CHEMOTHERAPY OF LEPROSY

Report of a WHO Study Group

World Health Organization
Geneva 1994
WHO Library Cataloguing in Publication Data

WHO Study Group on Chemotherapy of Leprosy
Chemotherapy of leprosy : report of a WHO study group.

(WHO technical report series ; 847)
1. Leprosy -- drug therapy I. Title II. Series

ISBN 92 4 120847 3 (NLM Classification: WC 335)
ISSN 0512-3054

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Printed in Switzerland
94/10091 – Bolek – 8000
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Geneva, 1–5 November 1993

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1. **Introduction**

A WHO Study Group on Chemotherapy of Leprosy met in Geneva from 1 to 5 November 1993. Opening the meeting on behalf of the Director-General, Dr S.K. Noordeen, Chief Medical Officer, Leprosy Control, recalled that a WHO Study Group on Chemotherapy of Leprosy for Control Programmes had recommended the introduction of multidrug therapy (MDT) for leprosy in 1981, at a time when global efforts to control the disease were meeting with little success, owing to the widespread occurrence of dapsone resistance. Describing this as a bold and balanced decision, Dr Noordeen noted that the critical role of MDT in the successful control of the disease was now well recognized.

Some 4.3 million patients had already been cured through MDT and the number of cases of leprosy had been reduced by two-thirds. Efforts still had to be made, however, to simplify the administration of MDT, to improve accessibility for patients with special needs (e.g., those living in remote areas), and to derive the maximum benefit from the new antileprosy drugs. Even though leprosy could be successfully controlled through chemotherapy, it was important to monitor the situation constantly for problems such as drug resistance and to develop even more effective drug combinations.

The objectives of the present Study Group were as follows:

- To review the information collected since 1981 (the year when the WHO MDT regimens were introduced) and to recommend any modifications of these regimens that seemed appropriate in the light of the data collected.
- To make recommendations regarding the use of the new antileprosy drugs in the chemotherapy of leprosy.
- To make recommendations regarding changes in the operational aspects of chemotherapy of leprosy which would further strengthen efforts to control and eliminate the disease.
- To identify further research needs in order to improve the chemotherapy and control of leprosy.

1.1 **WHO Study Group on Chemotherapy of Leprosy for Control Programmes, 1981**

When the WHO Study Group on Chemotherapy of Leprosy for Control Programmes met in 1981, leprosy control programmes faced a variety of serious constraints that not only threatened to hinder further progress but, left unchecked, could have resulted in a serious deterioration of the world leprosy situation. Widespread secondary dapsone resistance was being reported in up to 19% of patients previously treated with dapsone.

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1 As of April 1994, it is estimated that over 5.6 million leprosy patients have been cured through MDT.
monotherapy. Of equal concern, primary dapsone resistance, mostly low degree, was being detected in some areas in as many as 50% of newly diagnosed, previously untreated cases (1). Furthermore, cases of resistance of *Mycobacterium leprae* to rifampicin and the thioamides had been reported among patients receiving these drugs as monotherapy. However, most control programmes had failed to appreciate the seriousness of the situation and thus had not implemented even the limited MDT regimens recommended in the fifth report of the WHO Expert Committee on Leprosy (2).

After reviewing the situation and data on the available drugs and from ongoing drug trials, the 1981 Study Group recommended that all leprosy patients (paucibacillary and multibacillary) be treated with regimens that would be effective in cases of dapsone resistance, but were also of relatively short duration. The recommended regimen for paucibacillary leprosy involved rifampicin and dapsone, administered for 6 months, while the regimen for multibacillary disease involved both these drugs, together with clofazimine, given for 24 months or until skin smears became negative. In addition, new simplified definitions of paucibacillary and multibacillary leprosy were introduced and operational guidelines were drawn up to help assure the successful implementation of the new regimens.

Within a few years these now standard WHO MDT regimens were widely implemented and the level of implementation has steadily increased over the past 12 years. The regimens have proved highly successful in preventing relapse. Indeed, the success of these regimens and the concurrent efforts by Member governments and nongovernmental organizations to strengthen leprosy control programmes led the World Health Assembly in 1991 to set a goal of elimination of leprosy as a public health problem (reducing the prevalence to below 1 per 10000 population) by the year 2000.

Although progress towards this goal has been excellent, it is appropriate at this time to review the chemotherapy of leprosy in the light of 12 years of experience with the current MDT regimens and the recent introduction of several new bactericidal antileprosy drugs.

### 2. The present situation

During the past 8 years, the numbers of estimated and registered cases of leprosy have fallen from 10-12 million to 2.7 million and from 5.4 million to 1.9 million respectively. On the other hand, approximately 690000 new cases were detected in 1992. This represents no significant change from previous years. Intensified case-finding efforts and earlier detection of cases as a result of improved control programmes may, to some extent, have obscured any downward trend resulting from MDT. It is also likely that many cases now being detected are in people who were
infected before the introduction of MDT. None the less, in some long-standing, well organized control programmes where there has been a prolonged high level of coverage, there has already been a significant fall in the case-detection rate since the introduction of MDT. This trend may become more widespread in the future, although many factors other than the introduction of MDT are undoubtedly involved, such as improved case management.

Currently, the level of MDT coverage of estimated and registered cases is about 38% and 53% respectively and the cumulative MDT coverage is around 76% and 86% respectively. Many of the patients not yet on MDT are those who are difficult to reach or who live in countries where efforts to control the disease have proved inadequate. There is therefore considerable room for improvement; this should be achievable through better control programmes, innovative systems of drug delivery, and adequate allocation of resources. Such improvement is essential to achieving the goal of eliminating leprosy as a public health problem by the year 2000.

Another encouraging observation is the extent to which disability in newly diagnosed patients is decreasing. Although treatment with MDT does not have a direct effect on disabilities, implementation of the standard WHO MDT regimens has indirectly led to a marked reduction in the prevalence of disabilities among leprosy patients. Earlier detection of the disease, a reduction in the frequency of reactions and very low rates of relapse – all consequences of the implementation of MDT – have contributed significantly to the prevention of disabilities. Moreover, as a consequence of the dramatic decline in prevalence, health workers should be able to devote more time to the management of reactions and the prevention of disabilities.

2.1 Experience with multidrug therapy (MDT) since 1981

Data collected by WHO from several countries on cohorts of patients completing the recommended MDT regimens between 1981 and 1993 have presented a very favourable picture (3).

Out of a total of 20141 multibacillary patients (about 80000 person-years), 67 were reported to have relapsed, yielding a cumulative risk of relapse of 0.74% over a 9-year period of follow-up. Among a total of 51 553 paucibacillary patients (about 180 000 person-years), 306 cases of relapse were identified, giving a cumulative risk of relapse of 1.09% over the same period of follow-up. Moreover, in both multibacillary and paucibacillary patients, the risk of relapse remained almost constant for every year of follow-up.

¹ A composite indicator defined as the proportion of leprosy patients who are, or have been, treated with MDT since the programme based on MDT started, among all patients registered during the same period.
In comparison, among multibacillary patients treated with dapsone monotherapy and followed up over a similar period after their skin smears became negative, the expected cumulative risk of relapse would be between 10% and 20%.

Data are also available from several trials sponsored by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases through its Scientific Working Group on the Chemotherapy of Mycobacterial Diseases (THEMYC). Among over 7700 multibacillary patients involved in the trials, the risk of relapse was less than 1 per 1000 person-years, regardless of whether the patients were treated with the standard WHO MDT regimen for 2 years or until their skin smears became negative.

The generally excellent results reported with the WHO MDT regimens in the literature have clearly validated their efficacy, safety and acceptability. However, the results of studies on other MDT regimens have been variable. The interpretation of data from different studies is complicated by the use of a variety of regimens, including modifications of the WHO MDT regimens, the inclusion of variable numbers of patients previously treated with dapsone monotherapy for prolonged intervals, and confusion about the classification of paucibacillary and multibacillary cases, particularly since the definitions were changed in 1988 by the WHO Expert Committee on Leprosy (4). There has also been confusion about whether relapse or reaction was observed in those who reportedly relapsed, and uncertainty as to the level of patient compliance in some instances and, perhaps most important from the point of view of paucibacillary disease, whether treatment had been adequate. The Study Group therefore took all of these factors into account in reviewing the reports on paucibacillary and multibacillary disease.

2.1.1 **MDT for paucibacillary leprosy**

In general, the reports on MDT regimens for paucibacillary disease can be divided into three groups:

- those that found that MDT for less than 6 months was sufficient;
- those that found that the 6-month WHO MDT regimen was sufficient;
- those that found that MDT for more than 6 months was required by at least some, if not all, cases.

Among those reporting successful therapy in less than 6 months are Pattyn et al., whose regimens were generally markedly different from the standard WHO MDT regimen for paucibacillary leprosy and perhaps more potent (5–7). Thus, while their results do not relate directly to the

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1 Until 1991, this group was known as the Scientific Working Group on the Chemotherapy of Leprosy (THELEP).
question of the efficacy of the WHO regimen, they are of interest if the feasibility of devising a shorter MDT regimen for paucibacillary disease is to be considered.

Those in the second group, which reported excellent or satisfactory results with the standard WHO MDT regimen or a minor modification thereof, generally noted that, even if skin lesions had not totally cleared within 6 months, clearance continued eventually to complete healing (8-13).

Those in the third group found that up to 1 year or more of therapy, either with the standard WHO MDT regimen throughout or with dapsone monotherapy after the first 6 months, was necessary to obtain uniformly satisfactory results, although many of their cases may have shown a satisfactory response within 6 months (14-18). A key issue here is the question of what constitutes a satisfactory result. One definition is that all patients who comply with treatment should respond to MDT and that the relapse rate should be less than 1% per year (19). The Study Group considered that a satisfactory result from MDT in a patient who complies with treatment is one in which, after the start of therapy, bacteria begin to clear in multibacillary cases and lesions generally, though not necessarily rapidly, improve in both paucibacillary and multibacillary cases. Clearance of lesions is related more to the person’s immune response than to the antileprosy treatment; all lesions and bacilli should eventually clear, even though clearance may be incomplete at the time therapy is discontinued.

The question of a higher frequency of relapse among patients receiving the 6-month WHO MDT regimen than among those receiving longer regimens is more difficult to address without knowing the level of compliance and having independent confirmation of such relapses. Some of the reported cases of relapse may have merely reflected lack of clearance of the lesions, while others may have been reversal reactions. Relapses occurring during the first year after completion of treatment, however, are rare. Furthermore, Ekambaram & Rao found no difference in the number of relapses among over 14,000 patients receiving 6 or 12 months’ therapy in India (12).

On the basis of the data available, the Study Group concluded that the 6-month WHO MDT regimen for paucibacillary disease has been very effective and recommended that it should continue to be used. The Study Group noted that a recent review confirmed this view (20).

2.1.2 MDT for multibacillary leprosy

The results of trials of the standard WHO MDT regimen for multibacillary leprosy are easier to analyse than those for paucibacillary disease. There seems to be less disagreement about this regimen’s efficacy, which may in part be because treatment is open-ended: unlike
the recommended regimen for paucibacillary disease, which is given over 6 months, the regimen for multibacillary disease is administered over a period of at least 2 years and preferably until skin smears are negative. Consequently, there have been fewer modifications of the standard regimen for multibacillary leprosy and even those implemented are now being dropped. For example, the initial 14-day course of daily rifampicin used in India has proved to be of questionable value and is now being phased out (20, 21). In general, the WHO MDT regimen for multibacillary disease has been highly successful. As with paucibacillary disease, some very short-term regimens have been investigated by Pattyn et al. (7, 22–24), often with excellent results. This may be a reason to expect that the results of ongoing or future trials of other very short-term regimens will also be satisfactory. However, Pattyn et al. have argued that follow-up 9–10 years after completion of therapy is necessary to evaluate the efficacy of any MDT regimen for multibacillary disease.

A key question for the Study Group, however, was whether the WHO MDT regimen for multibacillary disease could now be fixed at 24 months and the proviso to continue it until skin smears are negative could be dropped. Most control programmes have already taken this step, but while an overview of the literature may give the impression that 24 months of treatment should be sufficient, specific data addressing this question are limited. A trial in Bamako, Mali, for example, reported only one relapse among 44 multibacillary patients treated with the WHO MDT regimen, but follow-up averaged only 42 months (25). This group also noted, on evaluating relapses after a variety of rifampicin-containing MDT regimens, that while relapses occurred an average of 5.5 years after completion of treatment, they occurred earlier in those who received the shortest period of treatment with rifampicin. Relapse was more likely if the bacterial index (BI)\(^1\) was high (5–6+) at the completion of treatment. Nearly all strains of \(M. leprae\) isolated from patients who relapsed remained fully sensitive to rifampicin, including the patient who relapsed after treatment with the WHO regimen (26).

Li et al. reported no relapses among 80 patients treated for 24–27 months and followed-up for 33 months (27). Katouch et al. reported on 15 highly bacillated (BI 4–6+) multibacillary cases lost to follow-up after 12–44 months of treatment. Those patients who were retrieved after being given only 12–18 months of therapy all deteriorated, whereas all those who had received at least 24 months of therapy continued to improve (28). Becx-Bleumink (9, 29) reviewed the literature and recommended that treatment for multibacillary patients should be limited to 2 years for operational reasons. Since increasing numbers of programmes are now limiting

\(^1\) Refers to the density of bacilli in smears or tissues. The BI is generally scored on Ridley's logarithmic scale, at one end of which the demonstration of 1–10 leprosy bacilli in 100 oil-immersion fields is graded as 1+ and at the other end the demonstration of over 1000 bacilli in a single oil-immersion field is graded as 6+. 

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therapy to 24 months in all multibacillary cases, more data will be forthcoming, but available information suggests that 24 months are sufficient.

2.1.3 Toxic and lepra reactions during MDT

Drug toxicity has not been a major problem with MDT. In one large study involving 10,426 patients with multibacillary disease and 35,013 with paucibacillary disease, 17 patients had hepatitis (two of whom died), three had renal failure and four had dermal hypersensitivity reactions (30). Toxic reactions to rifampicin such as renal failure or thrombocytopenia are occasionally reported but are rare. It has been reported (31, 32) that delayed-type hypersensitivity reactions to dapsone are more common among patients receiving MDT than among those given monotherapy, but there are relatively few data to support this.

The prevalence of lepra reactions does not appear to have increased following the introduction of MDT. Indeed, erythema nodosum leprosum (ENL or type II lepra reaction) is less common now, perhaps because of the clofazimine component of the MDT regimen for multibacillary leprosy, but the extent of this protection is not clear (33). Perhaps the most extensive data on reactions among patients receiving the WHO MDT regimens are those of Bexx-Bleumink & Berhe, who report the findings from the All Africa Leprosy Research and Rehabilitation Training Centre (ALERT) leprosy control programme. During the first 2 years of therapy, reversal reactions occurred in 43.6% of 266 borderline lepromatous cases and 19.2% of 109 lepromatous leprosy cases, whereas ENL developed in 2.7% and 11.1% respectively. Reversal reactions were most common in multibacillary patients in the first year of MDT and then gradually declined, but were still occurring in the fifth year of treatment. Among 438 borderline tuberculoid patients, the prevalence of reversal reactions was 10.3% during the 6 months of treatment and 7.3% during the first year after completion of treatment. Among paucibacillary patients, the risk was highest during treatment with MDT followed by the first 6 months after completion of treatment; however, reversal reactions were occasionally observed up to 4 years after therapy was discontinued. Other studies have found reactions to be relatively uncommon; for example, Ramesh et al. report that only 10.4% of 855 multibacillary cases treated with MDT developed ENL or reversal reactions. Few details are available of this study, however, and it is not clear whether this population and the ALERT cases were comparable in terms of disease activity, etc.

2.2 Drug resistance

Although primary dapsone resistance is thought to be widespread, patients infected with dapsone-resistant M. leprae have, to date, responded satisfactorily to the WHO MDT regimens.
Small numbers of cases of secondary rifampicin resistance have been reported among patients treated with rifampicin monotherapy or among dapsone-resistant cases treated with rifampicin and dapsone. Whenever rifampicin resistance is suspected, patients should be referred for full investigation, including drug-susceptibility tests in the mouse-footpad model. An appropriate MDT regimen incorporating new antileprosy drugs should be substituted for the WHO regimen (see section 4.3.1).

No confirmed cases of clofazimine resistance have been reported.

Relapses after treatment with the WHO MDT regimens have been rare. Among those who have been studied after relapse (including patients infected with dapsone-resistant *M. leprae*), no new cases of resistance have been detected by drug-susceptibility tests in mice. In addition, re-treatment with the WHO MDT regimen has been effective in all cases.

2.3 **Persistence of Mycobacterium leprae**

Data from the clinical trials organized by THEMYC (see page 4) in Bamako, Mali, and Chingleput, India, suggest that small numbers of drug-susceptible *M. leprae* often persist in patients treated with the WHO MDT regimen for multibacillary leprosy (35). However, the very success of this regimen so far indicates that persistence of *M. leprae* is not a frequent cause of relapse when treatment is completed.

2.4 **Immunotherapy**

A number of immunotherapy studies are in progress, but there are, as yet, insufficient data available to indicate the role of immunotherapy in the treatment of leprosy. In any case, immunotherapy is unlikely to play a significant role in leprosy control programmes.

2.5 **Lepra reactions**

Corticosteroids, clofazimine and thalidomide remain the mainstays of reaction management, with no promising alternatives in sight. The use of standardized prednisolone regimens has been proposed for the treatment of reversal reactions and neuritis under field conditions (36), and should help to prevent disabilities among leprosy patients until such time as better anti-reaction drugs or other treatments are found.

3. **Currently available antileprosy drugs**

Several new highly bactericidal drugs have become available since 1981, but only a limited amount of additional information is available on the five drugs that were considered for inclusion in MDT at that time, i.e. dapsone, clofazimine, rifampicin, ethionamide and protonamide.