Results of eight years follow up among multibacillary patients treated with Uniform Multidrug Therapy in China

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Summary
Objective: To analyse the results of treatment among multibacillary (MB) patients 8 years after treatment with 6 months’ multidrug therapy (MDT).
Methods: Newly detected and relapsed MB leprosy patients were treated with 6 months WHO-MDT. The patients were followed up for 8 years. The effectiveness of treatment was assessed by clinical status and bacteriological changes.
Results: A total of 114 patients were recruited. Forty two patients dropped out from the study for various reasons. Only 72 patients remained for the final analysis. The mean Bacteriological Index (BI) of all patients decreased from 2.93 ± 1.39 before treatment, to 0 at the end of the eight year follow up period, with an average annual BI decrease of 0.42. The rate of smear negativity of all patients was 100% at the end of follow up. 38 (53%) patients experienced leprosy reactions during the study and one patient relapsed, giving a cumulative relapse rate of 1.3% or 0.035 per 100 patient-years.
Conclusion: The finding that all MB cases with initially positive skin smears, who were treated with only 6 months of MB-MDT, became negative within 8 years showed that the response to this regimen is good in a majority of MB cases.

Keywords: leprosy, uniform multidrug therapy, bacteriological index, leprosy reaction

Introduction
Chemotherapy for multibacillary leprosy patients has gone through dapsone monotherapy, multidrug therapy (MDT) until skin smear negativity, MDT for two years and now for only one year. Leprosy is caused by Mycobacterium leprae, and the aim of chemotherapy is to kill all live bacilli, but not to clear all pathogens from the body. What is the best drug regimen for leprosy?
The question still has no a definite answer. In 1998, the WHO Leprosy Expert Committee recommended that multidrug therapy for MB patients could be shortened to 12 months without increased risk of a high relapse rate.¹ In 2002, the WHO Technical Advisory Group recommended pilot trials of Uniform Multidrug Therapy (UMDT) for all types of leprosy with a 6-month treatment regimen.² The UMDT project resulted in much debate, especially regarding its adequacy for MB patients. We have carried out a clinical trial of the UMDT regimen in Guizhou and Yunnan provinces in China under the support of WHO since 2003. Now we report the results of eight years follow up on MB leprosy patients treated with the UMDT regimen.

Patients and Methods

PATIENTS

Before starting the research, the UMDT trial was approved by the Medical Ethics Committee of the Institute of Dermatology, Chinese Academy of Medical Sciences. An approved patient consent form was also prepared to provide for the trial patients. During the early stages of the study, we have published several articles on the study of UMDT in China to report preliminary results.³ ⁴ The patients studied were all multibacillary leprosy patients with positive skin smears. They were recruited between November 2003 and July 2005. The criteria for recruitment were newly detected or relapsed multibacillary patients aged between 11 and 65, not currently receiving any anti-leprosy treatment. All patients who agreed to take part in the study were asked to sign a consent form.

The criteria for exclusion from the study were as follows:

1. Severe abnormality of liver or kidney function
2. Severe anemia
3. Mental disease
4. Other severe illness
5. Pregnancy.

Reasons for discontinuing in the study included:

1. Severe leprosy reaction
2. Migration from the study area
3. Death due to another cause
4. Dapsone allergy
5. Refusal to attend for follow up.

During long term follow up, some patients were lost due to various reasons, but if the patient can be followed up during eighth year, the patient will still qualify to be included in the study for analysis.

DRUGS AND STUDY METHODS

The UMDT drugs were provided by WHO. The regimen consisted of rifampicin 600 mg once a month, dapsone 100 mg daily and clofazimine 300 mg once a month plus 50 mg daily
for 6 months. After stopping treatment, all patients were followed up once a year by local health workers to check for leprosy reactions or neuritis. A skin smear test would be done by a professional technician working at county level to investigate the change of Bacteriological Index; smears were taken from at least four sites and repeated at the same sites every year.

The criteria for relapse were based on active skin lesions, increased BI of 2+ or more at any site, with intact staining of bacilli.

The patients’ data were collected on a special form provided by WHO, filled by local medical professional workers working at the county unit for leprosy control. The forms were then sent to the Institute of Dermatology. After checking, all data were entered into a computer to be analyzed by descriptive method using SPSS 16.0 software.

Results

Basic Situation of the Patients Before UMDT

A total of 114 multibacillary leprosy patients were recruited between November 2003 and July 2005. All were skin smear positive, with an average BI of 3.01 ± 1.50. Twenty-one (18.4%) patients had a BI of more than 4.0. During 8 years of follow up, 42 patients dropped out of the study, so there were only 72 patients who were qualified for analysis. Among 72 patients, 71 were newly diagnosed patients, while one had relapsed after dapsone monotherapy. Among them, 54 were male and 18 were female. The ages ranged from 11–65 years old with an average age of 36.3 ± 12.4 years. The mean Bacteriological Index was 2.93 ± 1.39 before the trial, and 18 (25%) patients had a BI ≥ 4.0. The Grade 2 disability rate was 18% (13/72) among all trial patients. Six (8.3%) patients had a leprosy reaction before the trial.

Dropping Out from the Study

During 8 years of follow up, 42 patients dropped out due to various reasons, as shown in Table 1. Of the 11 deaths during the study, reasons included malnutrition, organ failure associated with advanced age, alcoholism, drowning, suicide, diarrhea, pulmonary heart disease, acute hepatitis and other unknown reasons.

Table 1. The timing and reasons for discontinuing with the study

<table>
<thead>
<tr>
<th>Category</th>
<th>On UMDT</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDS allergy</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Migration</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Severe leprosy reaction</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Relapse</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Refused to check</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Additional MDT</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>42</td>
</tr>
</tbody>
</table>
CHANGES OF BACTERIOLOGICAL INDEX OF PATIENTS DURING THE STUDY

After therapy, the average Bacteriological Index declined from 2.93 before the trial to zero at the end, as shown in Table 2.

LEPROSY REACTIONS OCCURRING DURING THE STUDY

Thirty-eight (53%) patients developed leprosy reactions during the trial, with 12 Type I and 26 Type II reactions. Three patients with severe leprosy reactions dropped out during the first year and, five other patients also developed severe Type II leprosy reactions during follow up. They each had a relatively high BI. The patients worried that their treatment was not enough and asked to continue MDT. So the local health worker gave them routine MDT plus prednisone to treat the leprosy reaction. After treatment with prednisone, the leprosy reactions gradually subsided. They were also followed up regularly. Their BIs eventually became negative over the course of follow up (Table 3).

RELAPSE

There was one patient who relapsed 13 months after stopping treatment. The patient had borderline lepromatous leprosy with an initial BI of 3.6. At the end of treatment, the BI of the patient decreased to 2.6. However, the patient presented with many erythematous nodules with infiltration on the face, trunk and limbs, 13 months after stopping the treatment. The skin smear test was strongly positive with a BI of 3.4 and at the same time the skin smear test showed many intact anti-fast bacilli on staining; the BI at one site had increased by 2 as compared with previous results taken at the same site. The patient was checked up by two national leprosy experts. The patient was confirmed to have a relapse and was treated with routine MDT. After the first relapse, no more relapses occurred. The cumulative relapse rate was 1.3% during 8 years follow up, or 0.035 per 100 patient-years (one per 2836 patient-years during 8 years follow up (Table 4).

Discussion

The Bacteriological Index during and after treatment for leprosy is a sensitive and objective indicator for evaluating the effectiveness of treatment.

Li\textsuperscript{5} reported that for 56 newly detected MB leprosy patients treated with MDT until skin smear negativity, the negativity rate among these patients was 91.1% at the end of 5 years after starting treatment. Li\textsuperscript{6} also reported in another study that in 34 newly detected MB patients treated with MDT until skin smear negativity, the BI decreased from 2.0 before treatment to 0.01 at the end of 5 years after starting treatment with a negativity rate of 97.06%. Shen\textsuperscript{7} reported that in 79 newly detected leprosy patients treated with MDT until skin smear negativity, the BI decreased from 3.01 before treatment to 0.02 at the end of 6 years after starting treatment with a negativity rate of 92%. At the end of 7 years after starting treatment, the BI of all patients became negative. Sales\textsuperscript{8} reported that in 128 multibacillary leprosy patients treated with WHO multidrug therapy for one year, the BI decreased from 2.27 before treatment to 1.56 at stopping treatment and to 1.03 at the end of one year after stopping treatment, when 31.9% were negative.
Table 2. Changes of BI during the study among MB leprosy patients treated with UMDT

<table>
<thead>
<tr>
<th>Category</th>
<th>Before UMDT</th>
<th>Completed UMDT</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of smears</td>
<td>72</td>
<td>67</td>
<td>66</td>
<td>67</td>
<td>68</td>
<td>71</td>
<td>70</td>
<td>71</td>
<td>71</td>
<td>72</td>
</tr>
<tr>
<td>Mean BI</td>
<td>2.93</td>
<td>1.61</td>
<td>0.93</td>
<td>0.77</td>
<td>0.35</td>
<td>0.22</td>
<td>0.07</td>
<td>0.23</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Number of negative Smears (%)</td>
<td>0%</td>
<td>31.3%</td>
<td>39.4%</td>
<td>47.8%</td>
<td>69.1%</td>
<td>84.5%</td>
<td>95.7%</td>
<td>98.6%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
### Table 3. Leprosy reactions during the study among MB leprosy patients treated with UMDT

<table>
<thead>
<tr>
<th>Follow up time (year)</th>
<th>Before UMDT</th>
<th>On UMDT</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>71</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>69</td>
<td>68</td>
<td>71</td>
<td>71</td>
<td>71</td>
<td>71</td>
<td>72</td>
</tr>
<tr>
<td>No. of cases with type I reaction</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12 (16.9)</td>
</tr>
<tr>
<td>No. of cases with type 2 reaction</td>
<td>5</td>
<td>3</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>26 (36.6)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>6 (8.4)</td>
<td>8 (11.4)</td>
<td>10 (14.2)</td>
<td>4 (5.8)</td>
<td>3 (4.2)</td>
<td>3 (4.2)</td>
<td>3 (4.2)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>38 (52.8)</td>
</tr>
</tbody>
</table>
We found that the changes in BI in our patients after treatment was very similar to the reports mentioned above. In our study, 72 MB leprosy patients were treated with only 6 months MDT, and the BI decreased from 2·93 before treatment to 0·93 at end of 1 one year after stopping treatment with a negativity rate of 39·4%. At the end of the seventh year after stopping treatment, the BI of all patients became negative. This showed that there was no difference in BI changes and the rate of negative skin smears between patients treated with UMDT and one or two years of MDT.

A 2010 report indicated that 16% of BL-LLs patients showed viable leprosy bacilli growth in the mouse foot-pad test after 18 months’ MDT. We speculate that those viable leprosy bacilli might be leprosy persisters with a very low metabolic rate in the patient’s body. The non-sterilising immunity of the patients can kill these few viable bacilli. The very low relapse rate of leprosy patients treated with 12 months MDT, as recommend by WHO since 1998, should reduce concerns of a high relapse rate resulting from a few viable leprosy persisters.

The incidence of leprosy reactions during the course of the disease is also one of the indicators to evaluate the acceptance of a new treatment regimen. Sales reported that among 128 MB patients treated with one year MDT, 71·9%, 56·3% and 63·1% developed leprosy reactions during the first, second and third years after starting treatment, respectively. In a similar study with UMDT in Brazil, the authors reported that overall, reaction rates were similar in those patients treated with UMDT or regular MDT; patients on UMDT with BI however, had a slight but significant increase in reactions in the period 6–18 months after the start of treatment, compared to those on regular MDT, but this difference disappeared by 24 months. Feuth reported that among 94 MB leprosy patients treated with 2 years MDT, 41% developed Type II leprosy reactions within one year of starting treatment.

In our study, a total of 38 leprosy reactions were observed during the trial. Most leprosy reactions occurred during treatment or within the first two years of follow up. During the third year of follow up and afterward, the rate of leprosy reactions decreased gradually. We found that the total leprosy reaction incidence in our patients was lower than that reported by Sale, and the Type II leprosy reaction incidence was also lower than that reported by Feuth, even including the eight withdrawals during the early years of follow up.

One patient in the study relapsed, 13 months after stopping treatment, giving a cumulative relapsed rate of 1·3% or 0·035 per 100 patient-years during 8 years of follow up. This was very optimistic information. The only possible mechanism of this phenomenon is that the 6 months UMDT regimen has a similar bactericidal efficacy as the 1 year or 2 year MB-MDT regimens, which killed almost all viable leprosy bacilli harbored in the body of the patient. However, as there were only 72 patients available at the end of follow up due to the high

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**Table 4.** The number of patients actually followed up each year during study

<table>
<thead>
<tr>
<th>Follow up time (year)</th>
<th>Before UMDT</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>114</td>
<td>100</td>
<td>92</td>
<td>88</td>
<td>81</td>
<td>79</td>
<td>78</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td>Patient-years</td>
<td>–</td>
<td>100</td>
<td>184</td>
<td>264</td>
<td>324</td>
<td>395</td>
<td>468</td>
<td>525</td>
<td>576</td>
</tr>
</tbody>
</table>

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proportion dropping out over the 8 years, the possibility of bias arises. Thus further research should be done to confirm our results.

In conclusion, the UMDT trail in China with 8 years follow up, shows rapid bactericidal activity, definite decline of BI, very low relapse rate and an acceptable frequency of leprosy reactions among trial patients.

Acknowledgements

We are very grateful to WHO for support of the UMDT trial in China. We also thank Prof M.D. Gupte in India who played an important role in organizing and giving technical help for the trial. Lastly, we thank the health workers and clinicians working at county level in Qianxinan Prefecture, Bijie Prefecture and Anshun Prefecture in Guizhou province and Wenshan Prefecture in Yunnan Province of China for their good work in collecting data.

References