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RECENT ADVANCES IN THERAPY OF LEPROSY

by

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Recent Advances in Therapy of Leprosy

- a review based on the recent report of a WHO Study Group

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1 Introduction

In its fifth report in 1976 the WHO Expert Committee on Leprosy emphasized the need for preventing the much feared development of drug resistance, and in view of this, recommended that all active cases of multibacillary leprosy (LL, BL and BB in the Ridley-Jopling classification), whether previously untreated or relasped, should be treated with at least two effective antileprosy drugs. However, relatively few countries and individual centres have introduced multidrug therapy as a routine practice in their leprosy control programmes. Furthermore, there has been considerable uncertainty with regard to the selection of appropriate drug regimens for combined chemotherapy, both on the grounds of efficacy and of operational feasibility.

In the light of the above the World Health Organization constituted a Study Group on Chemotherapy of Leprosy for Control Programmes which met in Geneva from 12 to 16 October 1981. The objectives of the meeting were.

(1) to review information collected since 1976 (the year when the WHO Expert Committee on Leprosy held its fifth meeting), on the problems related to chemotherapy and chemotherapeutic regimens of leprosy,

(2) to recommend for leprosy control programmes appropriate multidrug regimens for multibacillary cases including new, treated, and drug-resistant cases, whether clinically suspected or proved,

(3) to recommend regimens for paucibacillary cases, and

(4) to identify further research needs in the clinical and operational aspects of chemotherapy of leprosy.

The Study Group reviewed the problem of dapsone resistance and the operational problems and proposed certain multidrug regimens to treat the different groups of patients, both multibacillary and paucibacillary.

2. The problems

2.1 Dapsone resistance and microbial persistance

Dapsone resistance and microbial persistance are two of the major problems in the treatment of leprosy. The first report of proven dapsone resistance came from Malaysia in 1964 By 1973 the prevalence of secondary dapsone resistance among institutionalized patients in that country was estimated to be 25 per 1000, and the estimate further went up to 100 per 1000 by 1981. The situation was even worse in Ethiopia with an estimated prevalence of 190 per 1000 Since then secondary dapsone resistance has been reported from several countries with prevalence rates ranging from 20 to 100 per 1000. In addition sporadic instances of resistance have been reported from more than 20 other countries.

Although primary resistance had not been reported until 1976, there have been several reports since then, the prevalence rates ranging from 33 per 1000 in Cebu, Philippines, to over 350 per 1000 in Chingleput, India, and Bamako, Mali Further strains of M leprae resistant to rifampicin and ethionamide have also been reported in recent years. Clofazimine is the only antileprosy drug on which resistance has not yet been reported.

The problem of microbial persistance in leprosy and its significant role in occurrence of relapses in lepromatous leprosy is now well recognized. It is expected that studies underway in the chemotherapy of leprosy (THELEP) component of the UNDP/World Bank/WHO Special Programme on Research and Training in Tropical Diseases will provide answers on the role of multidrug regimens in dealing with the problem of persisters.

2.2 Failure to perceive the urgency of the problems

The short-comings of dapsone monotherapy do not appear to have been fully understood, particularly with respect to the threat posed by dapsone resistance. It appears to have been assumed that provided dapsone was administered in full dosage (1-2 mg/kg body weight) and efforts were made to ensure regularity of treatment, the threat of dapsone resistance will be contained. Further it has remained the practice in some control programmes to interrupt dapsone therapy during lepra reactions, because of the belief that dapsone exacerbates the reactions. This practice has also added to the risk of the subsequent emergence of dapsone resistance. Another practice which led to poor patient compliance with the prescribed treatment was that, because of the fear of relapse, treatment was often continued indefinitely, even in cases meeting the criteria for stopping the treatment. The very large number of patients remaining under treatmnet put unnecessary pressure on leprosy clinics and consequently acted to the detriment of the quality of treatment. This situation further contributed to poor compliance.

2.3 Problems related to revised needs

There was frequent reluctance in the control programmes to undertake basic revisions needed for the introduction of multidrug regimens. Combined chemotherapy with more potent, somewhat toxic, and more expensive drugs requires much closer supervision than does dapsone monotherapy. The potential burden of supervision of combined chemotherapy, even for limited periods, appears frequently to have presented insurmountable problems to many control programmes. Further, although the earlier recommendations on combined chemotherapy regimens was based on sound scientific knowledge, clinical experience of combined therapy with rifampicin and clofazimine in combination with dapsone was too limited to decide on optimum regimens for different forms of leprosy. Moreover, there was undue fear of toxicity and other complications associated with such therapy.

3. Multidrug therapy

Since the publication of the fifth report of the WHO Expert Committee on leprosy the need to adopt combined chemotherapy has become even more urgent due to widespread prevalence of dapsone resistance, both primary and secondary.

There are two objectives of the chemotherapy of multibacillary leprosy. (1) to interrupt the transmission of the infection in the community; and (2) to cure the patient. Combined chemotherapy has the additional objective of preventing the emergence of drug-resistant strains of M.leprae and thereby preventing the spread of such strains in the community.

Up to now chemotherapy has relied almost entirely on dapsone monotherapy. This has led to a dangerous epidemiological situation with increasing numbers of patients relapsing with dapsone-resistant leprosy, and the spread of such strain among their contacts This is jeopardizing the whole strategy of leprosy control.

3.1 Treatment of multibacillary leprosy

The proposed multidrug regimen is designed for the treatment of all categories of multibacillary patients, including:

- those freshly-diagnosed, previously untreated patients;
- those who have responded satisfactorily to previous dapsone monotherapy;
- those who have not responded satisfactorily to previous dapsone monotherapy,
- those who have relapsed while on dapsone monotherapy or after cessation, and
- those who have relapsed with mouse footpad proven dapsone-resistant leprosy.

Since combined therapy can prevent or cure drug resistance in all patients, whether or not they are infected with dapsone-resistant M.leprae, there is no justification whatsoever for attempting to diagnose

dapsone-resistant leprosy by means of a period of supervised dapsone monotherapy. The following is the recommended standard regimen for multibacillary leprosy.

Rifampicin	-	600 mg once-monthly, supervised
Dapsone	-	100 mg daily, self-administered
Clofazimine	-	300 mg once-monthly, supervised together with 50 mg daily, self-administered

Where clofazimine is totally unacceptable, its replacement by 250-375 mg self-administered daily doses of ethionamide/prothionamide should be considered.

In identifying the above standard regimen the Study Group, among others, had taken the following factors into consideration:

(a) Only bactericidal drugs should be considered for multidrug regimens which are to be administered for finite periods of time.

(b) In view of the widespread occurence of dapsone resistance, both primary and secondary, at least two additional drugs should be combined with dapsone, one of which should be rifampicin in view of its great potency. Dapsone plus only one additional drug can increase the risk of multiple resistance.

(c) Even single doses of 10 mg per kg of rifampicin are rapidly bactericidal for M.leprae in man.

(d) There is no evidence that daily administration of 600 mg rifampicin is more effective than monthly administration of 600 mg on each of two consecutive days.

(e) Because of expense and toxicity regimens containing rifampicin should be capable of being administered under supervision.

(f) Regarding duration of treatment combined treatment should be given until the size of the bacillary population has been reduced to such an extent that resistant mutants are no longer present.

3.2 Treatment of paucibacillary leprosy

Since in paucibacillary leprosy the bacterial load is much lower than that in multibacillary leprosy (the maximum being about 10^6 organisms), the problem of drug-resistant mutants arising as a result of treatment is insignificant. Any persisters remaining are likely to be contained by the adequate cell-mediated immunity this type of patient possesses. Hence, as has already been shown, short-course chemotherapy of paucibacillary patients is feasible with the potent and rapidly bactericidal drug, rifampicin.

Additional reasons for recommending short-course chemotherapy with rifampicin for paucibacillary patients are.

- the ineffectiveness of dapsone monotherapy in the face of increasing incidence of primary dapsone resistance,

- the need for providing short-course effective treatment to a majority of patients in view of the fact that many patients do not come for regular treatment when it is of long duration; and

- the need for saving working time of the personnel, thereby enabling them to devote more time to the treatment of multibacillary patients and to other activities in the control programme;

Since patients with paucibacillary leprosy are usually not expected to harbour rifampicin-resistant M.leprae, monotherapy with rifampicin should theoretically be satisfactory. However, in order to avoid the risk of rifampicin resistance in patients who are wrongly diagnosed as paucibacillary, the Study Group recommended combined chemotherapy with rifampicin and dapsone for all paucibacillary patients.

The following regimen was recommended by the Study Group for treatment of paucibacillary leprosy.

Rifampicin 600 mg once a month for 6 months plus

dapsone 100 mg (1-2 mg/kg body weight) per day for 6 months.

The administration of rifampicin should invariably be supervised. Dapsone may be given unsupervised. If treatment is interrupted the regimen should be recommenced where it was left off to complete the full course.

Short-course chemotherapy of paucibacillary leprosy should be introduced in the following order of priority.

(1) to all newly diagnosed paucibacillary patients;

(2) to all dapsone treated paucibacillary patients who relapse, and, finally,

(3) to paucibacillary patients who are currently on treatment with dapsone monotherapy and who have not yet completed two years of treatment.

4. Operational aspects

No amount of improvement of drug regimens could lead to effective leprosy control unless the operational aspects are improved at the same time. The operational aspects, which were reviewed extensively by the Study Group, include case detection, treatment delivery, and caseholding. Improved chemotherapy makes it imperative that laboratory facilities for bacteriological examination and monitoring of patients be improved, and referral facilities for treatment of complications and side-effects upgraded. The ensuring of regular treatment of patients through effective defaulter control is of paramount importance in the new era of multidrug therapy. Retraining of leprosy control personnel and reorganization of the control activities to suit changing needs should be part of the planning process in the introduction of the improved chemotherapy. Lastly, the need for adequate logistic support to ensure regular delivery of drugs and other supplies to the periphery should not be underestimated.