Effectiveness of multidrug therapy in multibacillary leprosy: a long-term follow-up of 34 multibacillary leprosy patients treated with multidrug regimens till skin smear negativity

ISAAC NEERAJ SHAW, M. CHRISTIAN, K. JESUDASAN, NISHA KURIAN & GEETHA S. RAO
Schieffelin Leprosy Research & Training Centre, Karigiri, India

Accepted for publication 13 February 2003

Summary The World Health Organization (WHO) Field Trials of multidrug therapy (MDT) started at Schieffelin Leprosy Research and Training Centre (SLR & IC), Karigiri, India in December 1981. The patients were treated with two MDT regimens. The first (regimen A) consisted of 600 mg rifampicin and 300 mg of clofazimine given under supervision on 2 consecutive days monthly, 225 mg injection of acedapsone bimonthly and dapsone 100 mg daily. The second regimen (regimen B) was the conventional MDT (WHO/MDT), rifampicin 600 mg and clofazimine 300 mg supervised once a month, dapsone 100 mg and clofazimine 50 mg daily, unsupervised. Both the regimens were administered for a minimum period of 2 years or until skin smear negativity, whichever occurred later. Thirty-four newly detected previously untreated MB patients, 16 of whom received regimen A and 18 regimen B, were reassessed. Both regimens were well accepted and well tolerated by the patients. Clofazimine discoloration was the only adverse effect of MDT seen in these patients. After completion of treatment with MDT, the patients were followed up for a total duration of 466 person-years with a mean of 13.7 ± 1.4 years per patient. No relapse was seen.

Introduction

The World Health Organization (WHO) in 1982 introduced multidrug therapy (WHO/MDT) consisting of dapsone, clofazimine and rifampicin for multibacillary (MB) leprosy patients. It was to be administered for a minimum period of 2 years or until skin smear negativity, whichever occurred later. However, as there was increasing evidence that 2 years of MDT was adequate for MB leprosy, the WHO Study Group in 1993 recommended MDT for a fixed duration of 2 years (FDT), thus dropping the proviso to continue treatment until skin smear negativity.

Data from leprosy control programmes and projects indicate that the relapse rate in MB patients treated for a minimum period of 2 years or until skin smear negativity, whichever
occurred later, is very low, well below 1%.6–10 However, the majority of the patients treated until skin smear negativity and followed up for a long duration, 8–10 years after completion of treatment (RFT), had long-term dapsone monotherapy before receiving MDT. The long-term effectiveness of MDT until skin smear negativity in preventing relapse in previously untreated MB patients is not yet known. This study was undertaken to clarify the risk of relapse during a prolonged follow-up in previously untreated MB patients who received MDT till skin smear negativity.

Material and methods

The field trials of WHO-recommended MDT regimens in multibacillary (MB) patients commenced in 1981 at Schieffelin Leprosy Research and Training Centre (SLR & TC), Karigiri, India. From December 1981 to December 1982, 1067 BL and LL patients were inducted into the study. Most of these patients had had dapsone monotherapy prior to inclusion in the study. Only 44 patients were newly detected and had received no previous therapy for leprosy.

Two WHO-recommended regimens were used to treat the patients. The first regimen (regimen A) was a monthly supervised dosage of 600 mg rifampicin and 600 mg clofazimine given on 2 consecutive days under supervision, bimonthly injections of 225 mg of acedapsone and a daily dose of dapsone 100 mg unsupervised. The second regimen (regimen B) was the standard WHO regimen (WHO/MDT)6,10 consisting of a monthly supervised pulse of 600 mg rifampicin, 300 mg clofazimine along with a daily unsupervised dosage of 50 mg clofazimine and 100 mg dapsone. Both regimens were administered for a minimum period of 2 years or until skin smear negativity, whichever occurred later.

Allocation of patients into regimen A and regimen B was based on geographic location. The leprosy control area of Gudiyatham Thaluk is divided into four blocks. The patients from block I and block II were put on regimen A and the patients from block III and block IV were put on regimen B.

While on MDT, all the patients were reviewed monthly to assess the clinical status and complications. After release from treatment, patients were seen once every 3 months for a period of 5 years, after which they were seen annually. A detailed clinical assessment and a skin smear from routine as well as selective sites were done once every year. During treatment, the intake of dapsone was monitored regularly using the tablet count and urinary dapsone/creatinine ratio. After the patients were released from treatment, the urinary dapsone/creatinine ratio was measured at least once a year to rule out self-medication. Of the original cohort of 1067 patients inducted into the study, 980 completed their course of treatment and 723 patients were still under surveillance until July 1995, after which they were not assessed. Until 1995 no patients had relapsed.6

Of the 44 newly detected and previously untreated patients, 27 were males and 17 females. Twenty-one had received regimen A and 23 regimen B. Of these 44 patients, 34 had been followed up till 1995. Three had died and seven had migrated and were lost for follow-up. These 34 patients were re-evaluated 17 years after induction into the study. A detailed physical examination was carried out. Skin smear examination from routine and selective sites was performed. Nerve function impairments were assessed by using standard methods.12 For the purpose of this study, the term relapse was defined as an increase in BI of 1+ or more at any site seen on two consecutive skin smear examinations at a 6-month interval with or
without clinical evidence of activity. This is the same criterion which was used by Jesudasan et al. in judging relapse in the original cohort or 1067 MB patients.\textsuperscript{6}

Statistical analysis was performed using SPSS. Student’s t-test was done to test the statistical significance of mean difference between the regimens.

**Results**

The mean age of the 34 patients, at the time of induction into the study, was 37.2 ± 14.3 years: 21 (61.8\%) were males and 13 (38.2\%) females; 19 (55.9\%) were classified as borderline lepromatous leprosy (BL) and 15 (44.1\%) as lepromatous leprosy (LL); 13 (38.2\%) had a BI of 3+ or more and five (14.7\%) had a BI of 4+ or more. BI of only routine sites (right earlobe, left forehead, chin, and left buttock (or left thigh in female patients) were used to calculate the mean 61 of the patients. Lepromin test, done at the time of induction of patients in the study, was negative in all the patients. Sixteen (47.1\%) patients received regimen A and 18 (52.9\%) regimen B. The baseline characteristics of the patients who received the two regimens, including mean age, male/female ratio, classification of leprosy, average of mean BI, lepromin reactivity and duration of leprosy before the initiation of therapy, are given in Table 1. These did not differ significantly.

Fifteen (44.1\%) patients developed lepra reactions: 3 (8.8\%) had erythema nodosum (ENL), nine (26.5\%) reversal reactions (RR) and three (8.8\%) had only neuritis (Table 2). All three patients who developed ENL reactions had LL type leprosy. While one (2.9\%) patient had ENL at registration, two (5.9\%) developed ENL reactions after initiation of MDT. Eight (23.5\%) patients developed reversal reaction and three (8.8\%) only neuritis for the first time after initiation of therapy, either during treatment or surveillance. Two (5.9\%) patients developed reaction after RFT, during the first year of surveillance: in one only skin was involved and in the other only nerve. Both patients had received regimen B (WHO/MDT). They received further treatment, and the reactions subsided in 4 and 6 weeks, respectively. Altogether 13 (38.2\%) patients developed lepra reactions after initiation of therapy. Of these, five (14.7\%) received regimen A and eight (23.5\%) regimen B. Neuritis, with or without skin involvement, was seen in 7 (20.6\%) patients, three (8.8\%) of whom received regimen A and four (11.8\%) regimen B. However, the differences were statistically not significant.

There was no difference in the clearance of the bacilli in regimen A and regimen B, as shown in Figure 1. On an average a fall in BI of 0.5 to 1+ per year was

**Table 1. Baseline characteristics of 34 patients**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Regimen</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>No of patients (%)</td>
<td>16 (47.1)</td>
<td>18 (52.9)</td>
<td></td>
</tr>
<tr>
<td>Mean age in years</td>
<td>38.9 ± 13.49</td>
<td>35.6 ± 15.23</td>
<td></td>
</tr>
<tr>
<td>Sex male/female</td>
<td>10/6</td>
<td>11/7</td>
<td></td>
</tr>
<tr>
<td>Classification BL/LL</td>
<td>8/8</td>
<td>11/7</td>
<td></td>
</tr>
<tr>
<td>Mean BI</td>
<td>2.4 ± 1.15</td>
<td>2.3 ± 1.41</td>
<td></td>
</tr>
<tr>
<td>Lepromin (+) ve/(-) ve</td>
<td>0/16</td>
<td>0/18</td>
<td></td>
</tr>
<tr>
<td>Duration of disease at registration (years)</td>
<td>4.9 ± 5.83</td>
<td>3 ± 2.22</td>
<td></td>
</tr>
</tbody>
</table>
observed in both the regimens. The number of patients who became skin smear negative at the end of each of treatment with MDT is shown in Table 3. As expected, patients with higher BI took more time to achieve skin smear negativity. The patients with BI $\geq 4+$ took 4007 years to become skin smear negative. On average, each patient received 46-9 ± 20-05 monthly pulses of MDT. The average clinic attendance during the period of treatment was 94.5%, ranging between 80 and 100%. While on treatment, the tablet count tallied with the expected number and urinary dapsone/creatinine ratio remained positive in all the patients at each time of testing, thus confirming regular intake of the drugs. After RFT, during surveillance, dapsone/creatinine ratio was repeatedly negative in all patients, thus confirming that the patients were not taking the antileprosy drugs by themselves.

All the patients tolerated MDT well and no adverse effect to MDT (except clofazimine discoloration) was seen. Three normal children were born to mothers while on treatment. All the three children showed clofazimine pigmentation at birth. The clofazimine discoloration persisted as long as the mothers remained on MDT and the children received milk. One of the children died during infancy.

**Figure 1.** Fall in BI of patients on regimen A and regimen B.
Table 3. Attainment of skin smear negativity at the end of each year of treatment (cumulative)

<table>
<thead>
<tr>
<th>Initial BI</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1–0-9</td>
<td>2 (50)</td>
<td>4 (100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–0–1-9</td>
<td>3 (30)</td>
<td>3 (30)</td>
<td>7 (70)</td>
<td>10 (100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–0–2-9</td>
<td>0</td>
<td>1 (14)</td>
<td>2 (29)</td>
<td>5 (71)</td>
<td>7 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–0–3-9</td>
<td>0</td>
<td>0</td>
<td>2 (25)</td>
<td>6 (75)</td>
<td>8 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (60)</td>
<td>4 (80)</td>
<td>4 (80)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>5 (15)</td>
<td>8 (24)</td>
<td>15 (44)</td>
<td>28 (82)</td>
<td>33 (97)</td>
<td>33 (97)</td>
<td>34 (100)</td>
</tr>
</tbody>
</table>

All the 34 patients were followed up for at least 9 years after RFT, while 24 (70.6%) patients had a follow-up of 13 years or more after RFT. By the end of December 1999, the total duration of follow-up of the 34 patients after RFT was 466 person-years and the mean duration of follow up was 13.7 ± 1.38 years per patient. None of the 34 patients showed any evidence of relapse.

Discussion

The ultimate test of chemotherapeutic effectiveness of any regimen is the relapse rate among patients who have completed the prescribed course of treatment. As in leprosy relapse occurs long after completion of treatment with any rifampin-containing regimen,13,14 a prolonged follow-up of patients treated with MDT regimens is required. In this study, 34 MB patients who had no previous treatment for leprosy were followed up for a prolonged period without any evidence of relapse.

MDT was well accepted by all patients, including women, in spite of the clofazimine discolouration, which was seen in all the patients. Throughout the treatment, patient compliance remained very good. All the patients tolerated MDT and no adverse drug reaction was seen in any of these 34 patients. Forty four percent of patients developed lepra reactions. Although the lepra reactions and neuritis were more common in patients on regimen B, the differences were statistically not significant.

In the THELEP-supported field trials conducted at Karigiri6 and Polambakkam,7 MB leprosy patients were treated with WHO recommended MDT regimens for a minimum period of 2 years or until skin smear negativity, whichever occurred later. At Karigiri, 1067 BL and LL patients were included in the trial, of whom 980 (91.8%) completed the treatment. No relapse was reported until July 1995 during a follow-up period of 8244 person-years after RFT. However, most of the patients who had a follow-up of 8–10 years after RFT were either already skin smear negative or had low bacterial load at the time of inclusion in the trial, due to previous dapsone monotherapy. Out of 1067 patients, 1023 (96%) had long-term dapsone monotherapy and 710 (67%) were already smear negative before starting MDT. Only two patients, who had initial BI of ≥3+ and no treatment for leprosy before inclusion in the study, were followed up for 8 years of more after RFT.

During a follow up of 8–10 years after completion of therapy, five relapses were reported. One relapsed as MB leprosy and four as PB leprosy.7
The WHO Leprosy Unit, in the early 1990s, carried out two questionnaire surveys of post-MDT relapses. In the pilot study, in which 92,194 MB patients were covered, 467 relapses were reported, giving an overall relapse rate of 0.23 per 100 person-years. In the second extended questionnaire survey, information was obtained from 28 selected centres on patients who began treatment with MDT between 1982 and 1990. A total of 20,141 MB patients were observed during the period 1984–1992, of whom 1414 were followed up for 9 years after completion of treatment. Sixty-seven patients were reported as relapse during a follow-up period of 80,000 person-years, giving a cumulative relapse rate of 0.77%. The risk of relapse did not vary significantly with time. However, although patients were subgrouped into those treated for 2 years only and those treated until smear negativity, no separate analysis was done for patients who had previously received long-term dapsone monotherapy before receiving MDT and for previously untreated patients.

The Marchoux Chemotherapy Study Group have reported a relapse rate of 20% in a group of 35 multibacillary patients treated by WHO/MDT regimen for 2 years during a follow-up ranging from 27 to 84 months. All the patients who relapsed had an initial BI of ≥4+ before initiation of MDT and most of these patients had a BI of ≥3+ at RFT. Among the patients with initial BI ≥4+, the relapse rate was as high as 38.8%. Shaw et al. reported relapses as histoid leprosy in three MB patients 12–15 years after receiving FDT. In a comparative study, Gridhar et al. have found that in patients with BI ≥4+, the relapse rate was significantly higher in those treated with FDT as compared to those treated with MDI until smear negativity. Waters, Marchoux Chemotherapy Study Group and Gridhar et al. have suggested 4 years of MDT in highly bacillitlated patients with BI ≥4+.

However, in some other studies in which patients with high BI were treated with FDT, very few relapses were reported. At Karigiri, 261 MB patients treated with FDT were followed up for a mean duration of 6±14 ± 2.11 years per patient and total duration of 886 person-years after RFT. No relapse was seen. Forty-six of these patients with BI ≥3+, 17 of whom had a BI ≥4+, were revisited 9-26 ± 2-98 years after RFT. Only one relapse was reported. In the ALERT MDT Field Evaluation Study (AMFES), 256 MB patients treated with FDT were followed up for a mean duration of 4-3 years, ranging between 0 and 8.6 years.

In the current study, 34 newly detected, previously untreated MB patients who received MDT for a minimum period of 2 years or until skin smear negativity, whichever occurred later, were followed for a minimum period of 9 years after completion of treatment. By December 1999, the total duration of follow-up of the patients after completion of treatment was 466 person-years and the mean duration of follow-up was 13.7 ± 1.4 years per patient. The mean BI of the patients at the time of registration was 2.4 ± 1.3+. Thirteen patients had a BI ≥3+ and 5 a BI ≥4+. In none of the patients was relapse seen.

Thus, treatment of MB patients with MDT for a minimum period of 2 years or until skin smear negativity, whichever occurs later, is very safe, well tolerated and well accepted by the patients. It is also very effective in preventing relapse. However, as only five patients had a BI ≥4+, more reports of prolonged follow-up of patients with high initial BI, treatment with MOT till smear negativity, are required to establish the superiority of MDT till smear negativity over 2 years of MDT, especially in patients with higher BI.
Acknowledgements

The authors are grateful to Professor Charles K. Job, Consultant Pathologist, St Thomas Hospital and Leprosy Centre, Chettupattu, Dr P. S. S. Sundar Rao, Director, S.L.R. & T.C., Karigiri, Dr S. Arunathathi, Head, Department of Medicine, S.L.R. & T.C., Karigiri for their encouragement and guidance. They also thank Mr V. Nallathambi, Physiotherapy Technician, Mr S. Vincent, Laboratory Technician and Mr P. Dorairaj, Records Technician, for their technical assistance and Mr C. Lewis Kumar for secretarial assistance. The Field Trials of Chemotherapy in MB Leprosy received financial support from the UNDPI World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR).

References