Effectiveness of single dose chemotherapy in paucibacillary leprosy patients (O039)

Summary of evidence from clinical trials in India

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Introduction (1/2)

• Pauci-bacillary (PB) leprosy forms substantial proportion of new cases: 50-55% Bangladesh; Sri Lanka, Nepal & India (2012)
• Poor compliance for long-term therapy reported in leprosy programmes
• Experimental evidence suggests that 6-month treatment unnecessarily long for PB
• 1994-2003: Randomized double-blind placebo-controlled trials in India for PB with single or 2-3 or 2-5 lesions
Introduction (2/2)

• Objectives of these PB trials
  – **Primary**: Determine safety & efficacy of ROM regimen in terms of complete clearance of lesions
  – **Secondary**: Estimate & compare treatment failure or relapse rates

• Present a comparative analysis of findings from these trials
ROM for PB leprosy: Recent systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupte MD (WHO Report)</td>
<td>2006</td>
<td>0.95 (0.87, 1.02)</td>
<td>61.03</td>
</tr>
<tr>
<td>Deshmukh et al</td>
<td>2003</td>
<td>1.20 (0.75, 1.93)</td>
<td>1.64</td>
</tr>
<tr>
<td>MCT Group (2–3 lesions)</td>
<td>2001</td>
<td>0.82 (0.59, 1.14)</td>
<td>3.48</td>
</tr>
<tr>
<td>MCT Group (single lesion)</td>
<td>1997</td>
<td>0.86 (0.77, 0.95)</td>
<td>33.84</td>
</tr>
<tr>
<td>Overall (I² = 21.2%, P = 0.283)</td>
<td></td>
<td>0.91 (0.86, 0.97)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Tropical Medicine and International Health

M. S. Setia et al. ROM therapy in leprosy: a systematic review and meta-analysis
Trials on single-dose ROM for PB leprosy

• Initial study on single-lesion PB documented single-dose ROM as effective as WHO-PB-MDT
  – India implemented ROM regimen for single-lesion PB [subsequently given up]
• Comparable results in the second study among PB with 2-3 skin lesions
  – Follow-up only for 18 months & small sample size
• Similar study among PB with 2 to 5 lesions with adequate sample size & long-term follow-up
Methods (1/2)
Single-dose ROM trials for PB leprosy

- **Study design**
  - Randomised, double blind, controlled field trial with randomization at individual level

- **Sample size**
  - Based on equivalence for complete clearance of skin lesions; 80% power; 5% $\alpha$ error

- **Study drugs**
  - **ROM**: Rifampicin 600 mg, Ofloxacin 400 mg & Minocycline 100 mg & placebo equivalent of WHO-PB-MDT for 6 months
  - **WHO-PB-MDT**: Rifampicin 600 mg once monthly & dapsone 100 mg daily for 6 months
Methods (2/2)

Single-dose ROM trials for PB leprosy

• Inclusion criteria
  – Untreated; Negative skin smear & not more than one peripheral nerve trunk involvement

• Exclusion criteria
  – Age < 5 years; with reversal reaction & / or neuritis; pregnant women; known drug allergy; known HIV +

• Study settings in India
  – District leprosy control units, NGO operated leprosy service hospital and out-patient facility of a leprosy research institute

• Approvals of Ethics committees of NIE/WHO were obtained
## Sample size, study sites and follow-up

### Single-dose ROM trials for PB leprosy

<table>
<thead>
<tr>
<th># lesions</th>
<th>Sample size</th>
<th>Period</th>
<th># study sites</th>
<th>Post-treatment follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single lesion</td>
<td>1483 (ROM=744; MDT=739)</td>
<td>1994-95</td>
<td>9</td>
<td>18 months</td>
</tr>
<tr>
<td>2-3 lesions</td>
<td>236 (ROM=118; MDT=118)</td>
<td>1995-96</td>
<td>5</td>
<td>18 months</td>
</tr>
<tr>
<td>2-5 lesions</td>
<td>1526 (ROM=762; MDT=764)</td>
<td>1998-03</td>
<td>5</td>
<td>36 months (5 sites) 48 months (2 sites; n=1082)</td>
</tr>
</tbody>
</table>
Outcome assessment
Single-dose ROM trials for PB leprosy

• **Post-treatment follow-up every 6 months:** Assigned score based on clinical criteria

• **Efficacy:** Complete disappearance of all lesions OR reduction in clinical score from base-line

• **Deterioration or treatment failure:** New active skin lesion, definite signs /symptoms of new nerve damage, skin smear positive at any site

• **Relapse:** New active skin lesions with or without positive skin smear

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**Operational criteria for assigning scores**

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Assigned score</th>
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<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Appearance of lesion</td>
<td>Clearly visible</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>Marked</td>
</tr>
<tr>
<td>Erythema</td>
<td>Marked</td>
</tr>
<tr>
<td>Infiltration</td>
<td>Marked</td>
</tr>
<tr>
<td>Anaesthesia</td>
<td>Complete loss</td>
</tr>
</tbody>
</table>
Data analysis
Single-dose ROM trials for PB leprosy

• Calculated relapse rates per 100 person-years
  – Calculated rate ratio (RR) and 95% confidence interval (CI)

• For PB 2-5 study with additional follow-up
  – Used multiple longitudinal regression analysis by generalized-estimating-equations (GEE) to identify factors associated with clinical scores over follow-up period
### Primary outcome

**Single-dose ROM trials for PB leprosy**

<table>
<thead>
<tr>
<th>PB category</th>
<th>Primary outcome (ROM vs. PB-MDT)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>% complete clearance of lesions</td>
</tr>
<tr>
<td>Single lesion</td>
<td>47% vs. 55%  (p=0.004)</td>
</tr>
<tr>
<td>2-3 lesions</td>
<td>38% vs. 46%  (p=0.3)</td>
</tr>
<tr>
<td>2-5 lesions</td>
<td>72% vs. 72.1% (p=0.95)</td>
</tr>
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</table>
### Secondary outcome

Single-dose ROM trials for PB leprosy

<table>
<thead>
<tr>
<th>PB category</th>
<th>Secondary outcome (ROM vs. PB-MDT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single lesion</td>
<td>Treatment failure</td>
</tr>
<tr>
<td></td>
<td>0.9% vs. 0.9%</td>
</tr>
<tr>
<td>2- 3 lesions</td>
<td>3.8% vs. 3.8%</td>
</tr>
<tr>
<td>2- 5 lesions</td>
<td>Relapse: 1.13 vs. 0.35 per 100 PY; (p=0.001)</td>
</tr>
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</table>
Findings from follow-up of 48 months
Single-dose ROM trials for PB leprosy

- **Efficacy:** 75% vs. 79% (p=0.25)
- **Relapse:** 0.64 vs. 0.3 per 100 PY (p=0.07)
  - Majority occurred within 18 months of follow-up (14/17 vs. 6/8)
- Multiple regression analysis for clinical scores
  - Increased with age
  - Declined with follow-up time
Conclusions

• Single-dose ROM equally efficacious to six month WHO-MDT regimen for all types of PB leprosy
Recommendations

• Single-dose ROM could be an alternative treatment regimen for PB leprosy
  – Suggest careful post-treatment follow-up & counseling to watch signs of relapses

• Trials with additional dosing ROM may be done in treating relapses
THANK YOU
Acknowledgement

• The Director General of Indian Council of Medical Research for funding participation in the ILC 2013
• Dr. Sanjay Mehendale, Director, National Institute of Epidemiology
• Prof. MD Gupte, ICMR Chair in Epidemiology
• WHO for funding the studies