CLINICAL CHARACTERISTICS AND OUTCOME IN MULTIBACILLARY (MB) LEPROSY PATIENTS TREATED WITH 12 MONTHS WHO MULTIDRUG THERAPY REGIMEN (MDT MBR): A RETROSPECTIVE ANALYSIS OF 730 PATIENTS FROM INDIA

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Chemotherapy of leprosy

**Historical developments**

1854- Chaulmoogra oil (*hydnocarpus*)

1943- Sulphones

1962- Clofazimine

1972- Ethionamide, prothionamide

1968- Rifampicin

1970s- Secondary dapsone resistance

1981- Multidrug therapy (MDT), MB, PB regimens

1994- MDT MBR 24 months

1997- MDT (MBR) – 12 months
Ideal duration of MDT MBR?

- Time required to reduce the size of viable bacterial population to such an extent that the rifampicin (RMP) resistant mutants are completely eliminated and majority of drug susceptible organisms are killed.
7th WHO Leprosy Expert Committee (1997)
12 months MDT MBR

- RMP kills *M. leprae* very fast (99.9% with a single dose)
- RMP-resistant mutants in a LL case are likely to be eliminated by 3 to 6 months of treatment with DDS-CFZ
- Encouraging observations of good response even in defaulters taken MDT MBR < 1 year
Success of WHO MDT & Leprosy Control Programs

- Since 1985, about 16 million cases have been cured
- About 4 million handicaps have been averted
- There are only sporadic reports of drug resistance
- 2012- 1 endemic country (1985: 122)
Prevalence of leprosy - WHO region 2012 and end of first quarter 2013

(Weekly epidemiological record 30 August 2013)

<table>
<thead>
<tr>
<th>WHO region</th>
<th>No. of cases registered (PR) /10,000 population</th>
<th>No. of new cases /100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>African</td>
<td>17 540 (0.26)</td>
<td>20 599 (3.05)</td>
</tr>
<tr>
<td>Americas</td>
<td>33 926 (0.39)</td>
<td>36 178 (4.14)</td>
</tr>
<tr>
<td>South-East Asia</td>
<td><strong>125 167 (0.68)</strong></td>
<td><strong>166 445 (8.98)</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(India 134 752)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.78</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>4960 (0.08)</td>
<td>4 235 (0.72)</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>7 425 (0.04)</td>
<td>5 400 (0.30)</td>
</tr>
<tr>
<td>TOTAL</td>
<td><strong>189 018 (0.33)</strong></td>
<td><strong>232 857 (4.00)</strong></td>
</tr>
<tr>
<td></td>
<td>[India 91 743] (0.73)</td>
<td>(58% India)</td>
</tr>
</tbody>
</table>

NLEP Record 2012-13
Declining Leprosy Prevalence in India

- **June 2007**
  - National PR: 0.80/10,000
  - Elimination achieved in 33 States (35)

- **March 2001**
  - PR: 3.74/10,000

- **1981**
  - PR: 57.6/10,000
  - Elimination achieved in 32 out of 35 States/Union Territories

- **March 2013**
  - PR: 0.73/10,000
  - 528 districts (81.36%) – (total 649) PR<1/10,000 population
Objective:

- The reported follow up of patients treated with 12 months MDT MBR has not been for an ideal length of time

- To analyse the long term efficacy of this treatment regimen in MB leprosy patients
Methods

- Retrospective study - leprosy clinic records (1999 to 2010)
- Diagnosis: *Ridley-Jopling* classification & Clinical classification for control programs
- All patients were administered the MDT as per the recommendations of WHO
- 1369 leprosy patients registered, adequate clinical information available for 1210 subjects
- Slit Skin smears: baseline and 6 monthly
- Skin biopsy: baseline and end of treatment
Follow up

- After release from treatment (RFT), patients were followed up from a minimum of 9 months up to a maximum of 10 years, till the time of analysis.

- Initial 2 years - reviewed 1-3 monthly; later 6 monthly or less frequently.

- To report whenever they experienced symptoms suggestive of reactions/NFI. Incidence, type, severity, time of onset noted.

- Correlation with bacterial load or other parameters noted and analyzed.
Epidemiological profile (MB cases)

- Only 270 (37%) patients were local residents of Chandigarh
- Rest 460 (63%) were from other neighbouring Northern states of India states like
  - Uttar-Pradesh 139 (30.2%)
  - Bihar 85 (18.5%)
## Results

1210 patients: 480 (39.6%) - PB

730 (60.3%) - MB disease

### Demographic and clinical profile of study population (MB patients)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>≤20</th>
<th>21-30</th>
<th>31-40</th>
<th>41-50</th>
<th>51-60</th>
<th>&gt;60</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>BT</td>
<td>57</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>18</td>
<td>20</td>
<td>245 (33.5%)</td>
</tr>
<tr>
<td>BB</td>
<td>0</td>
<td>06</td>
<td>06</td>
<td>07</td>
<td>07</td>
<td>03</td>
<td>29 (3.9%)</td>
</tr>
<tr>
<td>BL</td>
<td>33</td>
<td>92</td>
<td>42</td>
<td>24</td>
<td>09</td>
<td>02</td>
<td>202 (27.6%)</td>
</tr>
<tr>
<td>LL</td>
<td>18</td>
<td>70</td>
<td>52</td>
<td>19</td>
<td>31</td>
<td>44</td>
<td>234 (32.%)</td>
</tr>
<tr>
<td>PNL</td>
<td>0</td>
<td>7</td>
<td>12</td>
<td>01</td>
<td>0</td>
<td>0</td>
<td>20 (2.7%)</td>
</tr>
</tbody>
</table>
Clinical Profile

- The majority of the patients belonged to the borderline group (476, 65.2%) followed by LL (234, 32%)

- BT - as MB case
  - skin lesions > 5 in number,
  - lesions located on ≥ 2 distant sites,
  - >1 enlarged nerve trunk or
  - a positive SSS

PNL - as MB (Two or more thickened nerves)
Disease Duration – at presentation

- < 6 months: 349 (47.8%)
- 6 to 12 months: 213 (29.2%)
- >12 months: 168 (23%)
Bacteriological Index (BI)

313 (42.9%) patient: BI ≥3+
Correlation (Clinical & Histopathological Diagnosis)

- Histopathological Diagnosis:
  - 29 (BB)
  - 6
- Clinical Diagnosis:
  - 234 (LL)
  - 202 (BL)
  - 245 (BT)

Total:
- Clinical: 245 (BT)
- Histopathological: 29 (BB)

49.5% correlation
Leprosy Reactions

Type 1 Reaction
243 (33.3%)

Type 2 Reaction
158 (21.6%)

Total cases
401 (54.9%)
Leprosy reactions

**Type 1 reaction:** Only skin lesions were affected in 78.1% (190/243) patients and the remaining had involvement of both skin and nerves.

Recurrent Type 1 reaction was observed in 12 patients in FU period (up to 4 years).

**Type 2 reaction:**

- 158 (21.6%) patients experienced type 2 reactions.
- Recurrent ENL were seen in 14 patients who had a high initial BI ≥3+ and half of these cases continued to manifest ENLs even after 5 years of stopping the treatment though with lesser frequency and severity.
Time of onset of type 1 reaction episodes

At Regn. | 0-6mths | 7-12mths | 2nd yr. | ≥ 3 years
---|---|---|---|---
5 | 2 | 1 | 2 | 1
59 | 20 | 1 | 3 | 3
11 | 3 | 1 | 2 | 2
95 | 28 | 6 | 4 | 4

LL(9/234) | BL(85/202) | BB(14/29) | BT(135/245)
Time of onset of type 2 reaction episodes

At Regn. 8 30
At 7-12 mths 1 17
2nd yr. 12 50
3-5 yrs 6 7
> 5 yrs. 2 7
0-6 mths 4 14

BT(0/245) BL(33/202) LL(125/234)
Deformities

372 (Total deformities)

Grade I: 107 (14.7%)
Grade II: 265 (36.3%)

At time of registration: 65%
During treatment: 20%
Follow up: 15%
Deformities
Follow up (skin lesions)

- Average time: 11-15 months
- Total clearance 9 months-3 years
- Took longer time to heal

Average time: 11-15 months
At the end of treatment - overall regression in the inflammation and reduction in the size of granulomas in all except 16.7% (122/730) patients.

14 of these patients suffered from recurrent ENLs. 2 relapsed 3 years after RFT
Follow up

- Four patients treated (persistent active skin lesions & BI) with alternative therapy (ofloxacin and minocycline along with dapsone and clofazimine) - clinical improvement in form of reduction in infiltration of the plaques started by 2 months and cleared by 18 months of therapy.

- Very few patients (1.2%) presented with vague neuropathic pain during the surveillance period.
Becx –Bleumink criteria for relapse

- Appearance of new skin lesions,
- New activity in previously existing skin lesions,
- Increase of bacteriological index (BI) 2 or more in two sets of skin smears,
- BI becoming positive in a previously negative patient,
- New nerve function loss,
- Histological evidence of relapse in skin or nerve biopsy
Relapse Cases

After 3 years of RFT – Total cases 13

13 Clinical & Histopathological features

- Males
- Initial Bl>=3+
- LL features

2 Recurrent ENL

All patients were restarted on MDT MBR - clinical & histopathological improvement on completion of 12 months MDT.
## Relapse rates in MB cases: 12 months MDT MBR

<table>
<thead>
<tr>
<th>S.No</th>
<th>Study</th>
<th>Treatment regimen</th>
<th>Number of patients</th>
<th>Follow up duration</th>
<th>Relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kaur I et al. (2002)</td>
<td>12 months MDT MBR + Mw vaccine</td>
<td>136</td>
<td>2-3 years</td>
<td>2.2</td>
</tr>
<tr>
<td>2</td>
<td>Desikan et al. (2008)</td>
<td>12 months MDT MBR</td>
<td>660</td>
<td>Few months to 12 years</td>
<td>0.76</td>
</tr>
<tr>
<td>3</td>
<td>Kyaw et al. (2008)</td>
<td>12 months MDT MBR</td>
<td>200</td>
<td>Few months to 8 years</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>Katoch et al. (2008)</td>
<td>12 months MDT MBR + Mw vaccine</td>
<td>100</td>
<td>9-10 years</td>
<td>5.7</td>
</tr>
<tr>
<td>5</td>
<td>Present study</td>
<td>12 months MDT MBR</td>
<td>730</td>
<td>9 months to 10 years</td>
<td>1.7</td>
</tr>
</tbody>
</table>
Major highlights of the study

- Lesions in majority of the patients had healed at the end of therapy

- Nearly 50% patients presented with lepra reaction. Type 1 reactions were more often seen as compared to Type 2 reactions

- Both types of reactions became less frequent after the introduction of MDT MBR and finally ceased. However, it took longer in case of Type 2 reactions
WHO Grade 2 deformity was observed in 265 patients (36.3%) and 107 (14.7%) had Grade 1 deformity at the time of presentation.

Grade 1 deformities worsened in a considerable number of patients (93/107) after initiating MDT (reactions/continued nerve damage), however overall improvement in grade 1 & 2 deformities during treatment/FU
Major highlights of the study

- Clinico-histological correlation was seen in 49.5% of the patients

- Patients who relapsed had a higher initial Bl of ≥3+, male sex, LL disease, high MI (up to 20%)

- All patients had tolerated the MDT MBR treatment without any significant adverse reactions
Conclusions

- Thus, the recommendation for 12 months MDT MBR for all MB patients is robust and an operationally practical decision.

- It will positively help in further reducing the overall prevalence, transmission, ANCDR, and reducing the rate of new cases with Grade 2 deformities as envisaged in the WHO enhanced global strategy (plan period 2011-2015).
“Enhanced Global Strategy for Further Reducing Disease Burden due to Leprosy”

(WHO plan period: 2011-2015)

Moving towards -

**Equity, Quality, Sustainability & Prevention of Disabilities**
The battle against leprosy...

WORKING TOGETHER

Thank you