Original Article

Long Term Follow-up Results of 1 Year MDT in MB Leprosy Patients Treated with Standard MDT + once a Month Minocycline and Ofloxacin

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Abstract

Background : This study was initiated in consultation with the National Leprosy Eradication Programme (NLEP) in mid nineties to try new treatment regimens for leprosy which were more robust in terms of control of reactions, long term relapses, operationally easier to undertake and feasible in field conditions. It was also envisaged to see if the addition of newer bactericidal drugs would be beneficial.

Objectives : (i) To test the feasibility, safety and response of the patients to the new regimen. (ii) To observe the incidence of reactions during and after stoppage of therapy, for a period of 8-10 years after release from treatment.

Materials and Methods : A total of one hundred skin smear positive MB patients (15 LL, 35 BL and 50 BB) patients were included in this study. All the patients received the standard MDT + once a month supervised 100 mg of Minocycline and 400 mg of Ofloxacin for 12 months during the treatment phase. Thereafter, the treatment was stopped in all the patients which were followed-up on placebo (B complex tablets). Of these, 70 patients completed the treatment schedule of one year therapy and the post treatment follow-up of 9 to 10 years.

Results : All the patients tolerated the drugs well. The clinical response of the patients to the treatment was very good of which 32.85% of cases had history of reactions before starting treatment. During treatment, the incidence of reactions increased marginally to 38.5%, but these were easily controlled with concurrent administration of steroids. After

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completion of treatment the incidence was much less i.e. 10% and 3% after 1 and 2 years of post treatment follow-up respectively. The overall relapse rate is 5.7% (4/70) with an incidence density of 0.05/100 patient years. Relapses were confirmed by clinical, bacteriological, molecular biological (rRNA probes and 36 kD targeting PCR) as well as ATP bioluminescence. The relapsed patients presented with the appearance of new lesions, slit-skin smears were again found to become positive after becoming negative. Three of the four cases who relapsed had the initial mean BI of 2 to 2.9+ whereas one had the initial mean BI of 1.5+. Also, 2 of the 4 relapsed patients had positive PCR signals at the time of stoppage of treatment.

Tentative conclusions : The addition of Minocycline and Ofloxacin to the standard FDT has been observed to be a well tolerated regimen. The results of 1 year fixed duration MB-MDT have not been published yet and therefore cannot be compared. Overall as of now, the incidence of reactions observed with the newer treatment regimen is found to be significantly lower than that of 2 years fixed duration MB-MDT. The efficacy of this regimen regarding bacteriological clearance and relapse rates could not be compared due to non-availability of the results of experience with standard 1 year MDT regimen. However, this regimen appears to be operationally feasible and safe for the users.

Key words : MB leprosy, MDT, FDT, Minocycline, Ofloxacin

Introduction

India has successfully achieved elimination of leprosy at the national level and prevalence rates at the end of 2007-2008 was 0.72/10,000 (NLEP 2008). Despite major reduction in patient load, new cases of leprosy continue to occur and are treated with the standard MDT. The standard MDT is a fixed duration MDT (WHO 1998), comprising of once a month Rifampicin (supervised) and daily Dapsone for 6 months in PB cases; and a combination of once a month Rifampicin + Clofazimine (supervised) combined with daily Dapsone and Clofazimine for 1 year in MB cases. This treatment schedule was adopted to make the implementation of the programme easier and feasible in providing the treatment to all patients of leprosy. Implementation of the treatment strategy has helped in achieving the goal of elimination of leprosy. However, some problems do remain which include relapses and reactions after completion of the treatment schedule. Moreover, reports on long term follow-up and documentation of reactions and relapses are not published. The general belief based on the observations of several workers is that, in few patients (especially those who are skin smear positive), problems do remain and more choices of treatment strategies are required for effective treatment, preventing transmission and eradication of the disease. Several potent bactericidal drugs are now available and can be tried for improving the treatment of leprosy. This study was undertaken in smear positive MB patients in consultation with the NLEP to assess the safety and feasibility of the regimen as well as to assess the incidence of reaction and relapses after a long term follow-up of 8-10 years.

In the present study, smear positive MB cases were treated with a monthly supervised dose of 100 mg of Minocycline plus 400 mg of Ofloxacin in addition to the standard MB-MDT regimen. The initial results of this study with a follow-up of 2-3 years have already been reported (Katoch et al 2000). Effect on viability was also reported separately (Singh et al 1999, Gupta et al 2000). Briefly, the regimen was well accepted, safe and

operationally feasible to administer in the field. The post treatment follow-up of 9 to 10 years is being reported in the present study.

Patients and Methods

One hundred untreated or less than 3 months treated, smear positive BB, BL and LL cases of 16 to 60 years of age, attending the OPD of National JALMA Institute for Leprosy and Other Mycobacterial Diseases, Agra and who agreed to be a part of the study, were included. After obtaining their written consent, these patients were examined clinically, clinical scoring (Iyer et al 1977) was done and recorded. Slit-skin smears were taken from four sites, stained by the Zeihl-Neelsen method and bacteriological index (BI) were recorded in Ridley Jopling logarithmic scale. Smear positive (BB, BL and LL) cases who consented to take part in the study, were administered this study regimen while the rest of the smear negative cases as well as the non consenting cases were administered the standard therapy. A skin tissue biopsy was taken from an active site and processed for routine histopathology, mouse foot-pad inoculation (Shepard 1960, Desikan and Venkataramaniah 1976), bacillary ATP estimation (Katoch et al 1989), detection of rRNA of *M. leprae* (Katoch et al 1992, Sharma et al 1997) and 36 kD targeting PCR (Hartskeerl et al 1989).

These patients as detailed above, received a regimen comprising of the standard MB- MDT + (100 mg of Minocycline and 400 mg of Ofloxacin), once a month, supervised for a period of 1 year (12 doses). After completion of schedule, treatment was stopped and patients were followed up on placebo (B complex tablet). During treatment period the patients were examined every month and the clinical details were recorded. Any adverse effect noted were recorded while administering the supervised dose. The daily medicines were given for consumption at home and the patients were advised to report immediately in case of any adverse effect. At the end of treatment the patients were examined again, clinical scores noted (Iyer et al 1977); slit-skin smears were repeated from the same sites and recorded. Biopsies were also repeated for mouse foot-pad (MFP) inoculation, ATP estimation and rRNA as well as 36kD PCR. Thereafter, during the follow-up, the patients were examined at an interval of 3 to 6 months or whenever the clinical condition warranted.

The following definitions were used and followed in the study:

Treatment failure

Treatment failure is defined as appearance of new lesions and / or a definite worsening of existing lesions, not related to or accompanied by reversal reaction during the treatment period. Bacteriologically, this could be associated with an increase in average BI.

Relapse

Relapse is defined as occurrence of smear positivity after achieving negativity at the completion of treatment at any site with the appearance of new lesions or definite worsening of the existing lesions. The increased / detectable bacillary ATP levels (Katoch et al 1989), rRNA (Katoch et al 1992, Sharma et al 1997), 36 kD PCR (Hartskeel et al 1989) and/or positive mouse foot-pad results to confirm the viability/diagnosis (Shepard 1960, Desikan and Venkataramaniah 1976), were taken as the additional confirmatory evidence.

Results

A total of one hundred patients were included in the study which comprised of 15 LL, 35 BL and 50 BB patients. There were 17 females and 83 males. All the patients tolerated the drugs well. Only 2 patients had

nausea after taking the supervised dose which decreased after taking a glass of milk thirty minutes after the supervised dose. One patient had jaundice during treatment (3rd month) and treatment had to be temporarily suspended in him. After recovery from jaundice treatment was re-started and there was no recurrence of the symptoms. He probably suffered from concurrent Infective Hepatitis which regressed subsequently and was not related to the drugs used in the treatment.

As mentioned earlier, out of 100 patients recruited in the study, 70 patients completed the treatment schedule of one year therapy and the post treatment follow-up of 9-10 years. Thirty patients were irregular and stopped treatment at various durations. The profile of all these patients at the time of starting therapy is given in Table 1. It can be observed that profiles of patients, who were regular in treatment, were similar to those patients who did not complete the treatment and the follow-up and therefore, their exclusion did not create any bias in the analysis.

Clinical progress

The clinical response of patients to the treatment was very good. After starting the treatment the lesions started regressing, erythema subsided and the lesions showed wrinkling of the skin in a few months. In LL and BL patients, the infiltration regressed gradually and the infiltration was slowly replaced by wrinkling of the skin. No case of treatment failure was observed.

Bacteriological progress

Bacteriologically, the response of the patients was very good. All patients were skin smear positive at the start of treatment (average BI ranging from 4+ to 1+). The progress of the 70 patients available for follow-up at the end of treatment is being reported of which, 25 (35.7%) were still-skin smear positive while the rest were negative. For detailed bacteriological analysis the patients have been further subdivided into 4 sub-groups depending on the average BI observed in the skin smears.

(a) Pre-treatment mean BI grouping of 4+ and more

Eight patients belonged to this group with a mean BI of 4.4. There was a fall in BI in all the patients during treatment which, however, varied in each of them. In 1 patient, there was no change in the highest BI at the end of 1 year of treatment while in others it ranged from 3+ to 1+ with a mean BI of 2.3. After stoppage of treatment, all the patients were followed-up on placebo (tablet B complex as mentioned earlier) and the BI continued to fall. It also fell in the patient who had a stationary BI at first year of treatment ranging from 3+ to negativity in the four sites tested. Six patients became skin smear negative by the end of second years of follow-up when the mean BI at the end of this period was 0.65. In the third year of follow-up,

Table 1: Profile of patients at the time of starting therapy

Type of patients	Sex		Type of disease			Clinical score	Average BI
	Male	Female	LL	BL	BB		
Regular	57	13	12	25	33	13	1.83
Irregular	26	4	4	9	17	12	1.79
Total	83	17	16	34	50	-	-

1 more patients became skin smear negative. The lone patient who was positive in the third year became skin smear negative in the fourth year.

(b) Pre-treatment mean BI grouping of 3 to 3.9+

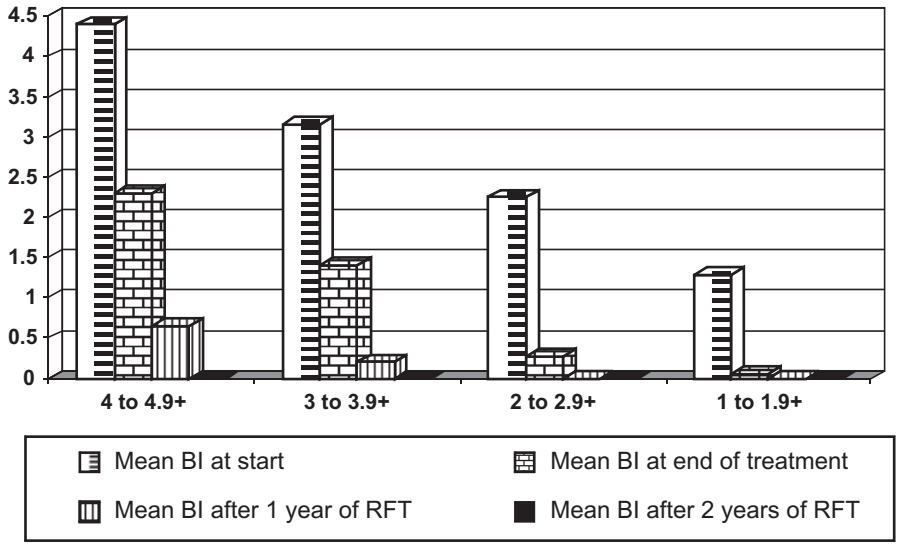
There were 7 patients in this sub-group. None of the patients of this group became skin smear negative by the end of one year of treatment and the mean BI at this time was 1.4+. By the end of 2 years, 5 patients became skin smear negative, the average BI in the 2 positive patients was 0.2. By the end of 3 years all the patients became smear negative (Figure 1).

(c) Pre-treatment mean BI grouping of 2 to 2.9+

Thirteen patients belonged to this group with a mean BI of 2.25. The skin lesions regressed rapidly in these patients and at the end of 1 year, 4 of these patients became skin smear negative. The rest of patients also had very few bacilli in their skin smears and the mean BI in these patients was 0.27. All the patients became skin smear negative by the end of 2 years of follow-up. There have been 3 relapses in this group.

(i) One of these three relapsed patients who became skin smear negative by 2 years, relapsed after 4 years. He had an initial BI of 4+, 2+, 2+, 2+ from the respective four sites with a mean BI of 2.5+. He was still bacteriologically positive at the end of treatment but became negative in the subsequent year. He had history of ENL reactions before treatment during treatment and also 1 year after stopping treatment. During reactions, he was treated with steroids. After 4 years he presented with another bout of ENL, his slit-skin smears were again positive 2+,1+,1+,1+ and the case was diagnosed as relapse and treatment re-started. Steroids were given concomitantly for ENL reaction. Although, there was no growth from his skin tissue biopsy specimen in the mouse foot-pad, viable

Figure 1 : BI status of patients at different time points of treatment and follow-up in the four sub-groups



bacilli were detected by ATP bio-luminescence, presence of *M.leprae* specific rRNA and PCR targeting 36 kD gene region. He has completed a further 2 years course of standard MB-MDT. His smears have become negative, the reactions have also subsided and he is well and the treatment has been stopped.

(ii) The second patient with relapse in this sub-group had an initial BI of 3+, 2+, 2+, and 1+ from the respective four sites. He progressed well during the treatment phase. At the end of the treatment phase, he was still smear positive and his smears were 2+,1+,1+ and negative respectively, from the four sites tested. By the end of the subsequent year, he became skin smear negative. In the fifth year of follow-up, he presented with ENL lesions over his body with orchitis and arthritis. His smears were 2+, 0.2+, negative, negative. Due to low yield of bacilli from his tissue biopsy, it could not be inoculated in the mouse foot-pad but bacillary ATP was detected in the bacilli isolated from the tissue biopsy and it was also positive in the test of 36kD PCR. He was diagnosed as a relapse case and put on standard MB-MDT and steroids for ENL. He was given standard MDT further for 2.5 more years. He intermittently continued to have ENL lesions which have now completely subsided and his smears are negative after re-treatment. He did not suffer from any fresh episodes of reaction after re-treatment.

(iii) The third patient had an initial BI of 2+ from all the four sites. She progressed well during treatment and at the end of 1 year of treatment was skin smear negative. Her lesions regressed and condition remained uneventful for the next 8 years after which she presented with new lesions on her body. Over a period of 3 months, many more lesions appeared without signs of acute inflammation. Her smears now became 1+, 1+, negative and negative from the respective four sites. Her biopsy was positive for 36kD targeting PCR. Lepra bacilli obtained from the tissue biopsy specimen were inoculated into the mouse foot-pad but the results were negative. She was diagnosed as a relapse case and is being re-treated with standard MB-MDT and is well.

(d) Pre-treatment mean BI grouping of 1 to 1.9+

Seventeen patients belonged to this sub-group and their mean BI as 1.28. Sixteen patients became smear negative after 1 year of treatment and the lesions regressed. The lone patient who was positive had very few bacilli with a mean BI as 0.045. He had reversal reaction and became skin smear negative by the end of 2nd year.

One patient in this group has relapsed who had an initial BI of 2+, 2+, 1+, 1+ from the respective four sites at the start of treatment (mean BI 1.5). He progressed well and was skin smear negative at the time of completion of treatment. He remained asymptomatic for the next 6 years after which there was appearance of new lesions without any signs of inflammation. Over the next 4 months, a few more lesions appeared and his skin smears were 2+, 2+, 2+ and 1+. A biopsy was performed from the active lesion but the yield was too low to be inoculated in the foot-pad of mice. His biopsy showed viable bacilli by ATP bio-luminescence and by rRNA and 36 kD PCR. He was diagnosed as a case of relapse and put on standard MDT. He has now had 2 years of standard MB-MDT, his lesions have regressed and his smears are now negative.

(e) Pre-treatment mean BI grouping of less than 1+

Twenty five patients belonged to this group. In most of these patients, smear positivity was observed in one or more of the active lesions on the body surface while skin smear from the other sites was negative. The average BI was 0.55. All these patients became skin smear negative by the end of 1 year of treatment. None of these patients have relapsed in the follow-up period.

Reactions

Twenty three patients (32.85%) gave history of lepra reaction [12 cases reversal reaction (RR) and 11 with ENL] before starting treatment. The study regimen had to be supplemented with steroids to control the reaction and was gradually tapered off after its subsidence. In 27 patients (38.5%), there were episodes of both type 1(RR) and type 2 (ENL) reactions during treatment. They were also treated concurrently with appropriate doses of steroids. In none of the patients, treatment had to be stopped because of reactions. Neuritis was present as a part of ENL and/or RR and in no case only neuritis was present. None of the patients suffered from deformity while on treatment or after stopping treatment. Eight patients had episodes of reactions after stoppage of therapy and were managed by steroid treatment and placebo. These episodes continued up to 2 years of post treatment follow-up.

ENL reactions

Eleven patients gave history of ENL reaction, recurrent episodes of fever before starting therapy. Five patients continued to have ENL reaction after completion of one year therapy. They were treated with steroids while continuing the placebo. All these patients belonged to the mean BI grouping of 2+ and more. Three patients among them continued to have ENL in the second year of follow-up also. In the third year of post treatment follow-up, none of the patients had ENL reactions. One patient with the mean BI of 2.5+ (who also had ENL in the second year of post-treatment follow-up and was skin smear negative), presented with ENL in the fourth year of post-treatment follow-up period. He was found to be skin smear positive as detailed above (2+,1+,1+,1+) and diagnosed as relapse case. He was re-treated with the standard MB-MDT.

Another patient with a mean BI of 2+ had ENL reaction accompanied by orchitis and arthritis, in the fifth year of follow-up. As detailed above, his skin smears also became positive and was restarted on standard MB-MDT and steroids.

Table 2 : Incidence of reactions in the patients before, during and after therapy

Mean BI grouping	No. of patients	Before treatment	During treatment	After stoppage of MDT
4+ and more	8	6	4	3
3 to 3.9+	7	5	7	2
2 to 2.9+	13	3	9	2
1 to 1.9 +	17	7	7	1
Less than 1+ but positive	25	2	Nil	Nil
Total	**70**	**23 (32.9%)**	**27 (38.6%)**	**8 (11.4%)**

Reversal reaction

Twelve patients gave history of reversal reaction before starting therapy and had to be treated with the trial regimen and steroids. After the stoppage of therapy, 3 patients continued to have RR and were treated with steroids in addition to the placebo. All of these patients were slowly weaned out of steroid therapy while continuing on placebo. On the average, it took 4 to 8 months for the withdrawal of corticosteroids.

Viability assessment

For assessment of viability tissue biopsies obtained from patients were inoculated into foot-pads of normal mice as well as bacillary ATP was measured in the bacilli obtained from tissue biopsies at the start of therapy after one year of therapy and also as when required during the course of follow-up.

(a) Mouse foot-pad inoculation

At the start of therapy, positive mouse foot-pad results were observed in 35/89 (39.3%) of the patients. In rest of the patients, no growth was observed as these patients had low BI The viability results of mouse foot-pad inoculation have been described earlier (Gupta et al 2000) and are summarized in Table 3. None of the specimens were positive for viability at one year of therapy.

Biopsies from all the four patients who relapsed subsequently were obtained. However, it could not be inoculated in 2 patients as the bacilli isolated from the tissue biopsy was low.

(b) Bacillary ATP measurement

Bacillary ATP was detected in all the patients at the start of therapy. This test was found negative in all the patients after 1 year of therapy indicating, thereby, that no viable bacilli could be detected after 1 year (Gupta et al 2000).

In the four patients who relapsed subsequently ATP estimation was done from the bacilli obtained from their tissue biopsies. In all the 4 patients, bacillary ATP was detected in the tissue biopsies (Figure 2).

(c) Gene probe and gene amplification

In the present study using the 36kD gene region as the target, PCR was done from the bacilli isolated from the tissue biopsies at the start of therapy after completion of 1 year of therapy and whenever required during the follow-up period. PCR was found positive in all the patients at the time of starting therapy, in 3 patients at the end of 1 year treatment (Singh et al 1999) and weak positive in 2 patients after 2 years of follow-up (Katoch et al 2000). The comparative results using these viability parameters are shown in Table 4.

Of the 3 patients (5.26%) who were positive for (36 kD PCR) at the time of stoppage of therapy, 2 relapsed later in the

Table 3 : Viability results as determined by normal mouse foot-pad inoculation method

Time duration	Growth observed (positive)	No growth (negative)	Death of mice (discarded)	Total
Start of therapy (Day zero)	35 (39.3%)	54 (60.7%)	11	100
Completion of 1 year therapy	0	55 (100%)	2	57*
During follow-up period	0	2*	0	2*

* In rest of the patients, mice could not be inoculated due to low bacillary count

Figure 2 : Comparison of MFP and bacillary ATP results with therapy

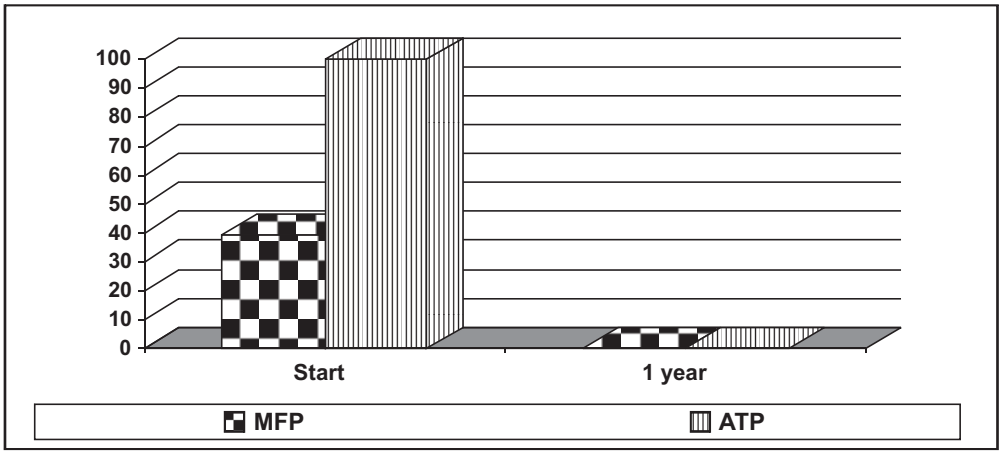


Table 4 : Comparison of skin smear positivity, mouse foot-pad (MFP) inoculation, ATP and PCR results at the start and completion of therapy

Duration	Skin smear positive	MFP positive	ATP positive	36 kD PCR positive
Start of therapy	100% (100/100)	39.3% (35/89)	100% (100/100)	100% (100/100)
Completion of 1 year of therapy	35.7% (25/70)	0%	0%	5.26% (3/70)

follow-up period in which PCR signals had persisted. Presence of rRNA was used as additional proof to detect viable bacilli in relapsed cases. All the specimens were positive for *M.leprae* specific 16S rRNA.

Discussion

The regimen was found to be is well accepted, safe and there were no major side-effects observed (Katoch et al 2000). There was no case of treatment failure. The clinical response to the treatment regimen was very good and it can thus be easily administered in the field.

Reactions

Twenty three (32.8%) patients had history of reactions before starting treatment. During treatment, the incidence of reactions increased marginally to 38.5% (27/70) but these were easily controlled with concurrent administration of steroids. In no case the treatment had to be stopped due to severe reactions and none of the cases suffered from deformities due to reactions. Both types of reactions were observed in these patients. In the first year of post treatment follow-up, 8 patients (11.4%) had reactions which were controlled with the concurrent administration of steroids along with placebo. One of the patients who became smear negative in the second year of post treatment follow-up continued to have ENL reaction intermittently in the post treatment follow-up. He was treated with steroids but when his skin smears became positive in the fourth year of post-treatment follow-up he

was treated as relapse with ENL reaction and MDT was again restarted along with steroid therapy. Another patient also had ENL reaction with multiple system involvement presenting as orchitis and arthritis. He also became skin smear positive and was treated both for reaction and relapse.

There are not many reports of the incidence of reactions after 1 year of standard MDT in smear positive patients. However, in the symposium on leprosy reactions organized by the Indian Associations of Leprologists (2003), the incidence of reactions at the end of 1 year of FDT (fixed duration treatment) in MB leprosy patients was observed in 75 out of 134 (55.9%) cases while with the use of the present regimen the incidence of reactions was observed to be lesser in 27 of the 70 patients i.e. 38.6%. The difference in the two observations was found to be statistically significant (p=0.0269). The incidence of reactions after of 24 months of FDT was 35.8% (24/67) in the IAL symposia analysis and 38.6% (27/70) in the present regimen at the end of 1 year of treatment as already stated above. This difference was not found to be statistically significant (p=0.875). However, results from the ALERT programme (Becx-Bleumink and Berhe 1992) showed lower incidence of reactions among 375 BL/LL patients who were treated with 2 years FDT. During the first year of treatment, 24.8% patients had reactions which decreased to 12% in the second year of treatment. In the subsequent years during follow-up 6.1% and 2.4% of reactions were observed in third and fourth year respectively. These continued to occur intermittently even in the fifth year. With the use of the present regimen, the incidence of reactions was 38.6% during the treatment and 11.4% and 4.3% after 1 year and 2 years of post treatment follow-up respectively.

Bacteriological clearance/progress

The fall in the bacteriological index in the patients was good and 45 of the 70 patients (64%) became skin smear negative at the end of the treatment period of one year. The bacteriological decline in smear positive MB patients has been reported to fall by about 1 log per year (THELEP 1987). With the present regimen, 45 of the 55 patients (81.8%) with a mean BI of 2+ and less became skin smear negative after 1 year of treatment. Of the 20 patients with a pre-treatment mean BI of 3+ and more at the start of therapy, none became negative at the end of the treatment period but 11 of the 15 patients (73.3%) became negative after first year of post-treatment follow-up.

Cellona et al (2003) have reported the results of follow up in smear positive MB cases after 2 years of FDT. In their series of 500 patients, 281 cases (56.2%) became smear negative after 2 years of standard FDT. This rose to 79.2%, 86.3%, 91.9%, 98% and 99.52% in the years 1, 2, 3, 4 and 5 during follow-up (after completion of MDT). All these patients became skin smear negative by 6 years. The number of patients attaining skin smear negativity with the present regimen are 45/70 (64.3%) after the treatment period of 1 year. The notable difference between the two groups was the initial BI which was 3.39 (for the group as a whole) in the study by Cellona et al (2003) and the corresponding figure in the present study was 1.52.

Ganapati et al (1997) compared the fall in BI in groups of BL/LL patients who received 1 and 2 years of standard FDT respectively. The mean pre-treatment BI was 3.2 in the 12 month FDT regimen group which fell to 2.4 after 1 year of FDT. The patients were followed-up after stopping treatment and the mean BI was 1.7, 0.9, and 0.5 after 1, 2 and 3 years respectively after stopping treatment. The fall in BI in patients on 24 months FDT

followed the same trend was surprisingly lesser than in patients who received 1 year FDT.

Relapses

In leprosy, a more reliable final measure of the efficacy of a regimen is the relapse rate. The reported relapse rate after continuous MDT till the attainment of smear negativity has been quite low (WHO 2001, 2002; Norman et al 2004). A relapse rate of about 1.1% (2/173) has been reported in MB patients treated till smear negativity and followed up for 16.4 ±1.8 years (Norman et al 2004). Similarly, in another study 1.84% relapse rate in BL/LL cases treated till smear negativity was reported (Poojabylaih et al 2008). As the experience grew it was felt that treatment is not required till smear negativity as the smear positivity is due to dead bacilli and their debris and treatment can be stopped earlier. Fixed duration treatment (FDT) concept was introduced and MB patients were treated for 2 years (24 doses) and later for 1 year (with 12 doses). The risk of relapse after 2 years, FDT is also reported to be generally low. As no published experience with one year FDT is available, we have tried to compare the relapse rates with some important 2 years MDT treated patient series (Table 5).

Data about relapse rates following 2 years WHO-MDT is contradictory and wanting on several grounds particularly about the duration of follow-up and proportion of high initial bacterial burden (Gelber et al 2004). Becx-Bleumink (1992) had reported a relapse rate of 2.4% in a follow-up of 4.7 years. Marchoux Study Group (1995) observed relapses in 20% (7/35)) of MB patients treated with 2 years of standard FDT with a follow-up of over 6 years. However, this relapse rate was much lower when patients were followed up for only 4 years. Girdhar et al (2000) have reported a relapse rate of 7% (20/260 MB patients) with a mean follow-up of 4 years with a 2 year FDT.

Table 5 : Comparison of relapse rates in cases treated with two years MDT versus present regimen

Study name	Year	No. of patients	Duration of treatment	Initial BI status	Duration of follow-up	Relapse/relapse rates
Cellona et al at field area	2003	498	2 years standard MDT	≥ 2.7+	10.8 years	15/498 (3%)
Cellano et al at clinic in Phillipines	2003	142	2 years standard MDT	≥ 2.7+	12 years	13/142 (9%)
Marchoux study group	1995	35	2 years standard MDT	>2+	6 years	7/35 (20%)
Girdhar et al	2000	260	2 years standard MDT	<2 -6+	4 years	20/260 (7.7%)
Katoch et al	Present study	70	1 yr	1-5+ (Mean BI= 1.51)	9-10 yrs	5/70 (5.7%)

Cellona et al (2003) reported a relapse rate of 3% (15/498) with a mean follow-up of 10.8 years per patient in the field study v/s 9% (13/142) in those attending the Cebu Skin Clinic. In the present study, the overall the relapse rate is 5.7% (4/70) with an incidence density of 0.05/100 patient years. All the relapses occurred in patients with mean BI between 1.5 + to 2.5+. In all the patients new lesions appeared gradually, acid fast bacilli were present in the lesions and/or the ear in patients who had become skin smear negative earlier. Although no growth could be demonstrated in the mouse foot-pad experiments, viable bacilli were detected by bacillary ATP estimation, rRNA based probes and 36 kD gene targeting PCR . All the four patients responded to the standard MDT regimen thus suggesting that the relapse was due to drug sensitive organisms. Other workers have also reported relapses due to drug susceptible organisms.

Relapses occurring with drug sensitive organisms after this long period are probably due to multiplication of these few organisms persisting in the body. It is, however, very difficult to predict which patient will relapse, although patients with a higher initial BI relapse more frequently.

The viability tests (MFP and bacillary ATP estimation) done at the end of treatment did not show the presence of live bacilli in these patients. It is possible that the live bacilli could not be detected due to error in the biopsy sampling which did not contain live bacilli which could have been detected by these tests (Table 6). Bacillary ATP could be detected in all the 4 patients who relapsed

Table 6 : Profile of relapsed patients

Patient code	Pre-treatment mean BI	BI at the end of treatment	Reactions after treatment	MFP result at the end of treatment	ATP result at end of treatment	36 kD PCR at the end of treatment	Characteristics at the time of relapse
MY	2.5+	1+	ENL	Neg	Neg	Pos	ENL reaction, skin smear (+)ve, ATP and PCR (+)ve
PI	2+	2+	ENL, Orchitis, Arthritis	Low yield	Neg	Pos	New lesions, Skin smear, ATP and PCR (+)ve. Relapse after 5 years
SN	2+	Neg	No	Neg	Neg	Pos	New lesions gradually. ENL, orchitis, arthritis. ATP and PCR (+)ve. Relapse after 7 years
NF	1.5+	Neg	No	Low yield	Neg	Neg	New lesions gradually. Skin smear (+)ve, PCR (+)ve. Relapse after 9 years

and can be taken as confirmatory test for relapse. While the normal mouse foot-pad cannot pick up the few viable organisms due to the low number of bacilli in the specimen as well as limitation of inoculation in more number of mice, bacillary ATP estimation appears to be a better good alternative. Amplification using PCR targeting 36kD fragment as well detection of *M.leprae* specific rRNA was done to determine the viable organisms in relapsed cases. Two third cases with persisting PCR signals relapsed clinically. However, this approach needs to be tried in more number of patients before making a definitive conclusion of its usefulness as a predictor for relapse.

Tentative conclusions

(i) The addition of Minocycline and Ofloxacin to the standard 1 year MDT (MB) regimen in MB cases has been observed to be a well tolerated and robust regimen.

(ii) There is rapid fall in bacteriological index (BI). However, the results of the use of 1 year FDT are not published and therefore, can not be compared. The relapse rates also can not be compared as the results with standard with 1 year FDT is not published.

(iii) There are lesser reactional rates with present regimen as compared to the similar data with 2 year FDT studies.

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