Bacteriological results and leprosy reactions among MB leprosy patients treated with Uniform Multidrug Therapy in China

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Summary
Objectives: To investigate the changes of bacteriological index and leprosy reactions among Multi-bacillary (MB) patients treated with uniform multi-drug therapy (UMDT).

Methods: Newly diagnosed leprosy patients were recruited after taking informed consent in three districts in Guizhou Province and one district in Yunnan Province China during November 2003 to June 2005 and were treated with Uniform Multidrug Therapy. All patients were followed up once a year for 3 years after completion of treatment. All data on bacteriological index (BI) and the frequencies of leprosy reaction were collected and analysed.

Results: A total of 166 patients were recruited for UMDT trial. Among them 114 patients had positive BI smear, and 83 patients had been followed up for 42 months. The mean BI of 83 patients decreased from 2·84 before treatment to 0·33 at the end of 42 months follow-up. At the end of this period, 61 patients (73·5%) had become BI

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negative. There were 13 (14.6%) patients who had a Type I reaction during 24 months of follow-up. One patient in the study group relapsed 13 months after stopping treatment of the UMDT.

**Conclusion:** There was a significant decrease in the mean BI and 73.5% of patients treated with UMDT became BI negative during 3 years’ follow-up. The frequency of Type I reaction seemed a little higher among patients treated with UMDT, but the numbers of patients enrolled were too few to determine statistical significance. Future studies on U-MDT should also study Type I reactions in these patients.

**Introduction**

The WHO Technical Advisory Group (TAG) in 2002 proposed a pilot trial of 6 months of Uniform MDT regimen for all types of leprosy patients to assess its effectiveness and usefulness, because the evidence from clinical studies and mouse footpad experiments suggested that 6 months treatment would be adequate for most leprosy patients. We took part in this study from November 2003 as the part of a multi-centre study. This study was also proposed from the points of operational and cost benefits in the situation of integrated leprosy services.

Concerns were focused on likely under-treatment of MB patients. We present data on the bacteriological results among patients treated with UMDT, as changes in the bacteriological index is one of best indicators to test the effectiveness of the regimen, and the frequency of leprosy reaction is also an important indicator. Here we only analysed bacteriological changes and frequencies of leprosy reaction among MB patients treated with UMDT regimen. This is the first report on bacteriological changes of 83 MB patients and leprosy reaction in 89 MB patients treated with UMDT.

**Patients and Methods**

The study was initially supported by WHO from November 2003, and later was supported by UNICEF/NUDP/World Bank/WHO Special Program for Research and Training in Tropical Disease (TDR) from 2005, and the special blister packs of UMDT drugs were supplied free of charge by the Novartis Company. When preparing the study protocol, organisers and experts from National Institutes of Epidemiology, India, and principal investigators from six sites in India and one site in China attended several working meetings which were held at National Institute of Epidemiology, India to discuss the study protocol in 2003. Each step of the flow chart for recruiting patients including informed consent form was discussed and formulated during these meetings.

**BACKGROUND OF STUDY AREAS**

Bijie, Anshun and Qianxinan districts, Guizhou province and Wenshan district, Yunnan province are the ‘leprosy pocket’ areas in Southwest China. There are special units or departments for leprosy control with professional health workers working at county and district levels. A well organised leprosy control programme has been carried out there since the 1980s. Various training courses on leprosy at district and provincial levels have been held in these areas each year. Most professional health workers have been trained to improve the
quality of leprosy services. As two thirds of newly-detected leprosy patients were MB BI positive, and many were without apparently visible skin lesions at the early stage of the disease, the guideline of the National Leprosy Control Programme stipulated that the slit-skin smear test should be a routine test at diagnosis. Each patient should be followed up once a year by investigation of clinical improvement and possible leprosy reaction. Each patient should also have a skin test once a year until the slit-skin smear test became negative; the patient was then released from surveillance.

PATIENTS IN THE STUDY

After getting approval to conduct the study from Ethical Committee of the Institute of Dermatology, Chinese Academy of Medical Sciences, PR China, we recruited only newly-registered leprosy patients who signed a consent form to agree to take part in the UMDT trial in Bijie, Anshun and Qianxinan districts, Guizhou province and Wenshan district, Yunnan province from November 2003 to June 2005. The consent form was designed at the working meeting held at NIE, India in 2003 and was translated from English into Chinese in China. The local health worker should read all the contents of the consent form using a local language to the trial patients (or parents of child patients), and let them know that they had the right to withdraw from the trial at any time. Only patients with an initial positive slit-skin smear test were classified as MB patients and included for analysis in this study. All patients had been treated with UMDT regimen for 6 months. Those patients of less than 5 years or more than 70 years of age, those with severe systemic diseases, or those who were pregnant were excluded from the study.

DIAGNOSIS OF LEPROSY REACTION AND RELAPSE

A sudden inflammation on skin lesions and peripheral nerves accompanied with pain, malaise, fever and other distressing symptoms and signs were considered to be a leprosy reaction. Type I reaction was diagnosed if the patient’s skin lesion was suddenly and markedly red with edema, their peripheral nerves suddenly enlarged, tender or painful, or the patient developed new paralysis on the face, hand or foot. Type II reaction was diagnosed if the patient suddenly developed crops of rose-coloured tender nodules (erythema nodosum leprosum, ENL). The ulcerated ENL, lymphadenitis, iridocyclitis, orchitis, fever and arthralgia may also be indications of leprosy Type II reaction. During follow-up, leprosy reaction was strictly differentiated from leprosy relapse based on the evidence of onset, clinical course, treatment status, bacterial test and biopsy if necessary. Relapse was diagnosed by the appearance of new symptoms and reappearance of signs of the disease after the completion of treatment and meanwhile with an increase of at least 2 in BI at one site of the slit-skin smear test or with many definite solid M. leprae.

INVESTIGATION AND FOLLOW-UP

After completion of the treatment, patients were followed up actively at least once a year by local health workers working at county level. Patients treated with UMDT had slit-skin smear tests at the end of the treatment, then once a year during follow-up. All slit-skin smear tests were taken by health workers and examined by the local experienced technician working at county level. During treatment, patients were seen every month to give monthly drugs, and
leprosy reaction was investigated for each patient at the same time. After completion of treatment, patients were informed and encouraged to report to health workers by telephone or to visit the clinic when feeling unwell or suffering any symptoms and signs related to leprosy. If local health workers suspected a patient had a relapse or severe leprosy reaction, they were advised to report to, or consult with experts at provincial or national level by telephone. The experts would go to the field to see the patients and give adequate management such as antileprosy reaction treatment or continuing MDT if necessary.

**DATA COLLECTION AND STATISTICAL METHODS**

The data for patients treated with UMDT were collected once a year from the county units of leprosy control using a specially designed form. All data were entered into the computer, and were analysed using Statistical Program for Social Sciences software, version 10.0. The independent two sample student t test and Chi-squared test were used for comparing the significance of difference in data.

**Results**

A total of 166 patients were recruited for the UMDT study from November 2003 to June 2005. Among them there were 31 patients who dropped out from UMDT during the trial, 11 due to migration, five due to serious leprosy reaction, seven due to death, two due to DDS allergy, one due to relapse and five due to extended treatment given by local health workers who saw there were still many active skin lesions and were worried about the adequacy of short course UMDT. If 10 patients related to UMDT were excluded, the drop-out rate was 12·7% in the study. There were eight child patients aged less than 14 years old. Among 166 patients treated with UMDT, there were 114 patients with slit-skin smear test positive at diagnosis. Among these 114 patients, 21 (18·4%) patients had BI of more than 4·0. Eighty-three patients had been investigated for 42 months since treated with UMDT and had full bacteriological data.

Before UMDT, the clinical basic information about 89 patients was shown (Table 1). The mean BI of 83 patients in the UMDT group decreased from 2·86 at diagnosis to 0·33 at the end of 42 months of investigation. At the end of this period, 61 patients (73·5%) became BI negative. There was a significant decline in the mean BI change and in the slit-skin smear test negativity at the end of 42 months’ investigation among patients treated with UMDT (Table 2).

**Table 1.** Basic information about 89 MB patients treated with UMDT

<table>
<thead>
<tr>
<th>Category</th>
<th>Basic information</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of MB patients</td>
<td>89</td>
</tr>
<tr>
<td>M/F ratio</td>
<td>3·05</td>
</tr>
<tr>
<td>Mean age at detection</td>
<td>35·2 ± 12·8</td>
</tr>
<tr>
<td>Mean BI at diagnosis</td>
<td>2·86 ± 1·38</td>
</tr>
<tr>
<td>No. of patients with BI &gt; 4·0 (%)</td>
<td>21 (18·4%)</td>
</tr>
<tr>
<td>No. of G2 disability (%)</td>
<td>18 (20·2)</td>
</tr>
<tr>
<td>No. of Child cases (%)</td>
<td>5 (5·6)</td>
</tr>
</tbody>
</table>
In order to reflect the real profile of leprosy reaction during the trial, five patients with severe leprosy reaction and one patient with relapse who were withdrawn from the trial were included which formed a sample of 89 not 83 patients when analyzing the frequency of leprosy reaction. We found that the patients treated with UMDT developed many leprosy reactions during the trial. There were 13 (14.6%) and 13 (14.6%) patients developed Type I and Type II reaction, respectively with a total leprosy reaction rate of 29.2% (Table 2).

The BI of patients decreased continuously with a mean decrease of 0.06 per month. There were 61 (73.5%) patients whose slit-skin smear test became negative (Table 3).

Regarding the 21 patients with a BI of more than 4.0 before UMDT, two patients died, three migrated, three withdrew and two had not been tested for BI at the end of 42 months’ investigation; there were only 11 patients who had full bacteriological data. The mean BI of these patients also decreased from 5.19 before UMDT to 1.09 at the end.

The patient with relapsed leprosy was a male aged 38. He was diagnosed as BL with an initial BI of 3.6. He started the UMDT from April 2005 and completed treatment in October 2005. At the end of treatment, the BI was 2.6. Thirteen months after stopping UMDT, the patient developed many erythematous areas and nodules on his trunk and limbs; the BI was 3.4 with many M. leprae in full anti-fast staining. The patient was diagnosed as relapse and with the Type II leprosy reaction. The patient was given routine MDT for two years and withdrawn from the UMDT study.

Leprosy reactions occurred in 9.0%, 5.6%, 6.7% and 4.5% of patients among patients treated with UMDT during 6, 12, 18 and 24 months after starting treatment. There were 13 (14.6%) patients who developed Type I reaction within 24 months’ investigation and nine

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**Table 2. End of follow-up indicators among patients treated with UMDT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Results at 42 months (<em>n = 89</em>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BI</td>
<td>0.33 ± 0.73*</td>
</tr>
<tr>
<td>No. of slit skin smear negativity (%)</td>
<td>61 (73.5)*</td>
</tr>
<tr>
<td>No. of Type I reaction (%)</td>
<td>13 (14.6)</td>
</tr>
<tr>
<td>No. of Type II reaction (%)</td>
<td>13 (14.6)</td>
</tr>
<tr>
<td>Total No. of leprosy reaction (%)</td>
<td>26 (29.2)</td>
</tr>
</tbody>
</table>

* *n = 83, but when analysing the real profile of frequency of leprosy reaction in the trial, 5 patients with severe leprosy reaction and one relapse who dropped out were included in the study group.

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**Table 3. Bacteriological changes among MB patients treated with UMDT**

<table>
<thead>
<tr>
<th>Time from starting treatment (months)</th>
<th>Before Therapy</th>
<th>6</th>
<th>18</th>
<th>30</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BI</td>
<td>UMDT (<em>n = 83)</em></td>
<td>2.84 ± 1.36</td>
<td>1.52 ± 1.36</td>
<td>0.86 ± 0.97</td>
<td>0.54 ± 0.83</td>
</tr>
<tr>
<td>No. of slit skin smear negativity%</td>
<td>UMDT (<em>n = 83)</em></td>
<td>0</td>
<td>28 (33.7)</td>
<td>33 (39.8)</td>
<td>49 (59.0)</td>
</tr>
</tbody>
</table>

*The bacteriological data for five patients with severe leprosy reaction and one patient with relapse were excluded due to withdrawal from the trial.
patients who developed Type II reaction within the first 24 months’ of investigation (Table 4).

It is interesting that five patients with serious leprosy reaction, their BIs were different: three patients had a BI ranged from 3.5–5.6 and the other two patients had a BI ranged from 0.8–1.5 before UMDT.

Discussion

The UMDT project is still controversial because there are concerns that it is too short for MB patients, especially for those with a BI above 4. In our study group there were 31 patients who dropped out. Among them, 10 patients’ reasons were related to the UMDT, five were due to severe leprosy reaction and the other five due to extended treatment given by local health workers without reporting to upper units for leprosy control when still seeing many active skin lesions at the end of 6 months’ treatment and fearing that the course had been too short.

After 42 months’ follow-up, the BI in these patients decreased in a rate of 0.72 each year.

There is a report that among 136 MB patients with a mean BI of 3.6 before starting treatment and treated with 12 months’ WHO/MDT MB regimen, 54 (39.7%) patients became slit-skin smear test negative at the end of 2 years’ follow-up after stopping treatment, and 84.8% of patients with BI < or +3 had became smear-negative at the end of 2 years. In another report, among 68 patients with BI positive, 42 (61.8%) patients with BI less than 3.0 before treatment became negative at the end of two years’ MDT. In our study, 83 MB patients with a mean BI of 2.84 before treatment and treated with only 6 months’ UMDT, 61 (73.5%) patients became slit-skin smear test negative at the end of 42 months’ follow-up. The result of slit-skin smear tests among our MB patients was similar to that reported in the literature.

A comparative study in Brazil gave information that the reduction in BI at 24 months was similar between 128 MB patients who received 12 doses of WHO/MDT MB regimen and 85 patients who received 24 doses of the same regimen. The result further shows that the WHO/MDT MB regimen is a very strong bactericidal regimen in treating leprosy patients. It may not result in a significant difference in the reduction of bacteriological index when the regimen killed nearly all viable M. leprae in the patient’s body.

The frequency of leprosy reaction during therapy is also an indicator for evaluating the acceptability of the regimen. In a comparative study between 12 and 24-dose regimen for MB leprosy patients, no statistical difference between two groups was found in the frequency of reaction. However, Kyaw et al. reported that 67.0% of patients developed reversal reaction during MDT among patients treated with one year fixed WHO/MDT MB regimen and 40.5%
of patients developed reversal reaction after completion of MDT. The Type II reaction was seen only 8.0% during MDT and 9.5% after release from treatment. In our study, the frequency (8.1%) of the Type II reaction during investigation of 42 months was similar to that reported by Kyaw et al.\textsuperscript{10} But we found that the high rate of leprosy Type I reaction is a problem among UMDT patients, although the rate of Type I reaction among our patients was less than that reported by Kyaw et al.\textsuperscript{9} However, it increased anxiety about the short course of treatment among local health workers as total of 14.6% of patients developed leprosy Type I reaction within 24 months’ investigation. With respect to Type II reaction, there was no significantly high frequency of leprosy reaction developed among our patients. However, 14.6% (13/89) of the UMDT patients developed Type II reaction at the end of 42 months’ investigation.

Balagon et al.\textsuperscript{11} reported that the frequency of Type II reaction among patients treated with 1 year’s MDT was higher than that of patients treated with 2 years’ MDT within investigation of 48 months. The authors attributed the high rate of Type II reaction to possibly stopping MDT earlier before total clearance of \textit{M. leprae} from the patient’s body, especially to stopping the clofazimine treatment early. But what is the reason for the high frequency of leprosy reversal reaction in our study group? Because there were several reports that dapsone interferes with the activation or function of the G-protein that initiates the signal transduction cascade common to chemotactic stimuli\textsuperscript{12} and dapsone inhibits the release of tissue-damaging oxidants and proteases in the affected skin,\textsuperscript{13} we consider that the reason of the high reversal reaction rate may be linked to the too-short treatment - in particular to dapsone treatment. However, the real reason for a high reversal reaction rate among UMDT group needs to be further studied.

Acknowledgements

We are very grateful to WHO who initially supported the UMDT trial, and then to UNICEF/NUDP/World Bank/WHO Special Program for Research and Training in Tropical Disease (TDR) who funded the trial since 2005, and lastly to Novartis who generously supplied special blister packs of UMDT drugs. We also thank Prof M.D. Gupte who played an important role in organising and giving technical help for the trial. At last we thank all the health workers and clinicians working at county Station or Center for Disease Control and Prevention for their good work in collecting data.

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