ISSN 0377-4910

ICMR BULLETIN

Vol.32, No.2 February, 2002

SHORT COURSE TREATMENT OF LEPROSY: PRESENT STATUS

Leprosy, a chronic infectious disease affecting mainly the skin and the nerves, was among the first infection to be associated with a specific causative organism – Mycobacterium leprae. Despite this, till recently it was considered an incurable disease.

Following its introduction in late 1940's, dapsone was the main drug for the therapy of leprosy, for the next 3 decades. Though found effective and useful in all types of the disease the drug had to be given for long periods of 5 to 10 years and in some cases even life long. In the sixties it was observed that some lepromatous patients did not respond as well as others and in a few patients worsening occurred after initial improvement indicating the relapse. Following testing in mouse foot-pad, dapsone resistance was shown in these patients. Soon it became clear that dapsone resistance was on account of use of the drug as mono therapy, in sub-optimal doses and on irregular administration/intake especially in patients with large bacterial load. Further, it also became evident that these relapsed patients could spread resistance in the community.

With the realization of world-wide increase in dapsone resistance in M. leprae, the availability of equally effective drugs – clofazimine and rifampicin and from the experience in the therapy of tuberculosis, the concept of multi drug therapy (MDT) in leprosy was introduced. Based on the theoretical considerations, recommendations were made to treat leprosy with multi drug regimens[1]. Patients with fewer bacilli, the paucibacillary (PB) group were recommended to be treated with 2 drugs given for only 6 months, while for the remaining , called the multibacillary (MB) group, 3 drug combination for 2 years or till smear negativity, which ever was later, was advocated.

This was remarkable when one considers that the treatment of even lepromatous leprosy (LL) patients could be stopped in 2 to 5 years, in contrast to the need for almost life long therapy earlier. The main component of the treatment was rifampicin, which even today continues to be the main drug of all MDT regimens in leprosy. This is because of its very potent anti M. leprae action killing almost 99.99% organisms in 3 to 7 days[2]. This rapid reduction in the infectivity of smear positive patients helps in the prevention of further transmission of the disease in the community.

By 1985, these recommendations were adopted by almost all countries. The introduction of MDT resulted in increased confidence in treatment among the patients, the community and the health workers. Following the

completion of recommended length of treatment, exclusion of treated patients from the active case registers resulted in progressive decrease of prevalence rates. On account of difficulties, the initial PB definition was modified to restrict it to only those indeterminate (I), tuberculoid (TT), and borderline tuberculoid (BT) patients who were smear negative. Later, realizing the inadequacy of skin smear examination facilities in the field, a simpler clinical approach has been recommended for the leprosy field workers, wherein patients with 5 or less lesions and belonging to above categories only, are considered as PB type, and all other active cases are included under MB group for purposes of therapy.

Treatment of Multibacillary Patients

As stated earlier, since 1985 MB patients are being treated with MDT – a three drug combination given till smear negativity or for two years. Treatment results have generally been very satisfactory. The MB patients treated and followed up for over 2-5 years have responded well, with very few relapses[3]. Several reports indicated marked efficacy and practically no relapses. Studies were also undertaken to see, if the killing of M.leprae following MDT is complete. A few studies[4-6] have shown that despite 2 years of regular therapy, almost 10% patients continue to harbour viable persisters. This was independent of the regimens given, as the problem was similar in both groups of patients treated with intensive 3 drug regimens including daily rifampicin or given single dose of rifampicin (1500 mg) with daily clofazimine and dapsone. Similarly demonstration of ATP in 19% of bacterial suspensions obtained from skin biopsies of patients treated for 2 years[7] and viable bacilli in the nerves of a third of patients, as tested in mouse foot pad[8], indicates incomplete killing of M. leprae. These studies thus indicate, that though there is enormous killing of M.leprae with MDT, in a proportion of patients viable drug sensitive bacilli persist – possibly the dormant bacilli which have escaped the killing effect of drugs including rifampicin. The fate of these organisms has been the main concern, as in leprosy unlike tuberculosis, no drug is available which acts on dormant organisms. In addition, lepromatous patients lack the specific CMI to deal with these remaining organisms.

Field studies and clinical reports published till mid nineties indicated a very satisfactory outcome with the application of MDT. The relapse rates had varied from 0 to 1.6% among MB patients[3,9]. This low relapse rate contrasts with the experience of workers who had long follow up of cohorts of patients belonging to lepromatous group. Workers from Ivory Coast[10,11] and India[12] have shown that relapses following MDT are not uncommon. Further, the relapse rates were significantly higher in later years of follow up and in a subgroup of patients with large bacterial load (BI ³4+). It was observed that the bacteriological relapses occurred earlier than clinical worsening.

With the enlarged definition of MB group and reports of low relapse rates in field as also the studies involving retrieval of defaulters who had taken varying lengths of treatment[13-15], the recommendations were made more practical with limiting MB treatment to only 24 months – the fixed duration therapy or FDT[16]. Trials with 2 years MDT carried out in south India[17,18] have shown very low relapses. In fact only 1 among 46 patients, was found to have relapsed during a follow up of 9.20±2.98 years. Similarly workers from Ethiopia did not find even a single confirmed relapse among 256 MB patients who had had a mean follow up of 4.3 years after therapy following well tolerated 2 years MDT[19].

Regular intake of drugs for 2 years by practically asymptomatic patients detected in the field where the infrastructure is not optimal, is not easy . Thus, a need has been felt to further reduce the treatment duration in MB patients. Working on the length of time taken to kill possible rifampicin resistant organism, if any Ji et al[20] and Girdhar et al[21] found that it takes upto 3-9 months for biopsy inoculums to become negative for viable rifampicin resistant organisms when patients had been treated with only clofazimine and dapsone. This indicates that a minimum MDT of about 9 months is required for MB patients.

In the field, default from treatment is well known. Assessment of 41 MB patients, retrieved 1 to 5 years after stoppage of treatment of only 7 months (range 3 to 13 months) has shown continued clinical improvement in all and bacteriological improvement in 78% of patients[22]. Similarly those defaulting with less than 12 months treatment and others who had received 13-23 months therapy showed smear positivity in only 7.9 and 6.3% cases respectively after a drop out period of seven and a half years[23]. Prospective study in MB patients with BI ³ 2 comparing 24 months and 12 months efficacy has shown no relapses in 3-5 years after stopping treatment in the group given 12 months regimen (THEMYE Steering Committee: Unpublished data).

Based on above observations, together with the widened definition of MB (which now includes any active patient with >5 lesions, irrespective of smears) and decreasing

proportion of high bacteriological index (BI) patients in the field, WHO Expert Committee on Leprosy in 1995 concluded and recommended that therapy of MB leprosy should be shortened to 12 months. This has been adopted by various national agencies, including Government of India, for field application.

Twelve months FDT for MB leprosy has been applied only recently, as such no reports of its efficacy are available. As stated earlier field studies employing 24 months therapy in general have reported very low rates of relapse. Similar outcome has been made in the compilation of field observations made by leprosy unit of WHO[24]. Though low to very low relapse rates have been reported with MDT given till smear negativity or for 2 years, recently workers from all over the world have reported relapses in MB patients[25-28]. Earlier mentioned 2 well controlled institutional studies from West Africa[10,11] and India[12] involving large cohorts of patients, followed up clinically and bacteriologically, are important which reported significant relapses in patients given therapy for 2 years. The differences in the results of field studies reported above and the institutional observations are possibly on account of (i) large cohorts; (ii) inclusion of all MB cases in the field studies in contrast to mainly LL/BL patients included in the institutional studies; (iii) more close follow up including periodic clinical and skin smear examination in the later; and (iv) the longer duration of follow up in the later studies. It is important to mention that more of the relapses were observed in those with high BI at the start of treatment or on completion of 2 years therapy – the proportion being much higher in the later studies. Several other reports are available wherein on long term follow up patients who had had 24 months or longer MDT, were found to have relapsed[25-27].

In view of the fact that relapses occur late in leprosy, there is a need to follow up patients for at least 5 to 8 years after stoppage of therapy. Thus the outcome of 12 months MDT now being applied, has to be closely watched. It is nearly 3 years since it was introduced, hence not many patients have had 2 years of follow up till date – too short a period to know the long term efficacy. The proportion of various types of leprosy would also determine the outcome of short courses MDT.

Finally, for MB patients is the present therapy of 24 months adequate? remains the question. The answer depends upon as to what is the purpose of treatment. If it is to cut down the transmission of disease, as is the need of the programme, then the answer could be yes. This is particularly suitable for those areas where reasonable amount of field work for case detection and treatment has been going on for several decades. In such areas one does not expect too many patients with large bacterial load who appear to be at higher risk of relapse[28]. Further, if there is a relapse in a few patients they could be retreated with MDT, as all studies have shown that the relapses are due to drug sensitive persisters[11,12]. On the other hand for the institutional patients, where the aim, in addition is the cure of the individual patient , for all highly bacillated patients with BI ³4+ an extended treatment of 4 years or till smear negativity is desirable as has been suggested[12,30].

Treatment of Paucibacillary Leprosy

In contrast to the bacillated patients, the cure or end point of treatment of smear negative patients (the PB group) has been more difficult to define. Six months 2 drug therapy has been in use for almost 15 years. On the whole the experience of workers in several parts of the world has been quite encouraging. However, with the recommended 6 months therapy, consisting of supervised monthly rifampicin and daily self administered dapsone, completed in maximum of 9 months, few difficulties and problems have been encountered.

Disease regression

Unlike internal organ diseases, where the diseased part is hidden from oneself, in leprosy continued visibility of clinically active patch in a proportion of patients at the end of 6 month's therapy, has been observed in practically all studies. The proportion of active disease at the end of stipulated 6 months treatment has varied from 10 to 67%. Studies conducted in the institutions have shown larger proportion of patients who are still active[35,36] as compared to field situations[34,37]. This difference could be on account of relatively early diagnosis of the disease in the field.

When the pathology is evident on the surface, is it right to call the disease as cured has remained an issue. A group of workers have opined that this persisting activity is due to the presence of killed (dead) mycobacteria, fragments or antigens thereof, which may persist for long. As the length of treatment duration is not long enough for body to clear these out, continued inflammatory response results in persistent clinical activity. Indeed on follow up of patients after stipulated therapy, in about 30 to 80% of the patients, the clinical activity gradually comes down and patients get cured. The remaining patients continue

to have active disease beyond a year to 18 months. Other group of workers have reported that if DDS is continued for a further period of 6 months[34,37] or MDT is administered for 12 months instead of recommended 6 months, the proportion of patients staying active could be significantly reduced. These workers contend that with the recommended regimen anti-microbial action may not be complete in 6 months time. Similarly in several reports active granuloma has been found in over 50 % of patients on completion of therapy and even 6 month's later suggesting persisting disease activity.

Reactivation of disease

Another problem has been that during the follow up period in some patients the lesions may suddenly become active after subsidence. Further, a few patients may develop acute nerve problems. Most of these patients are still smear negative. Some patients show oedema plus CD4 cell influx on histology, suggesting inflammation due to increased cellular hypersensitivity. Such problems have been reported in all categories of patients and not limited to the PB group only. The disease becoming apparent again causes concern among the patients and has been interpreted as late reversal reaction (RR) by some and disease relapse by others. This is in contrast to the true relapses, which too, present as disease activation appearing albeit slowly and insidiously. Since there are no absolute clinical criteria to differentiate late RR and relapse, many workers have included these reactivations with relapses and thus higher relapse rates (up to 13%) suggesting that an extended therapy is required for this group of patients. Taking these events as RR and not relapse, a very low relapse rate has been reported by others[19,24,38]. A recent study has shown that clinical reactivation due to viable M. leprae can be associated with histological reversal reaction in almost half the cases.

Late nerve damage and silent neuropathy

Another problem is of late nerve damage and silent neuropathy. Whether these are on account of progressive pathology consequent to bacillary multiplication or fibrosis as part of healing is not clear.

In short the field experience in various parts of the world suggests that for patients with paucibacillary disease, six months therapy is adequate provided the patient is kept on follow up for 1 to 2 years after stoppage of treatment.

Therapy of Neuritic Leprosy

End point of treatment of neuritic leprosy – a form of disease almost limited to South-east Asia, is even more difficult. This is because the assessment and cure criteria are highly controversial. Studies have shown that even when one or few nerves are clinically affected, several of the patients show advanced disease and are positive for AFB on histology both in nerves[39-41] and in skin[42]. This suggests that these patients should better be included in MB group and given 3 drug combination. However, the national programme recommends that when up to 2 nerve trunks are thickened the patients could be treated as PB while those with large number of affected nerves should receive MB therapy. These recommendations seem justified from control point of view, as in these patients bacilli are deep in skin/or nerves and are not discharged for transmission – almost a closed pool. However, what happens in the long run is not clear as all the organisms may not get killed with the limited treatment and may result in deterioration of the nerve function. Further, despite adequate treatment, in some cases the nerve function can worsen on account of fibrosis causing concern.

Single Skin Lesion Leprosy

Active case detection programmes carried out in the recent years have brought forth an increasing number of single lesion leprosy patients in many of whom even the diagnosis is in doubt. If left untreated it is well known that majority of these will self heal, a few, however, may show progressive disease [43]. Since it is not possible to distinguish who would worsen, it has been considered necessary to treat all. A regimen consisting of single dose of 600 mg rifampicin, 400 mg ofloxacin and minocycline 100 mg (ROM) for adults has been tested in a multicentric trial and reported to be useful[44]. Similar clinical efficacy has been reported by other groups as well[45,46]. Comparative histopathology before and 6 and 12 months after completion of therapy, has shown improvement in a small cohort[47].

This is indeed revolutionary when one considers that not too long ago leprosy was taken as an incurable disease and later required to be treated for long or life long. The single dose regimen has been recommended by the WHO for treatment of leprosy patients with single skin lesion[48]. During the last 2 years several reports, based on field data have been published suggesting the efficacy of single dose therapy in patients with one lesion. Definitely this single dose treatment has been found to be operationally

attractive, feasible and acceptable by the community. Moreover, this regimen offers cure even before diagnosis and thus helps the planners in reducing the prevalence figures!

In contrast to the above the experience of workers in institutions has not been very encouraging and several issues have been raised including the very basis of this single dose therapy for an established infection. This includes theoretical insufficiency of drugs in killing of organisms as only a few bacilli (small proportion of M.leprae) are expected to be in the growth/multiplication phase during the time the drugs are available in the serum (half life of the drugs being small). Thus, those not in growth phase are likely to escape the killing effect of the drugs and may result in relapse later on. Indeed, though the follow up so far has been short, few problems of reactivation have been encountered[49,50]. Another problem is the diagnosis of single lesion leprosy itself.

Encouraged by the utility of one dose therapy for single lesion patients, the same group of workers have undertaken trial of single dose of ROM for two to three lesion patients belonging to PB group and have found cure rates comparable to PB treatment of six month in patients with two lesions. The effect of PB treatment was better than ROM in those with 3 lesions or in whom the disease affected more than one body part[51]. The cohort needs to be followed up for at least 2 years to know the real efficacy.

Conclusions

The length of multi drug therapy required or to be administered depends upon the aim, resources, motivation of the individual and his availability for follow up. The recent findings indicate that in the field 24 and even 12 months 3 drug MDT for MB patients is likely to help in achieving the goal of interrupting transmission of leprosy. Along with this the operationally feasible 6 months PB therapy for patients with 5 or less lesions and the attractive single dose treatment (ROM) for early patients with one lesion are likely to go a long way in reducing the active case load of leprosy. However, it is essential that the patients be kept under follow up for varying periods as we are not sure of the long term effects. With this length of treatment, many patients do show subsidence of disease. However, MB patients with high BI or those PB patients who have nerve trunk involvement need to be followed up very closely for any signs of deterioration. Retreatment with MB therapy should be instituted if there is a gradual/silent worsening.

A question on ethics is also important. There is a need to take moral concerns of individual patients vis-a-vis the community into account and a balance must be achieved between the cure of the patient and protection of the society at risk. This means where feasible, treatment till cure of the individual should be ensured and such individual should receive help, respect and compassion from the society, both during and after therapy.

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Printed and Published by Shri J.N. Mathur for the Indian Council of Medical Research, New Delhi
at the ICMR Offset Press, New Delhi-110 029
R.N. 21813/71