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REVIEW

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Recent Advances in Leprosy Chemotherapy

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Abstract

This study reviews the status and data for recent advances in leprosy chemotherapy since the WHO study group on chemotherapy of leprosy for control programs recommended multi-drug therapy (MDT) regimens in 1981, which were widely implemented globally. The implementation of MDT resulted in a dramatic decline in prevalence, leading the World Health Assembly in 1991 to set the goal of eliminating leprosy as a public health problem (reducing prevalence to below 1 per 10,000 population) by 2000. Although progress towards this goal has been excellent, it is now appropriate to review the chemotherapy of leprosy in the light of 25 years' experiences, and with the recent introduction of several new bactericidal anti-leprosy drug regimens. The latter were reviewed from the first alternative official regimens of WHO/MDT such as the new recommendation that the duration of the current MDT regimen for multibacillary leprosy (MB) could be further shortened from 24 to 12 months. The second alternative official regimen was a single dose of ROM (combination of rifampicin, ofloxacin and mynocycline) for a single-lesion paucibacillary leprosy (PB), the first fully supervisable, monthly-administered regimen. Furthermore, the common treatment of MB and PB by multiple monthly dose of ROM has been tested in the field trials. Another field trial was a combination of rifampicin-moxifloxacin and mynocycline (RMM) which was far more bactericidal than ROM. The fifth WHO-recommended regimen was that all leprosy patients, both PB and MB, were treated by the common MDT for MB leprosy for a period of only six months. The magnitude of MB relapse after MDT, and the possible existence of a higher risk subgroup of MB leprosy, together with the need for both flexible and reliable MDT treatments and drugs are reviewed and discussed with recommendations.

Keywords: recent advances, chemotherapy, leprosy

Introduction

The first moderned drugs used in the chemotherapy of leprosy as mass treatment in a leprosy control program was dapsone or diamino diphenyl sulfone (DDS) as monotherapy [1-3]. Later on, it became apparent that drug resistance and treatment failure resulted when dapsone monotherapy was used to treat active disease harboring large bacillary populations [4-5].

The pioneer prospective multidrug therapy program with limited treatment for leprosy was first conceived by Professor Freerksen of the Borstel Institute in Germany and was initiated in Malta [6] in 1973. The regimen consisted of dapsone, prothionamide, isoniazid and rifampicin. The second pioneer multidrug therapy program was proposed in 1974 by Professor Morizo Ishidate, Chairman of the Medical Board of the Sasakawa Memorial Health Foundation of Japan who initiated and sponsored joint multidrug-chemotherapy trials conducted in the Philippines, Thailand, and South Korea for eight years prior to the commencement of WHO-recommended multidrug therapy (MDT) in 1982. Professor Ishidate's regimen consisted of dapsone, rifampicin and lamprene [7].

In 1981, multidrug therapy (MDT) was first recommended by a WHO Study Group [8-9]. Its chief characteristics were as follows:

1) The regimens included several drugs acting by different mechanisms, in order to prevent the emergence of drug resistance, and to be effective even for strains of *Mycobacterium leprae* resistant to dapsone.

2) The duration of MDT was limited in contrast to the lifelong duration of dapsone monotherapy, to improve patient's compliance. To make this possible, only bactericidal drugs were included as components.

3) Rifampicin (RMP) was included as a key component because of its powerful bactericidal effect against *M. leprae*. It was to be administered only once monthly under supervision, to ensure compliance and because of its high cost. The recommended regimens were the minimal effective ones and there were no recommendations against the use of stronger or longer regimens.

The recommendations of WHO were based largely on empirical judgments of efficacy, practical administrative constraints, especially in field programs, and the cost involved. Two regimens based on a field classification – one of six months duration for paucibacillary (PB) patients and another of 24 months for multibacillary (MB) patients, were adopted. The chief goals of multidrug therapy were to cure the patient, prevent emergence of bacterial resistance, and interrupt transmission [8-12]. In recent years, the first goal has definitely been achieved because of cooperative efforts of the WHO, the governments of endemic countries and several national and international non-governmental organizations. By 1991, the estimated number of leprosy cases worldwide had dropped to about five millions, thus prompting the WHO in May 1991 to adopt a resolution to attain global elimination of leprosy as "a public health problem" by the year 2000. "Elimination as a public health problem" was defined as reducing prevalence to one patient or less per 10,000 population. Since then, remarkable progress has been documented, and by July 1997, application of multidrug therapy had reduced the prevalence rate of leprosy since 1981 by an astounding 85% [13]. It seems that although the goal of elimination by the year 2000 may not be achieved, leprosy is sure to be eliminated in the foreseeable future through the current level of efforts [14]. As for Thailand, the pioneer country in the leprosy control program, achieved its elimination target earlier, in 1994 [15].

Three official regimens of the WHO multidrug therapy

To date, three regimens have been officially recommended: (i) WHO/MDT for paucibacillary (PB) leprosy, (ii) WHO/MDT for multibacillary (MB) leprosy: and (iii) a single dose of the combination rifampicin-ofloxacin-mynocycline (ROM) for single-lesion PB leprosy, the last to be employed in those countries where the proportion of single-lesion PB patients is large.

The composition of the first two regimens, which were recommended by a WHO study group [8] has remained unchanged. However, the definitions of PB and MB leprosy have been modified several times, and the cut-off point between PB and MB leprosy has been simplified from a bacteriological index (BI) of $\geqslant$ 2+ in the initial skin smears at any site [8] to > 5 skin lesions [10]. Consequently, a larger proportion of newly detected patients are classified as MB leprosy than in the past. At the same time, the duration of MDT for leprosy has been gradually shortened, from at least two years, and whenever possible, until skin- smear negative [8] for a total of 24 months. At its 7th meeting, the WHO Expert Committee on Leprosy stated that the 24 month-duration for MB leprosy remained valid, which suggested it was possible for the duration of the current MDT regimen for multibacillary leprosy to be further shortened to 12 months [10]. This careful wording clearly indicated that the recommended duration of MDT for MB leprosy is either 24 or 12 months [11].

The third regimen, a single dose of ROM for the treatment of a single-lesion PB leprosy, which has obvious operational advantages, was recommended as an alternative by the WHO Expert Committee on Leprosy at its 7th meeting [10] and has subsequently been applied widely in India, Bangladesh and Brazil [16].

New MDT regimens

The need for new regimens that are more effective and operationally less demanding may be summarized as follows:

1. From the operational viewpoint, the recommended duration of treatment, particularly for MB leprosy, is still too long.

2. Two of the components of the current regimen for MB leprosy, daspone and clofazimine are only weakly bactericidal against *M. leprae* [17]. Since these weaker drugs determine the minimal effective duration of the current regimen, further shortening of the duration of treatment for this regimen might result in higher relapse rates.

3. Daily administration of dapsone and clofazimine can not be directly supervised, since the MDT regimen for MB leprosy is not resistance-proof, should patients fail to comply with treatment.

4. Patients who do not tolerate clofazimine because of its skin discoloration, or who cannot take dapsone or RMP because of allergy, or cannot get benefit from RMP because of intercurrent disease or the emergence or RMP resistance, require a safe and effective alternative.

The discovery of new drugs that demonstrate very promising bactericidal activity against *M. leprae* has made possible the formulation of new MDT regimens. A highly desirable new regimen is one that would permit all of the components to be administered once monthly under supervision and significantly reduce the risk of emergence of RMP resistance caused by irregular administration of the daily components. ROM is the first fully supervisable, monthly-administered regimen. The efficacy of multiple monthly doses of ROM for treatment of MB and PB leprosy has been tested in the field trials in three different countries [16], however, two of the trials have been terminated prematurely. It is critically important that post-treatment follow-up of the patients treated in the only remaining trial be carried out as originally scheduled. Furthermore, because of the success of a single dose of ROM for the treatment of single-lesion PB leprosy, the treatment of multiple-lesion PB leprosy with a single dose of ROM should be evaluated. Should this treatment be successful, the chemotherapy of PB leprosy could be much simplified, saving significant resources that may be used for the other important activities.

However, the bactericidal activities of both ofloxacin and minocycline are rather weak compared with RMP, the combination ofloxacin-minocycline is significantly less active than RMP alone, and ROM is no more bactericidal than RMP alone [18-19]. Replacing the components of ROM with more powerful bactericidal drugs would make possible a fully supervisable, monthly-administered MDT regimen. Recent findings from experiments in mice indicate that rifapentine and moxifloxacin are significantly more bactericidal than RMP and ofloxacin, respectively, and the combination rifapentine-moxifloxacin-minocycline (PMM) far more bactericidal than is ROM [20]. The efficacy of PMM is currently being evaluated in a short term clinical trial among lepromatous leprosy patients. If the trial confirms the stronger bactericidal effect of PMM, a field trial to evaluate the efficacy and safety of PMM over the long term treatment should be carried out.

A common regimen for both PB and MB leprosy

A common regimen for the treatment of both PB and MB leprosy is desirable. However, because PB and MB leprosy differ so greatly in terms of the size of the bacterial population and the underlying immunological response, the requirements for chemotherapy, especially in terms of the number of drugs and the duration of treatment, are bound to be very different. If a common regimen is formulated on the basis of the available drugs, it appears likely that it would overtreat PB or undertreat MB. The dream of a common regimen might be realized only if the new regimen contained several very powerful bactericidal drugs, which were capable of shortening the duration of treatment for MB leprosy to only a few doses or even to a single dose.

Recently, the WHO Technical Advisory Group (TAG) at its 3rd meeting recommended that all leprosy patients, both PB and MB be treated by the MDT regimen for MB leprosy for a period of only six months [21]. The TAG stated, in support of this recommendation, that:

- MDT has been proven to be robust in

terms of treatment efficacy and safety;

- relapse rates are very low, less than one percent; and
- resistance to MDT has been virtually non-existent.

However, a regimen is effective and safe is not sufficient to justify shortening its duration. A good example is THELEP regimen C, which composed of a single dose of RMP plus daily dapsone administered for a period of two years. This regimen was highly effective and safe, but 20% of the patients allocated to this regimen relapsed after an average of five years of follow-up [22]. Since 1998, almost all MB patients have been treated with 12 months MDT; however, no information is available regarding the 5-year relapse rate following 12 months MDT. Therefore, at least for the time being, there is no justification for further shortening the duration of MB chemotherapy to six months. Moreover, it appears hazardous to state that resistance does not exist because post-MDT surveillance has not been carried out in routine programs for almost ten year [11]. For these reasons, before the MDT regimen is implemented in control program as a common regimen for both PB and MB leprosy, it must be studied by controlled trials, with relapse as the outcome.

Magnitude of MB relapses after MDT and possible existence of a higher risk subgroup of MB leprosy

Among MB patients, the efficacy of MDT is best assessed by measuring the relapse rate after completion of treatment. The relapse rate was reported to be about 0.1% per annum among MB patients during post-MDT surveillance [18]. However, reports from the Institute Marchaux in Bamako and the Central JALMA Institute of India indicate the existence of a subgroup of MB patients who demonstrated high frequency of relapse after 24 months' MDT as high as 4-7% patient years among patients with initial mean bacterial index (BI) at 4.0, and higher than among patients with initial BI < 4.0, suggesting that the high initial BI is a most important risk factor for relapse. In addition, relapse was observed to occur late–five years after stopping treatment, on average, suggesting that follow-up of these patients may be important [23-27]. Because there is no ready explanation for the discrepancy between the two estimates for the risk of relapse among MP patients after 24 months' MDT, and the possible existence of a subgroup of MB patients who are more prone to relapse [23], it is necessary to collect more information for long term follow-up of MB patients after completion of 24 months' MDT. However, a number of difficulties are encountered in attempting to follow MB patients after completion of MDT [28]:

- In more and routine programs, patients are removed from the register as soon as they have completed MDT, and, very often, essential records eg identity, address, initial BI, and history of treatment are lost, making it difficult to retrieve patients for follow-up and analysis.
- Because of integration of the leprosy program into the general health services, responsibility for the detection of suspected relapse rests upon general health workers, many of whom do not posses the necessary skills. In addition, the general health services often lack the manpower and resources required to follow former patients who have already completed treatment with MDT, because they are no longer considered as "cases" [10].
- Because of the poor quality of skin-smears in the past, and because of a skin-smear service is no longer available in many programs, it is difficult to identify members of the higher-risk subgroup and to detect relapse.

Because no information exists with respect to the five year-relapse rate among MB patients after 12 months' MDT, determination of the relapse rate following 12 months MDT should be considered a high priority in those treatment centers in which post-treatment surveillance is possible. In addition, the results of ongoing trials, in which the relapse rates after treatment by various regimens, including the 12-month regimen are compared, should be published as soon as they become available.

The need for both flexibility and reliability of MDT treatment

To guarantee that all newly detected leprosy patients receive treatment with MDT, MDT

services should be available and accessible to patients. To accomplish this goal, a flexible patient-friendly system for delivery of MDT must be implemented. However, at the same time, the principle that monthly RMP is to be administered under supervision [8-10] should not be compromised, because RMP is the single, most important component of MDT, and non-compliance of leprosy patients with treatment has been well documented [29]. In addition, the importance of regular contact between patient and health worker to prevent impairment must not be underestimated.

In areas where the health infrastructure is weak, there are patients who may find it difficult to visit the health center or leprosy treatment clinic once monthly. Current policy states that "in such cases, more than a month's supply of MDT blister-packs may be provided to the patients" [10] and "that with accompanied MDT blister-packs for a full course of MDT should be provided at the time of diagnosis" [30]. Consequently, in an increasing number of national programs, it has become the routine to provide the entire quantity of MDT blister-packs – *ie* a six-month supply for PB and a 12-month supply for MB patients – to all newly detected patients. However, in many programs, those responsible for "accompanying" the patient's treatment either have not been recruited or lack proper training, so that many of them fail to carry out their mission. As a consequence, it is difficult to be certain that the MDT drugs are indeed self administered by the patients, not withstanding the fact that the success of MDT could be seriously jeopardized, should patients be non compliant.

Because the monthly component was expected to be administered under supervision, studies of compliance with MDT undertaken since the introduction of MDT focused on regularity of self-administration of the daily component, chiefly dapsone, by urine testing. While the results demonstrated better compliance with MDT than with dapsone monotherapy [31], only 70-80% patients were found to comply with the daily component [31-33] suggesting that the assumption that "patients who report for diagnosis and treatment may be considered as sufficiently motivated to take full responsibility for their own care" [10] may not be valid. Although one of the advantages of the blister-pack over the supply of MDT drugs in bulk was assumed to improve patient compliance with the self-administered component [34], this assumption has been tested in only a few studies: these studies have demonstrated Thai blister-pack either did not improve compliance [35-36], or improved it only marginally [37].

Because the monthly component is no longer administered under supervision in a significance proportion of patient [30-38], it appears very likely that reduction of the frequency of contacts between patients and health workers will affect the regularity of drug administration: therefore, compliance with both the monthly and daily components of MDT is certainly an issue far more important and complicated than before. It is important to measure the degree of non-compliance among those who are treated under the policy of flexible drug delivery with both the daily and the monthly component of the MDT blister-pack. This may have significant impact on MDT delivery policy, and even on the strategy of the chemotherapy of leprosy.

"Accompanied MDT'' is the term applied to a program in which a family or a community member supervises the monthly administration of drugs to the patient [38]. This concept appears reasonable, but before its wide implementation, this approach should be tested under field conditions to identify the requirements for its success. However, even with the best program of accompanied MDT, the justification for providing the total quantity of MDT drugs to the patient may be disrupted, because the family or community member cannot replace the health worker.

Absenteeism and default

A defaulter has been defined as a patient who has not collected MDT treatment for 12 consecutive months [39]. Information on the clinical and bacteriological progress of defaulted MB cases may shed some light on the efficacy of MDT with durations shorter than the standard one. In one study [40], 41 defaulted MB cases were retrieved. They had been treated with MDT for a mean duration of seven months (range

3-13 months), and had not taken treatment after defaulting. By the time the patients were retrieved from less than one year to more than five years after dropout, all 41 patients showed clinical improvement and 29 (71.0%) became smear-negative, while the BI was stationary in five (12.3%) cases. In another series of patients [41] who were skin-smear positive before defaulting, 139 and 95 of them had been treated, respectively, only 11 (7.9%) patients from the former and six (6.3%) patients from the latter groups were still smear-positive. The positive rates were very similar between the two completed 24 months of MDT, and were examined four years later. Although one has to be cautious in interpreting information from retrospective analyses, because the records are often incomplete, the sample size is relatively small and the pretreatment characteristics of the patients between the groups may not be comparable, they do suggest that treatment with less than 12 months of MDT exhibited promising therapeutic effects among the majority of MB patients.

It has been recommended that defaulters who cannot be retrieved be removed from the register [39] and that the register be up dated at least annually [38-39]. In a number of national programs, as many as 40% of newly detected patients have been considered defaulters [42]. Since introduction of the "flexible MDT delivery'' strategy, increasing numbers of patients have received the entire quantity of MDT drugs at the time of the first treatment dose. Although it has been stated that the percentage of defaulters has declined dramatically as a result of this approach, it is difficult to assess the actual rate of treatment completion.

Whatever the reason for default, every effort should be made to prevent it. A serious attempt should be made to trace absentees beginning from their first absence. Absentees who return to treatment should be treated according to the WHO recommendation with six doses of MDT within nine months for PB, and 12 doses within 18 months for MB. In conclusion, tracing and persuading the defaulters to return for treatment is most important.

For those patients who have become defaulters, those who have died or migrated from the country should be removed from the register, whereas those who have moved out of the district or are taking treatment elsewhere should be transferred rather than simply removed from the register. As long as defaulters continue to live in the district and have yet to complete the full course of MDT treatment, they remain, by definition, "cases''[10] and may continue to represent sources of transmission. Instead of removing these defaulters from the register, health workers should be encouraged to retrieve them actively, with assistance from the community. A new course of MDT should be given to every defaulter after his retrieval or return.

Drug resistance

To date, all of the official MDT regimens contain RMP, which is significantly more bactericidal than any other antileprosy drug or any combination of ofloxacin, clarithromycin and minocycline [19, 43]. The emergence of RMP resistance would create tremendous difficulties for the treatment of individual patients, and its widespread dissemination would pose a serious threat to leprosy control.

RMP-resistant leprosy was first documented in the 1970 [44]. It was rare [44-45], probably because in that era RMP was seldom employed in treating leprosy. Later, it was reported that among a total of 404 MB patients treated with various RMP-containing regimens, 39 relapsed and 22 were found to harbor organisms resistant to RMP as proven by the mouse footpad technique [46]. Virtually all of the resistant strains were isolated from patients who had been treated with dapsone which indicated that these patients had in effect been receiving RMP monotherapy. Because many of the 22 patients developed RMP resistance in the decade after beginning treatment with RMP [46], it appeared that RMP resistance could emerge rather rapidly among patients whose treatment regimens were inappropriate.

Although more than 10 million leprosy patients in the world and more than 170,000 leprosy patients in Thailand in particular, have completed treatment with MDT, and RMP-resistant leprosy has not been reported among these patients [10,15], one must be cautious

in interpreting the findings. First, post-MDT surveillance for relapse is no longer carried out in most routine programs. Second, the standard means of diagnosing drug-resistant leprosy have required the use of the mouse footpad for survey. Dapsone resistance has disappeared during the last decade, which coincided with an intensive implementation of MDT. As a result, RMP-susceptibility testing is rarely carried out, and the results are not always reliable. In fact, one cannot exclude the possibility that a number of RMP-resistant leprosy patients remain undetected. Before RMP resistance becomes so frequent that it threatens leprosy control and sustainable leprosy elimination, more solid information about its magnitude should be collected in different parts of the world.

Although it is no longer feasible to undertake a relatively large-scale survey of RMP-resistant leprosy by means of the mouse footpad technique, PCR-based DNA-sequence analysis of the rpo B gene of *M. leprae* represents a cost-effective alternative technique [47-48]. At this stage, surveys of RMP resistance should focus on MB patients who have relapsed after completion of MDT, and surveillance for the emergence or RMP resistance among these patients should be carried out by special centers. For this purpose, a proportion of MB patients should be systematically examined clinically and bacteriologically after completion of MDT, and skin biopsy specimens should be obtained from those patients suspected of relapse for DNA sequence analysis of the rpo B gene of *M. leprae* [47-48].

MDT was developed mainly because of the widespread emergence of dapsone resistance, and the MDT regimens were designed on the principle that they would be effectively against all the strains of *M. leprae*, regardless of their susceptability to dapsone [8-10]. Hence, increase or decline is virtually irrelevant to the therapeutic effect of MDT, and there is no need to monitor trends of resistance to dapsone.

Recommendations

1) To guarantee the quality of integrated leprosy services and sustainable elimination of leprosy as a public health problem, training in leprosy should be strengthened among general health workers and leprosy supervisors.

2) The skin-smear remains an important tool for diagnosing MB relapse: wherever possible, it should be reintroduced, particularly in areas where there are a significant number of MB patients who have completed MDT, or the prevalence is greater than 1 per 10,000 population.

3) Currently, almost all MB patients are being treated by 12 months' MDT; however, no information is available regarding the five-year relapse rate among MB patients treated by this regimen. Therefore, field programs with adequate facilities should monitor relapse rates. Surveillance among relapsed MB patients for the emergence of rifampicin resistance should be carried out by special centers.

4) A flexible, patient-friendly interactive system for delivery of MDT must be implemented. However, the principle that monthly RMP be administered under supervision should not be compromised. Only in exceptional cases, who cannot be seen monthly, should more than a one-month supply of MDT blister-packs be provided.

5) Health workers should actively trace absentees and encourage them to complete their treatment, instead of passively awaiting their return and removing them as defaulters from the register after an absence of 12 or more consecutive months. Of course, during such 12 months' MDT delivery, a series of operational issues should be addressed, such as providing guidelines for the MDT management system, prevention of deformities and community-based rehabilitation, developing more effective geographical information, reporting and surveillance systems together with improving community participation for the detection of backlogs and new cases, and the earlier detection and treatment of leprosy reactions during and after completion of MDT.

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