
- Nepal/Mahottari
- India/Muzaffarpur
- India/Vaishali

DNDi
Drugs for Neglected Diseases initiative
Currently available drugs

- AmBisome
- Amphotericin B
- miltefosine
- Antimonials
- Paromomycin
Currently available treatments for kala-azar

Limitations of current treatment:
- costly
- poorly tolerated
- difficult to administer
- long dosing/treatment
- not adapted to high temperatures

What is needed:
- simple oral combination therapy
  - maintain or improve efficacy
  - prevent or delay emergence of resistance
  - reduce treatment duration and cost
  - pan-geographic use
  - could be used for PKDL, HIV-VL, asymptomatic carriers
Pentavalent antimonials failure rates 1980 -1997
Deaths due to cardiotoxicity
33% (8/23) deaths with the new batch died (Rijal 2003)

SEVERE CARDIOTOXICITY: 3/8 deaths
HIGH-OSMOLARITY LOT OF SSG (Sundar 1998)
Miltefosine

- Only oral drug for kala-azar
- 28 days regimen: compliance a challenge
- Potentially teratogenic: contraception for 4 months in women of child bearing age group
- Common adverse events
  - Vomiting: 38%; Diarrhoea: 20%
  - ↑ Transaminase: 15%; Renal dysfunction: 10%
  - 2% severe adverse event (phase 4 trial India) (Bhattacharya 2007)
Miltefosine: increasing treatment failure

- 85% Cure rate in per protocol analysis. *Rahman, 2011*

- Relapse in up to one-fifth of the MIL-treated patients observed. *Sundar, 2012; Rijal, 2013.*

- Treatment failure not associated with re-infection, compliance, drug resistance. Age < 12 = risk factor for failure *Rijal 2013*

- Achieving a sufficient exposure to miltefosine is a significant and critical factor for VL treatment success. *Dorlo 2014*

- Not (yet) MIL-resistance in natural populations; isolates with higher tolerance in PKDL-treated patients (2 rounds of treatment). *Bhandari, 2012*
Liposomal amphotericin B: Ambisome

- Shorter treatment, low toxicity.
- Cost US $ 200/ vial; requires cool chain (2 to 25 C)
- December 2011, Gilead to donate 445,000 vials of AmBisome over five years
- Single dose Ambisome (10 mg/kg): Cure rate
  - Phase III: 95.7% (95% CI 93.4;97.9) Sundar 2010
  - Feasibility study sub-district hospitals Bangladesh: 97% cure rates. Mondal 2014
- Currently 1st line treatment in Bangladesh, India and Nepal.
### Combination regimens

#### Multidrug treatment with standard therapy for VL in India  Non inferiority Phase III. Sundar 2010

<table>
<thead>
<tr>
<th>Regimens (no. of pt.)</th>
<th>Ampho B (157)</th>
<th>AmB+PM (158)</th>
<th>AmB+Milt (160)</th>
<th>PM+Milt (159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure 6 month % (95% CI)</td>
<td>93 (87.5-96.3)</td>
<td>97.5 (93.2-99.2)</td>
<td>97.5 (93.3-99.2)</td>
<td>98.7 (95.1-99.8)</td>
</tr>
</tbody>
</table>

#### A Phase III, Open Label, Randomized, Non Inferiority Study in Bangladesh, 2014.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Ambisome 156</th>
<th>AmB+PM 159</th>
<th>AmB+Milt 142</th>
<th>PM+Milt 142</th>
</tr>
</thead>
<tbody>
<tr>
<td>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>

#### Safety and Effectiveness of new treatment modalities at field level in India (2011-14)

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Ambisome 506</th>
<th>AmB+Milt 294</th>
<th>PM+Milt 302</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final Cure at 6 month (%)</td>
<td>94.7</td>
<td>90.1</td>
<td>97.4</td>
</tr>
</tbody>
</table>
• Resistance to the combinations miltefosine/paromomycin and SbIII/paromomycin is easily inducible.
• The outcomes have been validated in intracellular amastigotes.
• Long-term efficacy of drug combinations with paromomycin?
HIV-VL co-infection and outcome

- Screening 2077 VL patients (≥14 years) for HIV: 5.6% HIV +ve (Burza 2014)
- Estimated mortality risk:
  - 6 months: 14.3%
  - 12 months: 22.4%
  - 24 months: 29.7%
- Estimated risk of relapse:
  - 1 year: 16.1%
  - 2 years: 20.4%
  - 4 years: 25.9%
- ART treatment: 64–66% reduced risk of mortality and 75% reduced risk of relapse
Conclusions

- Access to care related to socio-economic class remains a challenge. Active case finding strategies would help.

- Treatment failure to current drugs trend to increase over time. Limited no. of treatments available at present.

- Resistance to drugs demonstrated. Monotherapy of miltefosine and paromomycin recommended to be stopped and replaced by SAB or combinations.

- **Recommendation to programme: Monitoring !**
  - Treatment effectiveness e.g cohort event monitoring
  - Drug resistance (also for drug-combinations)
  - Drug quality, dosage, access …
  - HIV co-infections
THANK YOU

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