1.7 Therapeutic Trials

1.7.1 Chemotherapy trials in MB leprosy using conventional and newer drugs: ofloxacin and minocycline


Duration: 1993-2005

Background and work done

As reported earlier this trial was undertaken in consultation with National Leprosy Eradication Programme (NLEP) to see if the addition of these newer drugs ofloxacin and minocycline to the standard MDT is effective in the treatment of leprosy. This study was undertaken with the following objectives:

(i) To investigate the therapeutic efficacy of newer drugs in monthly administration.

(ii) To study the treatment failure and/or relapse in MB patients. This is to be compared with standard treatment failure of 10% and cumulative relapse rate of 5%.

(iii) To measure the side effects of the newer drugs.

(iv) To measure the effect on complications such as reactions (reversal reactions, ENL, neuritis).

(v) To assess the relationship between the detection of persisting viable bacteria and relapses, if any.

(vi) To enable the NLEP and patients to have the opportunity to choose alternate regimens according to the needs of the programme and/or individual patients.

These patients were treated with the regimen (designed in consultation with ICMR and NLEP) comprising of rifampicin 600 mg once a month supervised, minocycline 100 mg once a month supervised, ofloxacin 400 mg once a month supervised, combined with dapsone 100 mg and clofazimine 50 mg daily unsupervised. Treatment was continued for 12 months followed by placebo daily. Intake of the patients was completed 7.5 years back. The progress was monitored by clinical, histological and bacteriological and other relevant parameters (BI, mouse foot pad, ATP and molecular probes).

The details of the clinical progress, the results of viability testing and molecular markers have already been described in the earlier Annual Reports.

In the post treatment follow-up of about 10 years, 4 patients (4%) have relapsed. Of them, three patients were with pre-treatment BI between to 2+ to 2.9+ and one with pretreatment BI
between 3+ to 3.9+. However, none of the patients with a pre-treatment BI of < 2+ has relapsed during this period.

**Conclusion**

This regimen has been observed to be robust for the treatment of MB leprosy. It was well tolerated and was effective in reducing persisters resulting in low relapse rates. This regimen could be one of choices especially for highly bacilliated groups.

**1.7.2 Relapses in MB leprosy following 2 years MDT**

**Scientists**

B. K. Girdhar, A. Girdhar, J. K. Chakma and Anil Kumar

**Paramedical and Technical Staff**

H. R. Dwivedi, D. Singh, Sukhas Ram and Kalicharan

**Duration**

1996 - 2006

**Background and work done**

Since the introduction of MDT, at the global level, there has been a marked and significant decline in the active case load of leprosy with several of the parameters showing a positive change. All this has been attributed to the marked efficacy of MDT across the leprosy spectrum. The early results from clinical laboratories and the field studies, with its use showed a very rapid decline of infectivity and practically no relapses when given till the point of skin smear negativity or till the end of 2 years, which ever was earlier. This had led to the concept and testing of fixed duration therapy of one year (FDT) for MB patients. For a long time, a 2-year treatment as opposed to therapy till smear negativity (TSN) was found to be equally effective. There was continued clinical and bacteriological improvement even after stoppage of therapy in all, irrespective of the initial classification or the bacterial load. With FDT too, the short term results were found to be satisfactory. In all the reports on efficacy, follow-up had been limited.

The results of our study conducted on the same lines, using WHO recommended three drug combination given for 2 years to 260 MB (BT /BB/BL/LL) patients and followed-up for 5 years, had shown a relapse rate of 7.69 % per 100 patients (20 relapses in 930.55 patient years follow-up) which is significantly more than what the field workers had observed in limited follow-up and reported.

The follow-up of the cohort has been continued. As reported in last year’s Annual Report 32 patients had completed almost 10 years follow-up, with a mean of 9.84 years. During this period, apart from earlier 5 relapses in these 32 patients, 3 additional patients have relapsed and these relapses have occurred at the end of 7.5 years, 10.25 years, and 9 years of follow-up indicating that a forth of patients relapsed over 10 years after stoppage of therapy. Two of the 3 patients who relapsed late, had LL and had initial BI of 5.5+ and 3.75+ (arithmetic
mean of BI of 4 sites). Occurrence of 2 of the 3 relapses, among initial high BI patients, re-enforces that with limited therapy, this group is at a higher risk of having problems of relapse. In both of them, the smears became positive again. Relapse in the third patient, who initially had been diagnosed as BT, was with appearance of new lesions appearing insidiously at the end of 9 years follow-up. Patients responded to re-treatment with same drugs indicating that the relapses were on account of reactivation and multiplication of persister organisms that were drug sensitive.

Further, 2 other patients, had acute onset of inflammation in the earlier skin lesions. Both of them responded well to corticosteroids and hence were labeled as reversal reaction and not relapse. Though this is unusual, long persistence of dead mycobacteria and/or their skeletons/antigens is well known as also is regain of some degree of specific hypersensitivity by the lepromatous patients long after smear negativity.

**Conclusion**

This follow-up study shows that cases with initial high BI are at a higher risk of having problems of relapse.

### 1.7.3 Long-term follow-up of lepromatous patients given therapy till smear negativity

**Scientists** : B.K. Girdhar, A. Girdhar, J. K. Chakma and Anil Kumar

**Paramedical and Technical Staff**

- H. R. Dwivedi, D. Singh, Sukhas Ram and Kalicharan

**Duration** : 1996-2006

**Background and workdone**

In this Institute, during the early years of MDT, all lepromatous (BL/LL) patients had been treated with three drug combination (with rifampicin being given once a month) for the entire length of therapy till they became skin smear negative.

Of the 301 lepromatous patients followed-up in this group, initially for mean duration of 3.6 years, 12 patients had shown bacteriological and/or clinical relapse over a follow-up period of 1085.46 patient years, giving a relapse rate of 1.11 per hundred patient year follow-up. Like in the other study, about half the cases showed bacterial worsening only.

This relapse rate is lower than that seen among the patients given the same drug combination but for 2 years fixed duration only. The difference was particularly marked and statistically significant when comparison was made of high BI patients in the two groups (1.27 Vs. 4.29 per 100 patient years).
As in the earlier study of long term follow-up in treated patients, patients are being continuously monitored in this group as well. Twenty one patients have had more than 10 years post treatment follow-up. Among them one has shown smear positivity again. This patient was initially 5+ and had LL type of disease. This is in addition to one relapse that had occurred in this group in the first five years of follow-up.

It has been observed that the risk of relapse is significantly higher in the MB patients given treatment for only 2 years. The long term follow-up does show that the outcome of the MB patients treated till smear negativity is significantly better as compared to those given 2 years FDT. This is despite the fact that the former group consisted of patients from BT to LL type, had low mean BI with many being smear negative right from the beginning. In contrast the later group had only BL/LL (majority LL) patients, who were all skin smear positive and had initially a large bacterial load.

The manifestation of relapses observed in both the groups was similar as about 40% patients in both the studies had only a bacteriological relapse and all the relapsed patients responded to re-treatment with same drugs and became skin smear negative in 12 to 24 months. This indicates that the relapses in MB patients, following MDT, are due to re-activation of drug sensitive persister organisms that escape the bactericidal effect of 3 drug combination.

Till last year, 10 more relapses have been observed among treated patients, who had been declared smear negative and cured several years ago. Some of them belong to the cohorts under follow-up, indicating continued need for prolonged surveillance of treated patients with smear positive disease.

During the year the follow-up of the patients was continued. Final comparison will be made at the end of study in 2006.
1.7.4 A comparative study of high dose Vs low dose oral corticosteroid therapy in reversal reactions in leprosy

Scientists: A. Girdhar, J.K.Chakma, A. Ravinderan, S. Husain, Anil Kumar, G. N. Malaviya and B. K. Girdhar

Duration: 2002-2006

Background and work done

The asymptomatic course of leprosy in some patients is complicated by the occurrence of reactions that are mostly responsible for disability, deformity and destitution. While in lepromatous (LL and BL) patients, this occurs due to deposition of immune complexes (ENL or type II reactions), in borderline cases it is the result of changes, more often increase in cellular hypersensitivity (RR or type I reactions). Whereas several drugs are effective in the therapy of former, corticosteroids are the main stay in the treatment of type I reactions in leprosy.

It has been observed that in RR, the outcome with steroid administration is better when steroids are started early and when given for fairly long duration and in adequate doses. However, what is adequate dose and duration is not settled. In this study we have tried to look at both immediate and long term response to two dosage (high and low) schedules of steroids in patients of leprosy with borderline reactions and nerve damage.

This randomized controlled trial has been undertaken with independent assessment of nerve function in borderline tuberculoid (BT) leprosy patients with type I reactions. Results of 30 months follow up have been published in the Annual Report of 2004-2005.

Important highlights were:

Patients of the age group 15-60 years of both sexes having recent problems of reactions and/or NFI (3 months or less) were taken for the study. Pregnant / lactating females, individuals with diabetes / hypertension and those unwilling to come monthly for follow-up were excluded.

Regimens

**Low dose regimen**: 30 mg daily for 3 months followed by 20 mg daily for 2 weeks and thereafter reduced by 5 mg every 2 weeks (Total 5 months).

**High dose regimen**: 60 mg daily for 2 months and thereafter reduced by 10 mg every 2 weeks till a dose of 10 mg is reached and subsequently the dose reduced by 5 mg every 2 weeks (Total 5 months).

Patients were examined every month. Formal periodic assessment, for clinical response and any drug related side effects, was done during and after steroid therapy.

Sensory assessment was done using common pin and graded nylon monofilaments for
touch sensation, moving two point discrimination using U clip and the vibration sense was assessed using tuning fork. Motor power was graded on scale 0-5.

Forty patients were included in the study and randomly allocated to the two regimens. Fifteen and 13 patients are available in the groups who completed the 5 month trial period and are being followed-up and have completed 10-12 months of surveillance. Skin lesions became flat with regression of erythema in 3.41.9 (range 1 to 9 ) months in those who received higher dose of corticosteroids as compared to 4.92 1.77 (2 to 12 ) months in the other group of patients given 30 mg , the difference being significant (p <0.05 : student t-test).

Both lesional and peripheral sensations were assessed. Some degree of sensory recovery was found in both the groups but there was no marked difference. In contrast, better motor function was seen in the former group. There were 2 patients in each group in whom no improvement or deterioration was seen in the 5 months' steroid trial period.

It was seen that the patients who were administered higher dose of corticosteroid did better in terms of no recurrence of RR and nerve function recovery or loss.

A total of 16 minor problems were seen in those given 60 mg corticosteroids as against 9 in the other group. These problems (Annual Report 2004-05) regressed soon after (1-3 months) of the stoppage of steroids on completion of 5 months.

In both the groups, none of the patients had increase in blood sugar or rise in blood pressure. However, in the higher steroid group, one patient had to be excluded from the study, in the second month, on account of psychosis. Another case in this group developed herpes zoster while on high dose of corticosteroids.

Further, follow-up of the patients was continued. Seventy percent i.e., 23 patients continued to come for review and treatment. They were assessed as before. Of the 13 patients belonging to the high steroid (60 mg prednisolone equivalent) group who came for follow-up, one had repeat reversal reaction. This was a sudden event with no precipitating factor and occurred 36 months after subsidence of the first reaction and this was 16 months after RFT. The reaction was confined to skin with no clinical new nerve affection or nerve function deficit. In contrast, 3 patients in the low dose steroid group had problems. In two patients fresh episodes of RR appeared. In one patient reaction occurred after 30 months of start of therapy and in the other 26 months after initiation of therapy. In the latter patient and also in another patients, the nerve(s) became painful and tender and there was functional damage to the nerves. All steroid related problems except striae had regressed in patients belonging to both the groups.

The observations over almost 30 months post steroid treatment showed that corticosteroids, administered in dosage of 60mg per day prednisolone equivalent and tapered over 5 months period not only results in better early response but also reduces reaction/ reaction related problems in the late phases of therapy and follow-up. Follow-up of these cases was continued during the year. Final analysis will be carried out after the end of follow-up in 2006.
1.7.5 Evaluation of the effect of addition of immunotherapy with $M_w$ vaccine to standard chemotherapy in borderline leprosy

**Scientists**: Raj Kamal, K. Katoch, M. Natrajan and M. Arora.

**Para medical and Technical staff**: N. Crispin, S. Shinge, Kalicharan, R.F. Lal, V. M. Sobti, S. D. Lal, S.N. Masih and P. Kaur

**Duration**: 2001-2006

**Background and work done**

Our earlier studies have shown that addition of immunotherapy to chemotherapy improves the therapeutic effect of chemotherapy in highly bacillated leprosy cases. This trial has been initiated to assess the additive effect of immunotherapy ($M_w$ vaccine) with standard MDT in borderline leprosy cases (BT, BB, BL). A total of 150 cases of leprosy (BT=61, BB=54, BL=35) and 50 patients (controls) on MDT but not on immunotherapy (BT=24, BB=18, BL=8) have been so far included in this study.

As reported in Annual Report of last year initial response of BT cases treated with MDT plus immunotherapy was compared with the controls. The clinical parameters like size of lesion, erythema, infiltration, sensation all showed faster improvement with $M_w$ vaccine as compared to controls (only chemotherapy) where the clinical improvement was slower. The clinical progress of all parameters in BB,BL cases was also observed after 4 doses of $M_w$ vaccine plus MDT. There was also good clinical improvement in these cases. Histopathologically, dramatic decrease in granuloma fraction has been observed in BT cases following $M_w$ vaccine plus MDT as compared to control group where we observed slower clearance of granuloma fraction.

The follow-up of the cases and controls was continued during this year.

**Future programme**

The study will be continued to include required number of cases and controls and their follow-up will be done as per the approved design.
1.7.6 Uniform MDT (U-MDT) regimen for all leprosy patients
(WHO funded multi-centric study)

**Scientists** : K. Katoch, P. Sachan and M.D. Gupte* (Chief Co-ordinator)
*(NIE, Chennai)

**Field and Laboratory Staff**
R. Singh, S. Singh and Rajendra Kumar

**Duration** : 2003-2008

**Background**
This uniform MDT (U-MDT) has been recommended by WHO for trials in India and other countries as if the same regimen is given to all types of leprosy patients it would be operationally much easier to treat them. Majority of cases which are currently detected under field conditions are early cases i.e., PB and smear negative MB cases. The use of clofazimine in the PB regimen for 6 months has been tried by us earlier at this Institute and was observed to substantially decrease the incidence of persisting activity, reactions and with no relapses in the post treatment follow-up of 5 years. Therefore, all the PB cases getting this treatment will be gainfully treated. For smear negative MB cases the bacterial load is low and theoretically, for most of these cases the duration of the present day MDT regimen can be reduced to 6 months based on the data obtained from animal experiments.

This study is a field based study in which the patients will be followed up for 5 years after stoppage of therapy and failures if any detected during the follow-up will be put on standard MDT. This study is a multi-centric study funded by WHO and we are one of the four participating centers in India.

**Work done**
Intake of patients was completed in October, 2004. Pure neuritic cases have been excluded in the study.

During the period under report follow-up of the cases was continued. 302 (94%) patients have completed six months treatment. (1 expired, 13 refused to take treatment and 6 have migrated out of the area after signing of the informed consent after various duration of treatment). Two hundred and three patients have completed a follow-up of 1 year after release from treatment. One patient developed acute neuritis during this period. He was given full doses of steroids and rest to the hand and is being followed up closely.

**Future programme**
The follow-up will be carried out as per approved plan.
1.7.7 Determining the efficacy and safety of Immunomodulator (Mycobacterium w) as an adjunct therapy in pulmonary tuberculosis


Supporting Scientific Staff: N. Chaurasia and S. Chandra


Duration: 2004-2007

Background

This project aims to study the differences in the sputum conversion rate, cure rate and relapses (occurring after 6, 12 and 24 months after stoppage of therapy) in Category I and II patients of pulmonary tuberculosis between the standard ATT (anti-tubercular therapy) and the addition of Mw as adjunct to the same ATT regimen in a double blind study.

It is proposed to carry out a house to house survey in the Ghatampur field area of the Institute to detect Category I and II patients of pulmonary tuberculosis, using the standard clinical radiological and bacteriological tests. The identified patients will be given the standard ATT required for the respective category in the control group and the trial group will receive 5 doses of Mw in the prescribed dosages in addition to the standard ATT therapy in a coded double blind manner. Clinical, bacteriological, blood and radiological tests will be repeated at the prescribed intervals during the study.

Work plan

A house to house survey of the entire Ghatampur (approx population 4.8 lakhs) and patients of pulmonary tuberculosis has been started to identify tuberculosis cases on the basis of clinical, bacteriological and radiological signs as per the standard RNTCP (Revised National Tuberculosis Control Programme) protocol. The identified patients will be being categorized into Category I, II and III as per the RNTCP definition.
Study design
This is a randomized, double blind, placebo controlled, multicentric, safety and efficacy study. The patients will receive either placebo or immunomodulator $Mw$ at the start of therapy and after every 2 weeks for up to 8 weeks of treatment (5 injections at the interval of 2 weeks, in the initial intensive phase of treatment i.e. 8 weeks) in addition to the prescribed DOTS for the respective category of patients as described in the protocol. The design of trial has been detailed in the Annual Report of 2004-2005.

Work done
The trial has been initiated in category II cases as per approved protocol following GCP (Good Clinical Practices) guidelines. A total of 49 cases of CAT-II pulmonary tuberculosis have been included in $Mw$ study of these 42 cases have been included this year while 7 were included in the previous year. These cases are being treated as per the approved protocol of the study. The details of all the 49 patients are being detailed here.

There were 39 males and 10 females in the study. Four percent of patients were below 20 years of age (18-19 years), 37% between the age group of 20-29 years, 28% between 30-39 years, 27% between 40-49 years and 4% of cases were between 50-55 years of age. Age wise distribution of cases is shown in the Fig.17.

Categorization of patients according to the previous history of treatment is shown in the table 5. All the patients were sputum smear positive, 49% (24/49) were 3+, 27% (13/49) were 2+, 16% (8/49) were 1+ and only 8% (4/49) had scanty AFB in their sputum. Sputum culture for $M.tb$ was positive in 43 of the 49 (88%) patients tested at the start of therapy.

![Fig. 17 Age wise distribution of patients](image-url)
Three patients have died during the study. In all the cases the death was due to the disease and its complications. In no case the death was attributed to the intervention.

**Future programme**

More cases will be included in the study and all the cases will be followed up after completion of therapy for 2 years as per the approved protocol of the study.

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<tr>
<th>Patients (%)</th>
<th>Treatment after Default (TAD)</th>
<th>Treatment Failure (TF)</th>
<th>Relapse (Rel)</th>
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<tbody>
<tr>
<td>30 (61%)</td>
<td>4 (8%)</td>
<td>15 (31%)</td>
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