RECENT TRENDS IN CHEMOTHERAPY OF LEPROSY *

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The chemotherapy of any bacterial disease is usually confronted with "drug resistance" and "bacterial persisters" resulting into relapse. The public health significance of these two phenomena is considerable especially in chronic diseases like tuberculosis and leprosy where poor compliance of patients, irregularity and dropout are often encountered during the long-term treatment period. Fortunately multidrug therapy or polytherapy was introduced long back in the case of tuberculosis to overcome problems like drug resistance and persisters. However, such approach for leprosy control programme was possible only very recently[1,2]. It is hoped that this new trend in chemotherapy of leprosy would change future of leprosy control programmes.

What is the necessity for polytherapy for leprosy?

Dapsone resistance both secondary as well as primary, bacterial persistence even after adequate treatment with dapsone, resulting in relapse in LL, BL and BB (multibacillary) types, continued transmission of the disease, poor compliance for long-term dapsone therapy and operational problems of leprosy control programmes urged the need for recommending polytherapy with available drugs like rifampicin, clofazimine and prothionamide along with DDS. The present recommendation is essentially for routine leprosy control programmes where at least minimum possible drugs can be delivered to leprosy patients satisfactorily under supervision.

What is expected from multidrug therapy?

a) To bring down quantum of infection in the community.

b) Prevent emergence of secondary dapsone resistance.

c) Treat already existing dapsone resistant leprosy.

d) To cut short the total period of treatment and thus obtain better compliance.

e) To offer cure to the patient.

f) To overcome bacterial persister problem.

What is the rational behind multidrug regimen?

Drug resistance :

An untreated lepromatous patient harbours at least 10^{10} viable M. Leprae out of which 10^{4} are resistant mutants. 10^{11} are already nonviable[3]. It has been shown that bacterial resistance is a selective one rather than inductive[4]. These genetically mutant strains are already resistant to each drug at various concentrations prior to exposure to these drugs. When dapsone monotherapy is used, resistant population to

* Presented at the work-shop on "Recent Trends in Dermatological Therapy including the therapy of leprosy", organized by the XIth Annual Conference of the Indian Association of Dermatologists, Venereologists and Leprologists held at Mangalore, India from 20th to 23rd January, 1983.

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Received for publication on 16—3—1983

dapsone multiply in due course and clinical relapse takes place. This is labelled as dapsone resistance. Multidrug regimen with rifampicin, a bactericidal drug and clofazimine, a bacteriostatic drug with dapsone in full dose is likely to look after each other's resistant strains. Thus already existing secondary dapsone resistance and further emergence of secondary resistance may be tackled in this way.

Bacterial Persistance

Dormant but sensitive strains, not acted upon by drugs till they become active[5] give rise to the persister problem. The frequency of the persisters is estimated to range from about $1:10^4$ to $1:10^6$ population[5]. Though no specific drug is available for treating persisters of *M. leprae* (unlike pyrazinamide in tuberculosis), synergistic effects of 3 drugs is hoped to affect this population and to bring down its quantum.

Pharmacological aspects of antileprosy drugs

Rifampicin which kills 99.9% *M. leprae* with a single dose of 600 mg brings down the population of viable bacilli[3]. Dapsone in full dose also has mild bactericidal effect and kills 99.9% of viable bacilli in 3–4 months[3]. With the presently recommended dose, the serum concentration is always much higher than the minimum inhibitory concentration (MIC). Hence a single dose of rifampicin given once a month (monthly pulse) appears to be sufficient to exert its bactericidal effect on available viable *M. leprae*, a dose which is convenient to administer under existing field conditions. As per WHO report there is no evidence to show that daily therapy with rifampicin is superior to monthly pulse therapy[1]. Similarly clofazimine at a dose of 300 mg per month as pulse therapy maintains the MIC even though daily intake of 50 mg of clofazimine is not assured.

Supervised therapy

It is recommended that pulse therapy of rifampicin and clofazimine should be given under supervision to make sure that these costly drugs are really consumed. This supervised therapy ensures emergence of resistant strains to rifampicin and clofazimine.

What are the multidrug regimen recommended for leprosy?

The multidrug regimens recommended for leprosy by WHO[1] as well as Indian Association of Leprologists[2] are framed from the point of public health as well as leprosy control programmes where minimum infrastructure is available.

Taking into consideration the mycobacterial population to be tackled, practically suitable regimen for control programme has been recommended.

A) **Regimen for multibacillary leprosy** (LL BL BB or Smear positive cases)

Rifampicin 600 mg once a month pulse (under supervision) plus Clofazimine 300 mg once a month pulse (under supervision) plus Clofazimine 50 mg daily or 100 mg alternate days (self administered) plus DDS 100 mg daily (self administered).

Prothionamide / ethionamide can be used in 500 mg doses on a monthly pulse basis. Where clofazimine is not acceptable, either prothionamide/ethionamide is given 375 mg daily.

Duration of treatment

Minimum of 24 months (24 doses of pulse)[1,2] or till smear negativity, whichever is longer[1,2]. Treatment is stopped after 24 months of uninterrupted pulse even if the patient is smear positive if his compliance is poor. It is expected that the control programme staff will be able to have a hold at least for 24 months.

The recommendation by Indian Association of Leprologists[2] is similar to that of the WHO except for an initial period of 21 days' continuous rifampicin administration under supervision followed by monthly pulse therapy.

Drug regimen for paucibacillary leprosy:

(TT, BT or smear negative cases[2]) According to WHO recommendation upto 2+BI patients should be included in the paucibacillary group[1].

Rifampicin 600 mg once a month (supervised) plus Dapsone 100 mg daily (self administered).

Duration of treatment

Minimum of 6 months[1]. After this rifampicin and dapsone may be stopped and patient followed up. However, IAL recommendation is that both drugs be continued till inactivity is achieved[2].

Reasons for short course rifampicin therapy for paucibacillary leprosy[1]

1) The bacterial load in paucibacillary leprosy is about 10^6 organisms. Hence the problem of drug-resistant mutants arising as a result of treatment becomes insignificant. Any persister if left over is likely to be tackled by the body's immune status.

2) Dapsone alone is found to be ineffective as indicated by increasing incidence of primary dapsone resistance.

3) Poor patient compliance is more frequent in regimen necessitating of long term treatment 5 to 10 years where dapsone monotherapy is used.

4) Cost/effectiveness of the treatment is increassed.

5) About 75% of the patients fall in the paucibacillary group. The short term combined therapy reduces workload on workers and allows them to spend more time to treat multibacillary cases and dapsone resistant leprosy cases.

Drug regimen for DDS resistant cases

According to WHO[1] combined drug therapy cures or prevents dapsone resistance in all patients. Whether or not they are infected with dapsone-resistant *M. leprae*, there is no justification whatever for attempting to diagnose dapsone-resistant leprosy by means of supervised monotherapy/ mouse foot pad study. Even if mouse-foot pad test is available, as soon as test is done the drug regimen as that for multibacillary cases is to be followed.

Iyer[6] recommended the following regimen for suspected dapsone resistant cases.

Rifampicin 600 mg daily
Clofazimine 100 mg daily
Dapsone 100 mg daily

This is given for 2 years. After 2 years clofazimine 100 mg daily/on alternate day should be continued as long as possible. In place of daily rifampicin, pulse therapy can be substituted.

It is important to note that so far, the recommendations by various bodies, are based on minimal experience both clinical and laboratory. Hence recommendations are tentative. The period of treatment is fixed on arbitrary basis.

Success of multidrug therapy

The success of this therapy depends upon the following factors.

a) Proper selection of cases.
b) Motivation of patients.
c) Proper explanation of drugs and their side effect to the patient.

d) Maintenance of minimal but proper recordings through pulse therapy books, date cards, etc.,

e) Minimum infrastructure including smear facility.

f) Support with basic general medical facilities.

Long term observations in both laboratory and epidemiological aspects are essential to study the relapse rate and behaviour of mycobacteiral population with this short term regimen termed as "Minimum" that can be given to a patient under supervision to tackle huge mycobacterial population under existing difficulties of leprosy control programme.

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