ORIGINAL CONTRIBUTIONS

MULTIDRUG THERAPY IN LEPROMATOUS PATIENTS

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The short and long term results with two multidrug regimens were compared in 40 untreated lepromatous cases. The drug combinations investigated were, (a) rifampicin, clofazimine and DDS, and (b) rifampicin, prothionamide, INH and DDS. There was good improvement in patients in both the groups, but no additional benefit was obtained in the form of, (1) quickly reaching the point of non-infectivity (when compared with the trials involving use of rifampicin alone), and (2) the frequency of persistors at the end of two years. No serious side effects were encountered.

Key words : Lepromatous leprosy, Multidrug therapy.

The emergence of dapsone-resistant strains of *M. leprae* in lepromatous patients who had been given dapsone monotherapy, is now an established fact.[1] What has varied in different parts of the world, is the magnitude of the problem. Recent surveys have given figures of 2.2% in Malaysia,[2] 3% per annum in Ethiopia,[3] and 6.8% among Costa Rican patients.[4] Levy et al[5] calculated a prevalence rate of 3.7% in patients from Israel. Figures from two centres in South India, where antileprosy work has been going on for several years, are 95 per 1,000 from Gudiyatham Taluk and 48 per 1,000 in Trivellore Taluk.[6]

Another problem which has been frequently encountered in the treatment of multibacillated leprosy patients is the persistance of drug-sensitive organisms despite several years of drug therapy.[7,8] Further, the long duration of treatment not only taxes the resources but also the drug compliance. This results in irregularity and default leading to increased resistance.

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The possible answer to the above problems, as has been learnt from the treatment of tuberculosis, lies in use of combinations of effective drugs. In contrast to tuberculosis where an in vitro system is available to test the efficacy of drug combinations, in leprosy one has to undertake clinical investigations.

Based on these theoretical considerations, multidrug therapy has been advocated for all multibacillated cases.[1,9] In the present study, short term and long term efficacy of two multidrug regimens have been compared in lepromatous patients. The two regimes consisted of, (1) Rifampicin 300 mg daily for 1 month (supervised), Clofazimine 100 mg on alternate days for 6 months, and DDS 100 mg daily for 5 years (RCD), and (2) Rifampicin 300 mg daily for 1 month(supervised), Prothionamide 500 mg daily and INH 300 mg daily for 6 months, and DDS 100 mg daily for 5 years (RPID).

Materials and Methods

Untreated lepromatous patients, who were otherwise healthy, were taken for this study. In each case, clinical classification was supported by bacteriological examination, lepromin reaction and histopathology. The patients were

randomly allocated to one of the two treatment regimens. The cases were periodically assessed for the clinical condition and bacteriological status i.e. skin bacteriological index (BI) and morphological index (MI) and nose-blow positivity. Assessment of the severity of the disease was done by the semiquantitative method of Ramanujam.[10] BI was done using Dharmendra scale. Morphological index was done using strict criteria as proposed by Shepard and McRae.[11] For nose-blows, the patients were asked to directly blow their noses on the slides held about 10 cm away. Slides were air dried, heat fixed and stained for AFB.

Biopsies for mice inoculation, for viability study of *M. leprae*, were taken before the start of treatment and at the end of 1, 3, 6, 12 and 24 months after the start of therapy. After the biopsies were homogenised, 0.03 ml suspension containing 5×10^3 bacilli were inoculated in the hind foot pads of 6 mice each time. Harvests were made after 6 months as per the method of Desikan and Venkataramaniah.[12]

A special watch was kept for the reactional state and any adverse effects. For this, apart from regular clinical examination, haemogram, urine examination, liver function tests and blood urea were estimated periodically.

Patients in both the groups were admitted to the ward for the first one month, during which rifampicin was given under supervision. Thereafter, the patients attended the O.P.D. every 2 to 4 weeks. Surprise urine checks for DDS were made in between, to ensure regular drug intake.

Results

Twenty cases were included in each of the two treatment regimens. Four patients in the RCD group dropped out within the first 6 months. In addition, one patient who was fair complexioned, discontinued the treatment himself on account of clofazimine coloration. Thus, there were 15 patients available for analysis in the RCD group. In the RPID group, one patient dropped out and one had to be excluded on account of persistent vomiting, leaving 18 patients for analysis.

Results of clinical improvement are shown in table I. The clinical score decreased gradually

Table I. Clinical assessment.

	Mean score following treatment with	
	RCD	RPID
Initial	12.0	12.14
1 month	10.0	7.27
3 months	7.15	4.38
6 months	7.0	3.1
12 months	6.15	2.6
24 months	4.15	2.25

in both the groups. Regression of the infiltration was however slightly more rapid in the RPID group. Time taken for healing of mucosal lesions (nasal ulcers/nodules and oral ulceration/nodulation) was around 8.0 weeks in RCD group and 7.6 weeks in RPID group. A total of 16 episodes of ENL, were encountered in the RCD as compared to 21 episodes in the RPID group.

As mentioned earlier, one patient in RCD group discontinued treatment on account of skin discoloration. Whereas, in one case from the other group, treatment had to be stopped on account of persistent vomiting. Apart from these, in RCD group, one patient had jaundice during the 3rd month of treatment which regressed within 2 weeks. Another patient in this group showed transitory thrombocytopenia without any clinical manifestations. On the other hand, in RPID none of the patients had any clinical problem or showed any abnormality in the laboratory investigations.

Table II shows skin BI and MI during the course of treatment. In both the groups, the BI came down significantly over the 2-year-follow-up. As expected, the fall in MI was

Table II. Skin smears.

	Mean value following treatment with			
	RCD		RPID	
	BI	MI	BI	MI
Initial	2.7	3.9	3.0	4.4
1 month	2.7	2.9	2.9	1.0
3 months	2.25	0.5	2.6	0.4
6 months	2.5	0.2	2.1	0.2
12 months	2.2	0	1.6	0
24 months	1.5	0	1.5	0

very rapid during the initial 3 months with all the patients showing only non-solid bacilli by the year end. Nose-blows also became negative quite rapidly with only 3 cases in RCD and 1 in RPID regimens showing bacilli at the end of 3 months (Table III). By the end of one year, none of the nose-blows was positive for acid fast organisms. However, one patient belonging to RCD group again showed occasional bacilli when the nose-blows were taken after 2 years.

Table III. Nose-blow positivity.

	Number of cases positive/Total number after treatment with	
	RCD	RPID
Initial	12/15	14/18
1 month	11/15	7/18
3 months	3/15	1/18
6 months	2/15	1/18
12 months	0/13	0/18
24 months	1/13	0/15

Results of viability studies done in mouse foot-pad are shown in table IV. Nine of the 13 in RCD group and 15 of the 17 in RPID group showed no takes in the mice by the end of first month itself. By the end of 3 and 6 months, 3 and 2 patients in the two groups showed positive yields, the harvest being very small (counts less than 1.25×10^4). Screening for persistor organisms done at the end of one and two years showed *M. leprae* multiplication in mice obtained from one of 12 patients in RCD and in 2 of 15 cases from RPID group.

Table IV. Mouse foot-pad results for viability of *M. leprae*.

	Number of cases positive/Total number after treatment with	
	RCD	RPID
Initial	12/13	17/18
1 month	4/13	2/17
3 months	3/13	3/17
6 months	2/13	2/17
12 months	0/12	1/15
24 months	1/12	2/15

Comments

In the present study, drugs with proven antileprosy effect have been used. The doses included are known to have a potent antileprosy effect. Rifampicin 300 mg daily has been shown to have efficacy similar to that of 600 mg daily.[13,14] Further, it has been shown in the above study[14] that organisms from most of the patients become non-infective to mice in about 4 weeks. It was therefore considered best to give rifampicin for 4 weeks. Clofazimine has been shown to take about 6 months to render the patients non-infectious,[15] hence in the present study duration of treatment with clofazimine was kept at 6 months. In the RPID group, prothionamide has been administered for 6 months in place of clofazimine for the sake of similarity, even though prothionamide is a potent bactericidal drug as against the weak bactericidal nature of clofazimine.[16] Based on observations of Freerksen[17,18] that INH develops synergistic effects when co-administered with other drugs and that it enhances the effect of combination, INH has been included in the latter regimen.

The findings of the study show that a similar improvement is seen with regard to rendering the patients non-infectious and in persistors as judged by the late (2-year) results in both the groups. The clinical improvement, healing of mucosal ulcers, rapid fall in MI and rapid decline in positive takes in the mice suggest a good

response due to the drug combinations. When one compares the response with studies involving use of 300 mg rifampicin monotherapy,[13,14] it is found that the response is similar indicating that probably the earlier part of the action is on account of rifampicin per se. Finding of positive takes in mice in 3 of the 27 cases at the end of 2 years is significant. This indicates that in 11% of the cases, viable bacilli continue to persist in the skin despite the initial 6 months multidrug therapy. This suggests that continuation of drugs, as administered in the present study, does not seem to affect the persistor organisms. Similar results have recently been reported from THELEP studies being carried-out at Chingalpattu (South India) and Bomako (Mali)[19] wherein ten per cent of the patients have shown persistor organisms irrespective of the multidrug regimen which the patients had received. In the present study, normal mouse have been used in contrast to thymectomized-irradiated mice used in THELEP trials and this probably accounts for the lower counts in the harvests obtained in mice in the present work.

In an interim report, Tripathy et al[20] reported identical clinical and bacteriological improvement using two treatment regimen, one with and the other without rifampicin. Pattyn et al[21] have reported the results of treatment with a combination of rifampicin, dapsone and prothionamide. Aschhoff et al[22] also reported beneficial results in a drug trial using rifampicin with Isoprodian. Cottenot et al[23] used a combination of rifampicin, prothionamide and dapsone and reported similar results with a rapid fall in MI and a gradual decrease in BI. These authors came across several cases of gastro-intestinal disturbances and acute toxic hepatitis. Though hepato-toxicity with the use of MDT has also been reported by workers from Bomako (Mali)[24] and from China,[25] in only one of the 7 cases the drugs could be incriminated in the study from Bomakoo.[6] In contrast to these, in the present series, none among the prothionamide group (RPID) and only one in the RCD group had jaundice. As this patient tolerated the same drugs well when these were reintroduced, it is more likely that the jaundice was on account of some other cause, probably a viral infection.

In the present study, only one patient (from RPID group) had persistent vomitting. This probably was on account of gastric irritation caused by prothionamide. It is noteworthy that though 5 of the patients in the RCD group developed clofazimine discoloration, these patients were not unduly concerned about it, except one patient who was fair complexioned and opted out of the trial. On the whole the combinations were well tolerated. Occurrence of ENL was also similar in the two regimens and was not severe in any case. Painful neuritis was not encountered. Jacob and Mani,[26] Cottenot et al,[23] and Alvarenga et al[27] had similar observation. In these studies, neither the frequency nor the severity (or nerve damage) was any more than that with DDS alone.

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