Clinical, bacteriological and histopathological study of 62 referral relapse cases between Jan 2004 and Dec 2009 at the Foundation for Medical Research, Mumbai

VANAJA P. SHETTY*, ANJU V. WAKADE*, SUNIL D. GHATE* & VIVEK V. PAI**
*The Foundation for Medical Research, 84- A, R.G. Thadani Marg, Worli, Mumbai – 400 018, India
**Bombay Leprosy Project, Vidnyan Bhavan, V.N. Purav Marg, Sion, Chunnabatti, Mumbai – 400 022, India

Accepted for publication 25 March 2011

Summary
Sixty two patients with relapsed leprosy seen between Jan 2004 and Dec 2009 were studied using clinical, bacteriological and histopathological parameters. The findings thus obtained were correlated to parameters such as trend and source of referral, clinical characteristics at diagnosis, treatment received, other events during or after RFT and duration between cessation of treatment and relapse.

Findings: Referrals per year have doubled since 2006. Most patients were referred by NGOs (58%), followed by Govt. hospitals (16%) and then by GPs (25%); 76% had received one of the WHO – MDT regimens including 16 treated with 24 months or more MB – MDT, 23 with 12 months MB – MDT and eight with 6 months PB – MDT. Of the remaining 14 cases, four had received DDS mono-therapy, seven had single dose of Rifampicin, Ofloxacin and Minocycline (ROM) and four Rifampicin and Ofloxacin (RO) daily for 28 days. The average incubation time of relapse, defined as duration between cessation of treatment and relapse was (SD) +6·4 years. 59% of patients had positive slit skin smears on relapse. Relapse for the second time occurred in six BL cases including five from group 2 and one RO treated patient and 11/23 cases from group 2 conferred to BT-BB leprosy. Clinical features at diagnosis and on relapse were comparable in 47% of cases.

Conclusion: All leprosy patients, regardless of their type and MDT regime, carry ‘risk of relapse’. A shorter treatment duration reduces the incubation time to relapse. In group 2 (treated with 12 months MB-MDT regime) 11/23 were BT-BB cases and 5/23 (21%) were relapse for the second time, which further supports our earlier documented findings14,23 and maybe the efficacy of WHO-MDT regime is poor in a small subset of patients.
Introduction

The success of multi-drug therapy (MDT) propelled WHO to propose a set target for elimination of leprosy by the year 2000.¹ In 2001, during the 54th World Health Assembly, WHO declared that leprosy had been eliminated as a global public health problem.² The failure to realise the target date for elimination in India and several other countries, caused WHO to propose a plan called “The final push: 2000 to 2005” where the target date was shifted to 2005.³ In keeping with the WHO guidelines, Government of India (GOI) in the year 1996 introduced fixed duration MDT i.e. 12 months with three drugs for patients with five or more lesions (multi-bacillary-MB) cases and 6 months with two drugs for patients with less than five lesions (pauci-bacillary-PB).⁴,⁵ In 2002–2004 integration of leprosy services with the general health system occurred and in 2005 India declared elimination of leprosy at the country level.⁶,⁷

A major thrust since 1996 has been on reducing the prevalence rate (PR). More than 14 million patients have received MDT since 1982 and the number of registered patients has decreased from 5 million in 1985 to less than 0·25 million in 2008.⁸ The WHO elimination goal indeed created a broad and strong commitment to the fight against leprosy. However, a number of new cases detected globally has changed very little indicating that the use of MDT has not impacted disease transmission.⁹,¹⁰

The rate of relapse is the single most important tool, to measure efficacy of MDT in leprosy.¹¹ However, there is no surveillance system to record the number of relapse cases occurring in the community particularly with untested short term regimens.¹² The duration between cessation of treatment and relapse (DCTR) lie anywhere between 2 and 15 years.¹³,¹⁴ Under these circumstances a careful documentation of relapse cases under different settings is of significant value in evaluating the underlying problem and assessing the efficacy of treatment. At the Foundation for Medical Research (FMR) we have been recording and investigating all the referral problem cases since 1997. The findings of 52 such cases during 1997 to 2003 were published in 2005.¹⁴ The trends and characteristics of an additional 62 relapse cases recorded during Jan. 2004 to Dec. 2009 are discussed here.

Objective

To document and study the characteristics of relapse cases referred to FMR.

Material and Methods

All patients referred with leprosy relapse were carefully documented using a pre-set format. Their history was taken to record the symptoms at diagnosis, treatment details, other events (if any) during and after release from treatment and its management. This was followed by a clinical and neurological examination; body charting and a slit skin smear (SSS). An incision biopsy was taken from one of the active lesions in all the patients after informed consent. Only cases confirmed as relapse, using both clinical and histopathological criteria defined as below are included in this study.

Clinical definition of relapse: Recurrence of lesions or increase in size and/or number of lesions over a period of time after the release from a prescribed treatment regime. Patients presenting with ‘sudden onset’ increase in size or number of lesions are first treated
with a course of corticosteroids (i.e. 40 mg tapering dose for 12 weeks). Histopathological definition of relapse: Granulomatous infiltrate indistinguishable from an untreated case. Histopathological findings were also used to classify the patient along the Ridley-Jopling scale.\textsuperscript{15}

Findings on relapse were further analysed in relation to source of referral, treatment received, presenting symptoms at diagnosis vs. on relapse, leprosy class, response to treatment, duration between recurrence of problem and health seeking, interim time between disease episodes etc.

**Results**

**TREND AND SOURCE OF REFERRAL**

The number of referred relapse cases at FMR has doubled since 2006.

Of these 62 patients studied, 36 (58%) were referred by Non Government Organisations (NGOs) within the city and suburbs of Mumbai, including the Bombay Leprosy Project (BLP), the Association for Leprosy Education Rehabilitation and Treatment (ALERT- India), Lok Seva Sangam (LSS), Maharasstra Lokhit Seva Mandal (MLSM) and Kusthog Nivarana Samiti (KNS); ten (16%) by Government hospitals and 16 (25%) by general practitioners (GPs) within the city of Mumbai. All the patients were residents of Maharashtra.

**DETAILS OF PREVIOUS TREATMENT**

Table 1 shows that forty seven cases (76%) had received one of the WHO MDT regimes to include; 16 treated with 24 months or more (till smear negativity) MB – MDT (Group 1), 23 treated with 12 months of MB – MDT (Group 2) and eight with 6 months of PB – MDT (Group 3). Of the remaining 14 cases (Group 4); four had received DDS mono-therapy (at a municipality hospital in Mumbai), 7 had received single dose of Rifampicin, Ofloxacin and Minocycline (ROM) and 4 Rifampicin and Ofloxacin (RO) daily for 28 days regime in a trial conducted by BLP.\textsuperscript{17–19}

<table>
<thead>
<tr>
<th>Rx Received</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCD in Maharashtra (MB%)</td>
<td>44192</td>
<td>11059</td>
<td>13844</td>
<td>11182</td>
<td>12397</td>
<td>14274</td>
<td>106948</td>
</tr>
<tr>
<td>MDT- MB x 24 m- (Gr1)</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>16 (25%)</td>
</tr>
<tr>
<td>MDT-MB x 12 m- (Gr2)</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>23 (37%)</td>
</tr>
<tr>
<td>MDT-PB x 6 m- (Gr3)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>Others* (Gr4)</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>15 (24%)</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>3</td>
<td>17</td>
<td>12</td>
<td>11</td>
<td>15</td>
<td>62</td>
</tr>
</tbody>
</table>

* Includes RO, ROM and DDS mono treated cases.
Key: NCD – new cases detected, NA- not available.
A significant proportion (30%) of them had history of reaction and had received corticosteroids. It was further noted that patients were treated and monitored at the sources mentioned above. Duration between recurrence of problem and help seeking varied between 3 to 12 months.

**RESPONSE TO TREATMENT**

On release from treatment (RFT) all had the history of remaining symptom free (clinically) for a period that ranged between 2 and 20 years.

Incubation time of relapse defined as duration between cessation of treatment and relapse (DCTR) in relation to leprosy class during relapse (Table 2).

Some notable observations are: (1) Patients on the lepromatous end of the spectrum had a longer DCTR as compared to the tuberculoid spectrum (BT-BB) thus showing a relationship between incubation time of relapse and leprosy Type. (2) Patients receiving inadequate treatment/shorter duration of treatment had a shorter DCTR. (3) In a significant proportion of patients in groups 2 and 3 the DCTR was less than 5 years. (4) Six out of seven patients receiving ROM treatment and five out of eight patients receiving PB-MDT, on relapse showed BL leprosy.

**CLINICAL FEATURES ON RELAPSE AND AT DIAGNOSIS (TABLE 3)**

Infiltration and nodules was the commonest presentation on relapse (35%) followed by hypopigmented patches (HPPs) seen in 19 (30%) and erythematous patches in 16 (25%). Of the 22 patients with infiltration and nodules on relapse, at diagnosis six had HPPs, 12 had infiltration and nodules while four had erythematous patches. Of the 19 with HPPs on relapse, at diagnosis 12 had HPPs, four had erythematous patches, two were pure neural and one had a nodule. Of the 16 patients with erythematous patches on relapse, at diagnosis nine had HPPs, five had erythematous patches and two were pure neural cases. On relapse, a high proportion of cases (35/58 = 60%) had DG1 or two including 27 with DG2 and eight with DG1.

These findings show that in most cases (47%) clinical features at diagnosis and on relapse were closely comparable exception being four of six pure neural cases who presented with skin lesions on relapse. There was no evidence of upgrading (BL to BT or TT) in any, while

<table>
<thead>
<tr>
<th>Type of Rx received</th>
<th>Total no. of cases</th>
<th>Range of DCTR in relation to leprosy class on relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2–5 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BT</td>
</tr>
<tr>
<td>MDT-MB (24 m)-Group 1</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>MDT-MB (12 m)-Group 2</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>MDT-PB (6 m)-Group 3</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>ROM –Group 4</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>RO-Group 4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>DDS mono-Group 4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Total (%)</td>
<td>62</td>
<td>4</td>
</tr>
</tbody>
</table>

V. P. Shetty et al.238
there was an indication of downgrading in 15 cases (24%). Three patients presented with histoid type of lesions on relapse while at diagnosis they had diffused lesions.

**SLIT SKIN SMEAR (AT DIAGNOSIS AND ON RELAPSE) AND HISTOPATHOLOGY FINDINGS ON RELAPSE**

Of the 62 relapse cases studied 37 (59%) were slit skin smear positive including 31/37 (83%) with an average BI of $\geq 3+$ in six cases the average was 2+. In the remaining 25 cases the slit skin smear was negative. Records of slit skin smear test findings at diagnosis were available in 21 patients (Table 4); 7/8 patients that were SSS negative at diagnosis were also negative on relapse while all 13 that were SSS positive at diagnosis were positive on relapse.

Classification using the Ridley-Jopling scale of the lesion, biopsy showed features of active BT type of leprosy in nine, BB in nine and BL-LLs in 44 cases. The pathology showed features of active leprosy in all and were indistinguishable from an untreated case thus assisted in confirming relapse.

**SECOND RELAPSE**

Six patients (i.e. five among the 12 months MB-MDT treated cases (20%) and one from the RO group – all BL cases) had second relapses. On both occasions the DCTR was 6–10 years. They had received the same regime of treatment when they relapsed first and their response to treatment was good even during the second relapse.

**Table 3. Clinical features on relapse and at diagnosis**

<table>
<thead>
<tr>
<th>Clinical features at diagnosis (no. of cases)</th>
<th>Neural/neuritis</th>
<th>HPP</th>
<th>Erythematous</th>
<th>Infiltration + nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Neural (no.=6)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>HPP (no.=28)</td>
<td>1</td>
<td>12 (43%)</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Erythematous (no.=15)</td>
<td>2</td>
<td>4</td>
<td>5 (33%)</td>
<td>4</td>
</tr>
<tr>
<td>Infiltration + nodules (no.=13)</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>12 (92%)</td>
</tr>
<tr>
<td>Total=62</td>
<td>5</td>
<td>19 (30%)</td>
<td>16 (25%)</td>
<td>22 (35%)</td>
</tr>
</tbody>
</table>

**Table 4. SSS at diagnosis and on relapse**

<table>
<thead>
<tr>
<th>SSS at diagnosis (no. of cases)</th>
<th>0</th>
<th>2+</th>
<th>3+</th>
<th>4+ -5+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (8)</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1+ (4)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2+ (2)</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3+ (5)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4+ -5+ (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total (21)</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>
Discussion

Over the years an increase in the number of relapse cases has been observed at several referral centres in Mumbai. Recently, the National Leprosy Elimination Programme (NLEP) in India has initiated collection of data on relapse. Of the 896 relapse cases reported during the year 2008–2009 from all over India, 141 were from the State of Maharashtra.\textsuperscript{20} The treatment of leprosy has undergone several quick modifications since 1982, and the relapse rate following fixed duration MDT has not been recorded systematically.

In this centre, yearly referrals of relapse cases have doubled since 2006 and the majority were treated with one of the WHO recommended MDT regimen. A large proportion of referrals were by NGOs, we think this reflects the timing of the study; until 2002–2003, most leprosy patients were managed by NGOs in the city and suburbs of Mumbai. The second major source of referrals was by GP’s (25%). It is widely recognised that many patients seek treatment in the private sector though there are no official figures available to support it. A study from north India showed that 13/28 self referral patients (46%) who relapsed at varying time intervals between 3 months and 22 years after stopping MDT were treated by private practitioners and the rest in urban leprosy centres between 2002 and 2007.\textsuperscript{21} More systematic data is indeed needed to know the situation better.

The time between recurrence of clinical symptoms and health seeking was reasonable (\(\sim 3–12\) months), however, 59\% of patients had an average BI of \(\geq 2+\) and 60\% had Grade 1 or 2 deformity, which suggests that there was considerable delay in them recognising clinical symptoms. In keeping with earlier documented findings, the DCTR ranged between 2 and 20 years, the average being (SD) \(+ 6.4\) years.\textsuperscript{13,14} The DCTR was highest (\(> 15\) years) among DDS monotherapy cases, who on relapse presented with nodular leprosy and BI of \(\geq 5+\). While relapse by itself is a very distressing experience to the patient concerned, from the public health point of view they remain the source of infection and transmission in the community.

The 12 months MB-MDT treated group of patients (Group 2) were heterogenous in leprosy type and incubation time of relapse. This is because the simplified classification based on number of lesions (\(> 5\) lesions) include a whole spectrum i.e. BT to LL type of leprosy patients when the Ridley-Jopling scale is applied.\textsuperscript{22,23}

Short course regimens viz ROM single dose for single lesion cases and RO x 28 days for MB cases was tried during the year 1995–96 in several centres across the world including India.\textsuperscript{17–19} Of the seven relapse cases from the ROM group, six were BL-LL, while all four cases from the RO group were BL-LL on relapse. It is very likely that the six cases treated with ROM were on the lepromatous end of the spectrum (BL), highlighting the dogma of classification of leprosy based on the number of lesions, resulting in inadequate treatment.

Notably, patients receiving inadequate treatment/shorter duration of treatment had a shorter DCTR. In a significant proportion of patients in Groups 2 and 3 the DCTR was less than 5 years. Six out of seven patients receiving ROM treatment and five out of eight patients receiving PB-MDT showed BL leprosy on relapse. These findings support the notion that ‘inadequate treatment’ is either due to the wrong classification of patients or the shorter length of treatment which results in the earlier onset of relapse.\textsuperscript{14,24}

The central criteria for the detection of relapse are the clinical determinants such as the reappearance of old lesions or the development of new ones, as it takes longer among lepromatous than tuberculoid cases. Secondly, the observation that all had responded well clinically and had remained symptom free for over 5 years regardless of the regime used as
seen in this as well as earlier studies, suggests that early detection of relapse cannot be relied on clinical parameters alone.\textsuperscript{25} There is a need for better vigilance, periodic slit skin smear examinations and more sensitive tests to detect the presence of viable \textit{M. leprae} to assist in early detection of relapses.

\textbf{IS LEPROSY ELIMINABLE BY MDT?}

Of concern is the occurrence of relapse in BT-BB (11/23 = 47\%) cases despite receiving 12 months of MB-MDT. These findings can be interpreted in two ways: (a) 12 months of MB-MDT in BT-BB cases does not effectively kill the bacilli and eliminate the risk of relapse, or (b) they are re-infected by an exogenous source. Of greater concern are six cases including five from the 12 months MB-MDT treated group (21\%) and one RO treated patient who were relapsing for the second time. Whilst poor efficacy of the RO regime and a high relapse rate has already been documented,\textsuperscript{25,26} it is believed that relapse rate after 12 months’ MB-MDT regime is low. In a multi-centric trial carried out at Cebu, the relapse rate was recorded in 189 multibacillary (MB) leprosy patients treated with four different regimens and followed-up for as many as 12 years after the initiation of treatment. Treatment regimens included WHO MDT – MB (12 m and 24 m), 1 month of daily RO, and 1 year of WHO MDT plus an initial 1 month of daily Rifampicin and daily Ofloxacin. Relapse rates after 9 and 12 years from the initiation of therapy in the three regimens that included WHO MDT were 0–3\%, whereas relapses occurred in those treated with the 1-month regimen alone at a significantly greater rate ($P < 0.05$): 11\% at 9 years and 25\% at 12 years.\textsuperscript{25} Findings from a recent prospective cohort study by FMR indicate poor efficacy of 12 months regime of MDT in MB cases. Over 15\% of 65 BL cases assessed at 6 months post release from 12 months MB-MDT regime showed the presence of viable \textit{M. leprae} as evidenced by the growth in the foot pads of non immunosuppressed mice.\textsuperscript{27} Together these findings pose a serious question with respect to the efficacy of MDT and its use as a tool in the control of leprosy.

Re-infection from an exogenous source at any point in time cannot be ruled out and therefore remains a subject for future research. It is hoped that molecular tools might provide some insights into this. The clinical presentations discussed above however, reiterate the earlier study findings,\textsuperscript{14} and are in favour of reactivation due to endogenous \textit{M. leprae} rather than re-infection. Occurrence of drug resistance (if any) is also an issue, is being investigated (and will be published separately). Clinically there was a set pattern seen in all patients i.e. a period of no clinical activity (2 to 20 years) followed by the reappearance of lesions. While in most cases relapse was detected > 10 years after the cessation of treatment, early onset of relapse is attributable to the inadequate killing of \textit{M. leprae}.\textsuperscript{14,24}

Our findings allow us to make some recommendations: firstly, data on relapse/problem cases should also be gathered from the private and public sectors through a common central registry in order to know the extent of problem. Secondly, as inadequate treatment brings down the incubation time of relapse it would be advisable to over-treat rather than undertreat. Thirdly, in order to facilitate the early detection of relapse and, more importantly, to prevent disease transmission in the community, all patients released from treatment should be examined periodically for at least 9–10 years.

The limitations of the current study are: firstly patients are derived from different treatment backgrounds and therefore provide a reflection of only the trend and not the relapse rate under a given regime. Secondly, an element of selection bias as well as recall bias cannot
be ruled out since they are referral cases and pre-relapse data collection is largely through
history. Bias may also be in the referral of only difficult cases for further investigation to
FMR. Nevertheless, the lessons learnt have far-reaching implications and call for a more
systematic recording of relapse cases from all walks of life.

Conclusion

All leprosy patients, regardless of their type and MDT regime, carry ‘risk of relapse’. The
occurrence of relapse among BT- BB (11/23 = 52%) cases despite receiving 12 months
of MB – MDT and 21% (5/23) of 12 months MB-MDT treated cases relapsed for the second
time allow us to argue that the WHO- MDT regime is not efficacious and there is a need
to look for alternatives.

Acknowledgements

This data was presented by VPS at the National Workshop on ‘Epidemiological trends in
leprosy’ held at Chennai on 30th January 2010. We are grateful to all the patients and their
families for their cooperation, all the NGOs (in particular, the Bombay Leprosy Project),
hospitals and GPs for the referral of patients. We also thank Dr Nerges Mistry
(Director, FMR) for her help in the preparation of this manuscript.

References

1 Elimination of leprosy: resolution of the 44th World Health Assembly, Geneva: World Health Organization,
1991. Resolution no WHA 44.9.
2 World Health Organization. Leprosy: Global Target attained- remaining endemic countries pose greatest
3 World Health Organization. The final push towards elimination of leprosy: strategic plan 2000–2005,
4 World Health Organization. Shortening duration of treatment of multibacillary leprosy. Wkly Epidemiol rec,
5 Ji B. Why multidrug therapy for multibacillary leprosy can be shortened to 12 months. Lepr Rev, 1998; 69:
106–109.
7 Joshi PL, Barkakaty BN, Thorat DM. Recent developments in elimination of leprosy in India. Ind J Lepr, 2007;
79: 107–120.
html accessed on 7th May 2008.
11 WHO leprosy unit, division of control of tropical diseases. Risk of relapse in leprosy. WHO document
12 World Health Organization. Report on the third meeting of the WHO technical advisory group on elimination
13 Cellona RV, Balagon MF, dela Cruz EC et al. Long-term efficacy of 2 year WHO multiple drug therapy (MDT)
14 Shetty VP, Wakade AV, Ghate SD et al. Clinical, histopathological and bacteriological study of 52 referral
15 Ridley DS, Jopling WH. Classification of leprosy according to immunity – A five group system. Int J Lepr, 1966;