Twenty five years follow up of MB leprosy patients retreated with a modified MDT regimen after a full course of dapsone mono-therapy

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Summary

Background The relentless emergence of dapsone resistance amongst M. leprae threatened leprosy control programmes, and increased the relapse rate of patients cured with dapsone monotherapy.

Objective The study aimed to analyse the effect on the relapse rate of dapsone-cured multibacillary (MB) leprosy patients, of re-treatment, using a multidrug therapy (MDT) regimen which differed from the WHO recommended regimen.

Design 794 MB leprosy patients who had been released from treatment after dapsone monotherapy were selected, amongst them 657 were re-treated for 1 year using the modified multidrug therapy regimen (mMDT) including rifampicin, clofazimine and dapsone, and 137 patients were observed as control cases.

Results The regimen was well tolerated with good compliance: 620 patients completed re-treatment with mild side effects and a low incidence of leprosy reactions. There was a statistically significant difference between the relapse rates of re-treated and control groups (chi squared = 57.44, \( P < 0.001 \)). Furthermore, the relapses in the re-treated group were significantly more likely to be later than those in the control group (\( t = 25.62, \ P < 0.001 \)).

Conclusions Re-treatment with this modified regimen is acceptable and can reduce the risk of early relapse in dapsone-cured patients. The problem of persisters causing late relapse is likely to remain.

Introduction

Organised leprosy control began in China in the mid 1950s with dapsone monotherapy. Patients were given dapsone at 50 mg or 100 mg daily and released from treatment (RFT) after at least 5 years for multibacillary (MB) cases or after 2–5 years for paucibacillary (PB) cases. A few patients were given life-long dapsone therapy. Dapsone being a weak bactericidal drug with slow action requiring long duration of treatment, monotherapy resulted in widespread poor compliance and the emergence of dapsone-resistant strains of M. leprae. Pettit first
Follow-up of re-treated patients after dapsone monotherapy

reported that the prevalence of secondary dapsone resistance was 0·1–0·2%, whereas the prevalence in Shanghai was 4·28%.\(^1\) By contrast the prevalence of primary dapsone resistance was as high as 44·0% in Shanghai by the mid 1980s or even up to 70% according to some reports.\(^2\) Relapses were increasingly seen amongst patients who had been declared RFT after dapsone monotherapy. At this time the registered prevalence rate of leprosy in Shanghai was 10/100,000 and the annual new case detection rate was 1/100,000 population.

Therefore, within the limits of available resources, it was decided that a cohort of MB patients who were RFT after dapsone monotherapy (‘dapsone-cured patients’) should be re-treated with a 1 year course of multidrug therapy, and compared with a control group, to assess the long term impact of re-treatment on the relapse rate. These patients, who were followed up over a 25 year period, are the subject of this paper.

Patients and Methods

Selection of Subjects

Patients were selected according to the following criteria: (a) the patient had been initially smear positive before dapsone treatment began, with a bacteriological index (BI) of at least 2\(^+\) at any one site; (b) the patient must have been ‘clinically and bacteriologically cured’ after dapsone monotherapy, with no clinical symptoms over a 1 year period and smear negative for at least 6 months and with no histological evidence of inflammation on a biopsy; (c) the patient must be less than 70 years old; (d) the patient had no abnormality on routine blood and urine screening tests, no renal or hepatic impairment and no other known disease.

According to the above criteria, 794 eligible patients were enrolled, of whom 587 were men and 207 were women, with an age range of 17–70 (mean 47·78\(^\pm\)8·36 years). Disease duration (before treatment) ranged from 1 month to 39 years (mean 4·5\(^\pm\)12·43 years) and duration of dapsone treatment of 3–30 years (mean 20·64\(^\pm\)21 years). The interval from RFT to re-treatment was 0·8–11·81 years (mean 4·31\(^\pm\)3·11 years).

These 794 subjects were randomly allocated to two groups with 657 being re-treated, between 1983 and 1988, and 137 cases as controls.

Treatment Used

The re-treatment patients were given a modified MDT regimen, not that recommended by the World Health Organization (WHO), as there were concerns about the acceptability of clofazimine discoloration of the skin in the light-skinned Chinese population. They received a 12 month course (within a maximum 15 month period) of the following drug combination: monthly supervised rifampicin 1200 mg plus clofazimine 1200 mg, and daily dapsone 100 mg self-administered.

Any patient who subsequently relapsed was given the standard WHO-recommended MB regimen of multidrug therapy for 24 months.

Surveillance

The initial assessment before re-treatment consisted of a clinical examination and skin smear, plus routine blood and urine screening tests for haematological, renal or hepatic impairment. These examinations were repeated at 3 months, 6 months after starting multidrug therapy and
at the end of the course. At the end of the mMDT course and 12 months later, patients were assessed for any adverse effects of mMDT and any leprosy reactions. For the first 8 years after RFT, patients were examined annually both clinically and bacteriologically; subsequent annual examinations were only clinical unless relapse was suspected (newly developed skin lesions or nerve symptoms) in which case bacteriological examination (and in some cases histological examination) was done.

**DEFINITION OF RELAPSE**

Diagnostic criteria for relapse are not yet generally agreed. The following criteria, based on WHO proposals and other suggestions, were adopted for diagnosis of relapse:

(a) insidious appearance of new lesions and/or reactivation of lesions which had previously disappeared; (b) finding of a positive BI in patient who was previously BI negative, i.e. evidence of fresh multiplication of surviving bacilli; (c) specific histological evidence of relapse on biopsy of suspected lesion, or acid-fast bacilli (AFBs) found in such a biopsy. Ideally relapses after dapsone monotherapy or after MDT should be confirmed by leprosy specialists.

There is no clear cut off point between ‘early-medium’ and ‘late’ relapse; generally 10 years after RFT is considered a reasonable cut off.

**STATISTICAL METHODS**

Descriptive data are presented with mean ± standard deviation. The ‘incubation period’ of the relapse was considered to be either the duration from completing re-treatment to the diagnosis of relapse, or – in the control group – from 1984 until the relapse occurred. The total number of relapsed patients and the sum of the follow-up periods for each patient, expressed as patient years at risk (PYAR) were used as the numerator and denominator for calculating cumulative relapse rates per 100 PYAR. Chi squared test was used for comparison of relapse rates in the two groups. The average incubation periods were compared using Student’s T test. Differences were considered to be statistically significant at $P < 0.05$ (two tailed, 95% confidence interval) or highly statistically significant at $P < 0.01$ (two tailed, 99% confidence interval).

**Results**

Whereas 657 patients were selected for re-treatment (Table 1), only 620 completed the course, accounting for 94.36%. Details of the other 37 with their reasons for withdrawal are given in Table 2.

**SIDE EFFECTS OF MDT**

Gastro-intestinal side effects accounted for 44.93% of cases, these occurred 1–2 days after taking supervised doses of medication, usually for only the first 2–3 months, then reduced to a tolerable level. There was pigmentation and dryness of skin in 41.8%, which was not conspicuous. Mild effects occurred in the eye in 7.72% cases (impaired eye sight, dryness of eye, discoloration of sclera and conjunctiva). There were three cases of liver disorder:
one case with SGPT raised to 200 units, and two cases of hepatomegaly (0.46%). One case of influenza-like syndrome occurred (0.15%).

**LEPROSY REACTIONS**

There were seven cases of reversal reaction (1.07%) amongst which five occurred 1–5 months after starting re-treatment, and two cases occurred 3 months and 26 months after completing re-treatment. Four cases had skin changes such as erythematous patches on face, hands & feet. Three cases had only nerve symptoms: one had footdrop, one had facial paralysis, one had dysphagia. After a course of prednisolone, by the end of the re-treatment course, six cases had recovered from their nerve function impairment.

**RESULTS OF FOLLOW-UP**

The 757 patients were followed up for 5–25 years (mean 17.98 ± 5.34 years). At the end of 25 years, apart from 48 who were lost to follow-up, 377 were still alive (314/620 from the re-treatment group and 63/137 controls).

Three patients had relapsed (as MB cases) in the re-treatment group and these relapses occurred in 12th, 17th and 24th years after completing re-treatment, giving a cumulative relapse rate of 0.484% or 0.269 per 1000 PYAR. However, 17 cases had relapsed in the control group (Table 3) mainly within the first 10 years after 1983, giving a rate of 6.90 per 1000 PYAR.

The difference in the cumulative relapse rates between the two groups was statistically significant ($P < 0.001$). In addition, the difference in mean incubation period was significant.

**Table 1. Conditions of 657 retreated cases**

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of patients re-treated</th>
<th>No. who completed course of re-treatment</th>
<th>Percentage of patients completed re-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983–1984</td>
<td>551</td>
<td>524</td>
<td>95.10%</td>
</tr>
<tr>
<td>1985</td>
<td>64</td>
<td>57</td>
<td>89.06%</td>
</tr>
<tr>
<td>1986</td>
<td>20</td>
<td>18</td>
<td>90.00%</td>
</tr>
<tr>
<td>1987</td>
<td>17</td>
<td>16</td>
<td>94.12%</td>
</tr>
<tr>
<td>1988</td>
<td>5</td>
<td>5</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Table 2. The reasons for discontinuing treatment in 37 patients**

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Cases</th>
<th>Months of treatment received</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver disorder</td>
<td>1</td>
<td>7 months</td>
</tr>
<tr>
<td>Mild hepatomegaly</td>
<td>2</td>
<td>7 months, 2 months</td>
</tr>
<tr>
<td>Type I leprosy reaction</td>
<td>1</td>
<td>1 month</td>
</tr>
<tr>
<td>Digestive symptoms</td>
<td>5</td>
<td>4–8 months</td>
</tr>
<tr>
<td>Influenza-like syndrome</td>
<td>1</td>
<td>3 months</td>
</tr>
<tr>
<td>Death from other causes</td>
<td>2</td>
<td>8 months, 9 months</td>
</tr>
<tr>
<td>Skin pigmentation</td>
<td>25</td>
<td>1–11 months</td>
</tr>
</tbody>
</table>
Over the past 50 years a considerable amount of information has accumulated about dapsone, but the mechanism of drug resistance remains uncertain. Mutation seems to be the most likely reason. The proportion of dapsone-cured patients who relapsed increased steadily in the 1970s and during 1980s–1990s, it settled at 13%–20% of all detected MB cases. However, after 1986 the number of relapses decreased, apparently due to the introduction of WHO-recommended MDT. Chen\textsuperscript{7} found an overall relapse rate of 8·14% or 5·91/1000 PYAR in MB patients by 13·8\textsuperscript{8}·4 years of follow-up from RFT after dapsone monotherapy. In Shanghai, the cumulative relapse rate was 14·63%, and 2·44% per annum, before re-treatment began; in Guangdong province it was up to 20·43%. However, it is difficult to make strictly accurate comparisons between reported rates after dapsone monotherapy owing to variation in dosages, duration of treatment, criteria for cure, classification methods, the type and period of follow-up and the different criteria used for diagnosing relapse.

We conclude from the results presented in Table 3 that the cumulative relapse rate, and percentage of patients relapsed, after re-treatment, was markedly lower than in the control cases. This 20–30 fold difference observed clearly indicates that re-treatment effectively kills bacteria which were dapsone resistant. Assuming the risk of relapse is 5–10% after dapsone monotherapy and 0·7% after 7–10 years follow up after MDT,\textsuperscript{8} using Bayes theorem\textsuperscript{9} it can be estimated that the risk of early relapse after re-treatment with MDT of dapsone treated patients is controlled to under 0·035–0·07%. This is a very exciting result.

No early relapses were seen after mMDT in this cohort: the earliest occurred 13 years after completion of mMDT and 38 years after cessation of dapsone monotherapy. This shows that re-treatment can prevent ‘early-medium’ relapses (i.e. those within 10 years of completing MDT). As Biswas and others have demonstrated ‘...it is once again established that MDT can prevent relapse in leprosy’\textsuperscript{10}.

The difference in the mean incubation period of relapse between the two groups indicates that relapses after modified MDT may be of the late type which is due to ‘persisters’
(Persisting bacilli or drug-resistant mutants). Although MDT rapidly interrupts the multiplication of bacilli, very small numbers of persisters may remain after any form of chemotherapy\textsuperscript{11} even after bacterial negativity in skin smears and biopsies is attained. To date there is no known way to eliminate them. Clearance seems to be dependent on the body’s immune capacity, including the activity of macrophages. There is little difference (below 1\%) between the rates of relapse found in this paper and those reported elsewhere.\textsuperscript{12–15} Late relapses after MDT in MB patients were under 1\%, the level considered unacceptable. It appears that late relapses cannot be prevented by the modified MDT used in this study, nor by WHO-recommended MDT regimen.

Unfortunately the data on BI prior to dapsone monotherapy were unavailable for the three late relapse cases in the re-treatment group. Jamet’s study\textsuperscript{16} indicated that relapse rate was closely correlated with pre-treatment bacterial load. In newly-diagnosed patients with bacilli sensitive to rifampicin, clofazimine and dapsone, and other drugs, the chance of \textit{M. leprae} becoming simultaneously resistant to two drugs is very low. However, with a total bacterial load of $10^6$ the absolute number of persisters before treatment is more than $10^5$, which may explain why three of the re-treatment group relapsed. Other possibilities must be considered and re-infection with viable \textit{M. leprae} cannot be excluded,\textsuperscript{17} but the probability is thought to be low as all those who relapsed either denied contact with other active leprosy cases, or lived in a non-endemic region.

The modified MDT regimen used was well tolerated, with relatively mild or transient symptoms only, although gastrointestinal disturbance, skin pigmentation, and dryness of skin were the main side effects, affecting 86-73\% patients. The rate of absorption of clofazimine was slower after monthly than daily intake, but the advantage was that there was no skin damage in re-treated patients; skin pigmentation was only slight. The larger monthly dose of rifampicin (1200 mg) compensated for the reduced clofazimine effect. The one year fixed duration course was acceptable to the re-treatment patients. The incidence of reversal reaction (1\%) was lower than reported by others,\textsuperscript{18,19} and no patients suffered ENL reaction during the Modified MDT course.

There is limited evidence on leprosy re-treatment. The present paper is a first report on re-treatment of dapsone-cured patients followed up for 25 years, showing that the modified MDT regimen, which was well-tolerated and resulted in good compliance, can greatly reduce the risk of early relapse of dapsone–cured patients.

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**References**


