Lepr Rev (1995) **66,** 1–9

Editorial

RELAPSE FOLLOWING VARIOUS TYPES OF MULTIDRUG THERAPY IN MULTIBACILLARY LEPROSY

Introduction

One of commonest questions asked by leprosy patients on their completing multidrug therapy (MDT) is, 'Am I cured?'. There are, of course, several different facets to this question, including the risk of subsequent physical deterioration due to damage to anaesthetic hands or feet. But, from the point of view of chemotherapy, the questioner is in effect enquiring whether all the leprosy bacilli in his or her body have been successfully killed, or, if tiny numbers of dormant living bacilli ('persisters') still survive, what is the risk that these may subsequently resume multiplication and eventually cause clinical relapse? The fear that the disease might 'come back' and that the patient could infect family members, especially new children or grandchildren, is very deep seated. How honestly can we reply, and what is the scientific evidence to date?

Relapse rates provide the ultimate proof of successful treatment of infectious diseases, even though regimens need also to be assessed in terms of acceptability, the incidence of toxic side-effects, duration and ease of treatment, and cost. In tuberculosis, an accurate assessment of relapse rates can be achieved within 2 years of stopping chemotherapy. Admittedly, small numbers of apparently cured patients may relapse years later, sometimes as a result of stress or intercurrent disease of immunosuppression, but these late failures do not materially affect the overall assessment of a regimen. Similarly, in cancer treatment, a good overall assessment is obtained by a 5-year survival rate, even though small numbers of patients may die from a recurrence a decade or even several decades later.

The duration of follow-up required in leprosy after completing MDT (release from treatment, RFT) to give an adequate overall assessment of subsequent relapse rates is not yet known. The WHO Study Group on the *Chemotherapy of leprosy for control programmes* report was published in 1982,[1] and therefore by 1994 we have at best only 10 years' post RFT experience in multibacillary leprosy (MBL). Therefore it is important to consider those results obtained, not only with WHO MDT, but with dapsone monotherapy and with other MDT regimens.

Perhaps dapsone monotherapy is the least helpful. But it is worth recalling that

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Pearson and his colleagues in Malaysia found that the average incubation period for dapsone-resistant relapse, in LL and BL patients *still* receiving dapsone, was 15·8 (range 3–24) years after commencing sulphone therapy;[2] in Ethiopia it was 8·7 (range 2–20) years;[3] and rarely, it can take over 30 years.[4]

Relapse rates and the timing of relapse after completing dapsone monotherapy vary somewhat, depending partly on the dose of dapsone given, and the duration and regularity of treatment. Becx-Bleumink[5] studied 1123 MBL patients who had undergone RFT between December 1983 and July 1987. All had been skin-smear negative at RFT. On a 6–7 year follow-up, 148 patients were considered to have relapsed, giving an overall relapse rate of 13·2%, or 24·8 per 1000 patient years. Although the annual relapse rate was significantly lower during the 5th to 7th years after stopping treatment (10·0–13·5 per 1000 patient years after relapse) compared to the first 4 years (25·2–39·4 per 1000 patient years), it was still unacceptably high. Cartel *et al.* followed a small group of 131 MBL patients for up to 36 years after RFT; the average risk of relapse was 1·39 per 100 patient years, and the risk did not vary significantly with time.[6] Waters *et al.*[7] studied 362 LL and BL in-patients treated with supervised dapsone monotherapy in Malaysia for 18·5–22 years until July 1970. All had been smear negative for at least 5 years at RFT. Over the next 8–9 years, 25 patients (8·6%) relapsed, with an average relapse risk of 1·04 per 100 patient years of observation, and there was no significant difference in the relapse rate throughout the 9 years. Of 8 strains of *Mycobacterium leprae* isolated from patients in relapse, 5 were found to exhibit some level of dapsone resistance in mice, whereas 3 were dapsone sensitive. If it can be assumed that in the remaining 17 relapse patients, whose strains of *M. leprae* were not tested, a similar proportion were also dapsone resistant, then the risk of relapse due to persisters was surprisingly small (0·4 per 100 person years). But, from among all the lepromatous patients who had commenced similar sulphone therapy in the leprosarium between 1948 and 1951, 52 had relapsed between 1960 and 1972 with proven dapsone resistance. Therefore failure of treatment due to the development of dapsone resistance proved to be a much greater risk overall than that of relapse due to microbial persistence on stopping treatment after 20 years of outstandingly good dapsone monotherapy. MDT is designed to prevent the emergence of drug resistance, but what effect it has on persistence is uncertain. Admittedly, untreated lepromatous patients who received rifampicin 600 mg plus dapsone 100 mg daily had at 6 months statistically fewer viable persisting bacilli detectable in immunosuppressed mice than did similar patients treated with dapsone 100 mg daily.[8] But this difference might have been due to the much faster rate of kill with rifampicin, the drug's ability to kill intermittently (by analogy with *M. tuberculosis*) or slowly metabolizing *M. leprae*, and also its ability to kill dapsone-resistant bacilli. What is important is to measure relapse rates after MBL MDT, whether given for 2 years only, or until skin-smear negativity, placing these results in the context of relapse rates obtained with other (non-WHO) MDT regimens, some of which have been followed up for long periods.

Relapse rates with various (non-WHO) regimens

1 THE MALTA PROJECT

Fear of persisters as a cause of relapse in LL and BL leprosy was reduced considerably

by the Malta project.[9] The trial commenced in 1972, at a time when most leprologists would not have had enough courage to stop chemotherapy after a limited period; it was brilliant in concept, although somewhat disappointing in details. Combined chemotherapy with daily rifampicin, dapsone, prothionamide, and isoniazid (the last 3 as Isoprodian) was administered to a mixed group of 257 patients, of whom about 200 were LL and BL, at all stages of treatment. Many had received years of dapsone monotherapy, and some had also received thiambutosine. The tuberculoid patients in general received about 6 months' treatment, and the LL and BL patients 21–25 months' treatment, although there was considerable variation, and the duration was longer for new patients. In about half the MBL patients, daily rifampicin was given for only the first 5–10 months, treatment being subsequently continued with Isoprodian alone. The criteria for stopping all treatment were not well defined. In 1992, a 20-year assessment was made of 92 MBL patients by Jacobson, which was reported to the Würzburg Symposium, and the 14th International Leprosy Congress.[10] Only 2 of the 92 patients were found to have relapsed. The first was diagnosed in 1949, received dapsone irregularly until 1972, and was smear positive in 1974, when she commenced 21 months of multidrug therapy. She relapsed in 1989 at the age of 85, with lesions which were clinically and bacteriologically LL. The second patient was diagnosed in 1967, and was smear negative on commencing, in 1972, 5 months of daily rifampicin and Isoprodian, followed by 16 months of Isoprodian. He relapsed in 1991 with BL leprosy. These results are undoubtedly very satisfactory, although almost all the patients had received years of dapsone monotherapy.

2 PARAGUAY LEPROSY CONTROL

Following the success of the Malta project, a similar treatment in the dosage of rifampicin 450 mg, prothionamide 350 mg, dapsone 100 mg, and isoniazid 350 mg daily, was commenced in Paraguay in 1979. To date, 5504 patients (MB 78%, PB 22%) have been treated, of whom 2396 were released, usually after 2 years (MBL), or 6 months (PBL), of treatment. In a post-therapy follow-up period of 5–10 (average 8·8) years, relapse has been diagnosed in 11 (0·6%) of 1846 MBL, but none in PBL patients. No relapses were detected during the first 5 years of follow-up (Alvarenga, Leguizamon and von Ballestrem; report submitted to the Pre-Congress Workshop on Chemotherapy, 14th International Leprosy Congress, 1993). It would be very helpful to know the number of previously untreated patients, as compared to those who had received dapsone monotherapy prior to rifampicin–Isoprodian MDT; nevertheless, these results strongly support the concept of limited duration MDT in MB leprosy.

3 STUDIES AT THE INSTITUT MARCHOUX

One of the most helpful pieces of opportunistic leprosy research in the past decade has been performed by the Marchoux Chemotherapy Study Group.[11] Influenced by short course chemotherapy in tuberculosis, Professor S. R. Pattyn of Antwerp and colleagues at the Institut Marchoux commenced in 1977 a series of chemotherapy trials of rifampicin-containing regimens of limited duration in LL and BL leprosy, and the Institut also joined the first THELEP controlled clinical trial in 1978. In these studies, in 11 of the 12 regimens, all drug doses were given supervised, 'daily' drugs being given on 6

days a week, and only in the 12th, the WHO MBL MDT regimen, were daily drugs given unsupervised 7 days a week. The first 2 regimens, given to untreated LL and BL patients, consisted either of rifampicin 600 mg twice weekly plus dapsone 'daily' for 6 months, followed by dapsone monotherapy for 6 months, before stopping all treatment (regimen A), or similar chemotherapy plus prothionamide 500 mg 'daily' during the first 6 months (regimen B). From 1978 to 1983, previously untreated LL patients were admitted to the WHO THELEP trial,[12] BL patients only being included during the second half of the 5-year intake. In all the other 7 studies, both LL and BL patients were admitted; untreated patients only were admitted to the 6-week (S6) regimen, otherwise the intake consisted of a mixture of untreated and relapsed patients (after dapsone monotherapy, or dapsone plus, usually, a single dose of rifampicin) or patients who had received dapsone for at least 5 years without clinical relapse, but still had a BI of 2+ or greater. Clofazimine-containing regimens were only given to patients who had received more than 5 years of dapsone monotherapy, or who had proven dapsone resistance. The THELEP and the WHO MDT regimens were given for 2 years, 4 regimens were given for 1 year (including regimens A and B), 2 for 3 months, 1 for 6 weeks, and 1 for 4 weeks. Thereafter, no chemotherapy was given. Of the 532 patients admitted to trials, 437 completed the prescribed treatments, and 384 were followed up for at least 1 year after RFT.

The Marchoux Chemotherapy Study Group studied subsequent relapses in the 384 patients. Relapse was carefully defined. It was suspected whenever the BI at any site showed an increase of at least 2+ greater than the previous value, or when a new lesion was observed with a BI greater than any pre-existing lesion. In most cases, biopsies were taken, both for histopathology (for the presence of young histiocyte granulomas containing solidly stained bacilli), and for separation of *M. leprae* for inoculation into the footpads of normal mice. The careful definition of relapse, together with confirmation of the presence of viable bacilli by mouse footpad inoculation, makes this study especially valuable.

By May 1991, relapse had been observed in 68 (17·7%) of the patients, and confirmed by multiplication of their strains of *M. leprae* in mice in 54 of the first 61. The relapses tended to occur late, about 5 ± 2 years after RFT; in general, the shorter the duration of rifampicin treatment, the earlier the appearance of relapse. It is unfortunate that the most powerful regimen THELEP A_2 ('daily' rifampicin, prothionamide, and dapsone) resulted in the frequent development of hepatitis so that intake was abandoned. Only 5 patients were followed long term; 1 of them relapsed in the 7th year, but it is notable that he had received steroid therapy for erythema nodosum leprosum for 1 year after stopping chemotherapy. The WHO MDT regimen had the shortest, inadequate follow up of only 4 years (see below). In the 2 oldest regimens from 1977, no patient had relapsed after 5 years, but at the end of 9 years, 5 of 18 (27·8%) regimen A and at the end of 10 years, 4 of 16 (25%) regimen B patients had relapsed. In regimen S_4, the 1-month regimen, the first relapse was detected in the 2nd year, at the end of 5 years 17 of 88 (19·3%) and at the end of 7 years 24 of 88 (27·3%) patients had relapsed. There was evidence that the risk of relapse was greater in patients with a high BI at RFT, than in those with a BI of $\leqslant 4+$, and the risk was also less in those who at some stage became smear negative.

A recent analysis of January 1993,[13] reported from 435 patients a total of 100 relapses, of which 66 had already been confirmed in mice; all the isolated strains

remained susceptible to rifampicin. Relapses occurred in the 2nd to the 14th (current) year after RFT.

At 5 years after RFT, the risk of relapse, 1·7%, was best in patients from the 12-month regimens, although it had risen to 20% at 10 years; the rate per 100 person years being 3·9; 3-month regimens gave a risk of relapse at 5 years of 5·1%, and the 1-month regimen of 12·5%. The 2-year regimens gave a 5-year risk of relapse of 5·2% (and 10 years of 33%), but it should be remembered that the THELEP C regimen consisted of only a single 1500 mg dose of rifampicin plus 2 years of dapsone, and their E_2 regimen of 13 weekly 900 mg doses of rifampicin plus 'daily' prothionamide, suggesting that the 2nd year of dapsone monotherapy had little effect on overall relapse rates.

4 PATTYN'S STUDIES

Not only was Pattyn associated with the Bamako studies, but also with other centres, especially in Zaire. Some regimens were common to both countries. Pattyn analysed both sets of figures,[14] although as he tabulated cumulative relapse rates calculated by a life table method, there is no straight comparison between the Marchoux results[11] and Pattyn's results.[14] Nevertheless, Pattyn made a number of important observations. Relapse rates were higher at the Institut Marchoux than in Zaire, where relapses tended to occur later. But BIs, at the start of treatment in the patients in Bamako were significantly higher than in the patients in Zaire. The higher the initial BI, the greater the risk of relapse, and this risk increased with time. Relapses occurring during the first 3 years after RFT at a rate higher than 1% might indicate a later high incidence of relapse, although the absence of relapses during the first 3 years did not exclude later high relapse rates. The combination of rifampicin with a thioamide in very short-course chemotherapy was insufficient (this surely indicates the need for careful controlled trials of combinations of rifampicin with ofloxacin, minocycline, and clarithromycin). Finally, he suggested that results with 'daily' rifampicin given for 8 weeks or 26 weeks were better than with intermittent rifampicin. However, the regimens given the 'best' results were only tried in Zaire and not at Bamako. Therefore, perhaps a full 10 years of follow-up are essential for the Zaire trails, especially as Pattyn himself emphasized that in the evaluation of the treatment of MB leprosy, it is necessary to follow up the patients for 9–10 years after RFT. Until then, an alternative explanation can be maintained, namely that the total dosage of rifampicin and to a lesser extent the total duration of treatment, are the important factors influencing relapse rates.

Relapse rates with WHO MDT

In chemotherapy research, once a drug or drug regimen has been shown to be active in a pilot trial, a controlled clinical trial is set up, in which individual patients are studied in detail, and if successful, the regimen is applied generally, and evaluated for its public health impact as well as individual effectiveness under field conditions. Because of the dapsone resistance epidemic in 1982, WHO MDT could not be evaluated in this classical programmed way, because it was considered unethical to set up controlled trials using dapsone monotherapy as the control regimen. Nevertheless, the WHO THELEP steering committee did set up, in 1982, very careful field studies in South India.

1 THELEP KARIGIRI AND POLAMBAKKAM MDT FIELD STUDIES

The aim was to include all LL and BL patients in the 2 control areas, save for those with significant intercurrent disease. Therefore, the majority of patients had received long-term dapsone monotherapy, although newly diagnosed LL and BL patients were admitted over the next 2 years. Patients received chemotherapy for 2 years, or until they achieved smear negativity, whichever was the longer. In all, 2 regimens were compared, WHO MBL MDT and a THELEP regimen in which 600 mg rifampicin and 600 mg clofazimine were given supervised on 2 consecutive days a month, plus unsupervised dapsone 100 mg daily. No significant difference has been found in their results as judged by relapse rates.

At Karigiri, about 980 patients were admitted to the trial, of whom almost 80% were LL. After a 7–8 year follow-up, relapses did not exceed 3 in number. A report on the Polambakkam results was presented at the 14th International Leprosy Congress.[15] Of 1174 patients admitted to the trial (of whom only 146 (12·4%) were smear positive), 979 were followed up for 8–9 years until 1993—8 relapses (0·82%) were detected, of whom 3 were smear positive BL, whereas the other 5 were smear negative, classified as PBL, BT or TT. The presence of viable bacilli from the first BL relapse was confirmed in mice, and the strain was fully sensitive to rifampicin, clofazimine and dapsone; 2 of the relapse patients had received the THELEP regimen and 6 WHO MDT. To date, therefore, 2 years of MDT given to long-term dapsone treated, smear negative LL and BL patients, appears to have been outstandingly successful.

2 KARIGIRI SECOND FIELD TRIAL

When the intake of the first field trial was completed, all newly-diagnosed MBL patients were given WHO MDT, for 2 years only. To date, patients' BIs have continued to fall at the normal rate, and by August 1993, no relapses had occurred.[16] Whereas in the first trial, almost 80% of patients admitted were LL, in the second trial almost 80% were BL. It is likely that, in this excellent control area, many were diagnosed relatively early, before their bacterial loads were high. The next 5 years' follow-up will be crucial.

3 INSTITUT MARCHOUX—EXPERIENCE WITH LIMITED DURATION WHO MDT

At Bamako, between 1984 and 1986, patients were recruited for limited duration MDT. Only 44 completed the course of 24 doses of monthly rifampicin, and 35 were available for long-term follow-up. By May 1991, 1 patient only had relapsed (in the 3rd year),[11] giving a relapse rate of 0·8 per 100 patient years of observation. By 1992,[14] the relapse rate had risen to 10%. In 1994, Ji and his colleagues reanalysed the WHO MBL MDT regimen (Ji, personal communication). By now, 7 of the 35 patients had relapsed, including 4 in the 6–7th years of follow-up and 1 in the 8th year, giving an overall relapse rate of 20%. The mean time of relapse, to date, was $62{\cdot}7 \pm 18{\cdot}7$ months. All 7 relapses had occurred in patients whose pretreatment BIs were $\geqslant 4{\cdot}0$. Therefore the risk of relapse was significantly greater in patients with an initial high bacterial load, which includes moderately advanced LL and advanced LL and BL patients. This series also suggested that follow-up needs to be greater than 5 years, probably 8–10 years to give a good assessment of relapse rates.

4 WHO POST-MDT QUESTIONNAIRE SURVEY

WHO has recently carried out 2 surveys of post-MDT relapse rates.[17] The pilot survey covered 92 194 MB patients; 467 were reported to have relapsed, giving an overall relapse rate of 0·23 per 100 person years. A 2nd, extended survey, of cohorts of patients at 28 selected centres, included 20 141 MB patients, of whom 1414 were followed until their 9th year after completing MDT—67 patients were considered to have relapsed, with a cumulative risk of relapse of 0·77%. Less than half the patients were followed for 5 or more years, therefore although the mean and median times of relapse were 3·42 and 3·0 years, respectively, it is important to note that the relapse rates in the 6th and 7th years were similar to those of the 3rd and 4th years. The WHO survey results are outstandingly good, fully substantiating faith in WHO MB MDT. But it should also be noted that no separate analyses have been made for patients who had previously received long-term dapsone monotherapy, and were smear negative on commencing MDT, and for previously untreated patients, subgrouped into those treated for 2 years only, and those treated until smear negativity. Further time is needed to collect these data.

Conclusions

The results for MBL following the introduction of WHO MDT have been excellent. The epidemic of secondary dapsone resistance has been aborted, and treatment of limited duration (even if continued until smear negativity) has been successfully introduced. Because of the epidemic of dapsone resistance, most thinking leprologists by the early 1970s concluded that some form of MDT was essential, analogous to combined chemotherapy in tuberculosis. The introduction of rifampicin in 1970,[18,19] and the early results from the pilot Malta project[20] showed that limited duration MDT was a real possibility. WHO MDT has proved very robust under field conditions.

The number of relapses reported to date have been minute, although the majority of patients followed for 8–10 years since release from treatment probably belong to the smear-negative long-term dapsone monotherapy group; as such their bacterial load of *M. leprae* at the start of MDT would have been tiny. In the first 5 years after the introduction of MDT most newly-diagnosed LL and BL patients and most relapse patients (whether from dapsone resistance or from discontinuing treatment) are likely to have been kept on MDT until becoming smear negative; that is for 4–10 years.

Criteria for defining relapse may vary from centre to centre,[17] and an apparently high relapse rate may reflect too loose a definition (Smith, Jesudasan and Jakeman, personal communication). This editorial has concentrated on centres where relapse has been defined clinically, bacteriologically, and histologically, and where the presence of viable *M. leprae* (proof of bacteriological relapse) has usually been confirmed by multiplication in mouse footpads. These results suggest that:

1 Risk of relapse is very low in old smear negative LL and BL patients, some of whom may relapse with localized BT lesions.[21]
2 Risk of relapse is not yet fully known in previously untreated LL and BL patients given WHO MDT until smear negativity, although provisional data suggest that the risk is very small.
3 In previously untreated LL and BL patients treated with WHO MDT for 2 years only,

the risk of relapse is related to the pretreatment load of *M. leprae*; the more severe the infection, the greater the risk of relapse.

4 The timing of relapse is important. Very few well-authenticated relapses occur in the first 3 years after RFT, and the claim that the majority occur in the first 5 years[17] is based on absolute numbers reported from large cohorts at 1–4 years, rather than relapse rates. Both from experience with WHO MDT and from other regimens, a follow-up of 8–10 years appears essential.

5 There is a great desire among leprosy control experts to give WHO MBL MDT for a set duration of 2 years,[22,23] especially in 'rolling programmes' with outside funding. Such short-duration MDT is operationally essential in such circumstances. It has been claimed that by lowering the incidence of tuberculosis (and by inference, of leprosy) by 80%, the endemic of disease should decline.[14] This is almost certainly true. But it is in those areas which previously had the poorest leprosy control which are likely to have the most advanced patients with the highest bacterial loads. Therefore, significant numbers of relapses will almost certainly occur in such circumstances, and therefore an effective residual structure must remain in an area to detect relapses early and to treat them well, both as a duty to the patients and to allay any threat to the credibility of the programme. Furthermore, Jamet, Ji, and their colleagues are now proposing that the duration of MDT should be doubled to 4 years in patients with an initial average BI $\geqslant$ 4·0 before commencing MDT.[24] This would be a simple measure to implement in high endemic areas. In low endemic areas with a declining endemic approaching the WHO 'elimination' target, where leprosy may already be tending to persist in 'clusters', and where the general health services are likely to be of a high standard, it may well be worth keeping patients on MDT until they achieve smear negativity as originally advised by the WHO Study Group in 1982;[1] this should ensure that the endemic continues to die out at the maximum possible speed, because of minimal relapses. For although the results with WHO MDT are still incomplete, experience in Africa does suggest that the relapse rates after different forms of MDT are usually related both to the initial BI and to the total number of rifampicin doses and the total duration over which they are given.

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