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Clinical characteristics and outcome in multibacillary (MB) leprosy patients treated with 12 months WHO MDT-MBR: a retrospective analysis of 730 patients from a leprosy clinic at a tertiary care hospital of Northern India

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Summary

Background: Shortened (12 months) multidrug multibacillary regimen (MDT MBR) was implemented in India in 1998, however there is yet a paucity of crucial data on its long term outcome.

Objective: To assess the efficacy of 12 months MDT MBR in multibacillary (MB) patients at our centre.

Design: This was a retrospective study undertaken analysing the clinic records of 1210 patients registered at the leprosy clinic of our institute from 1999 to 2010.

Results: 730 MB patients were treated with 12 months MDT MBR over this period. High bacillary index (BI) $\geq 3+$ was observed in 313 patients at the time of registration. Four hundred and one (54·9%) patients experienced lepra reactions. Recurrent ENL was observed in only 14 patients which manifested even after 5 years of stopping treatment. Clinico-histological correlation was noted in 361 (49·5%) patients. During follow up period ranging from 9 months to 10 years, nearly all patients had clearance of skin lesions including histopathological/bacteriological improvement. Only 13 (1·7%) patients relapsed.

Conclusions: All patients responded well with 12 months MDT MBR without significant side effects. The overall relapse rate was only 1·7%. Thus, the recommendation for 12 months MDT MBR for all MB patients is robust and operationally practical, a decision which seems logical.

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Introduction

A major breakthrough in the treatment of leprosy came when WHO introduced multidrug therapy (MDT) in 1982 to overcome the drawbacks of dapsone monotherapy. All multibacillary (MB) patients were treated with MDT multibacillary regimen (MBR) till smear negativity or atleast for 24 months whichever was later,[1] however, in 1994, the duration of MDT was fixed to 24 months irrespective of the degree of bacteriological index (BI) positivity.[2]

The MDT regimens recommended by WHO had demonstrated a high efficacy and tolerability, and by the beginning of 1997, upto 8·4 million cases were reported to be cured by it.[3]

In order to improve the compliance without compromising the efficacy, WHO 7th Expert Committee on leprosy (1997) recommended to decrease the duration of MBR to 12 months for MB leprosy.[3] Subsequent studies comparing 24 with 12 months MDTMBR also gave similar results in relation to treatment outcome and fall in BI in both of the treatment groups.[4–9]

The success of MDT and leprosy control programmes have been proved by achieving worldwide leprosy elimination status in the year 2000 as reported by WHO.

Despite all these encouraging success stories, the reported follow up of patients treated with 12 months MDT MBR has not been for an ideal length of time. The present study was planned with an objective of analysing the long term efficacy of this treatment regimen in MB patients at our centre.

Material and methods

A retrospective study was undertaken analysing the clinic records of patients registered at the leprosy clinic of our institute from 1999 to 2010. A total of 1369 leprosy patients were treated in the clinic during this period but adequate information was available only for 1210 subjects. In the rest, either the diagnosis was not fully documented or they were lost to follow-up. Slit skin smear (SSS) examination (was done prior to the start of treatment and then at 6 monthly intervals) for the first 3 years, and subsequently if required. Histopathology was done in all the patients at registration and at the end of therapy and later on when required. Clinic records were analysed for age, sex, family history, duration of disease, clinical form of leprosy, bacteriological index (BI), morphological index (MI) and reactional episodes in a predesigned proforma. Ours being a tertiary care institute, we receive patients from all over India thus the information about patients' native place was also noted so as to assess the indigenous disease burden. Depending on the number of lesions, their morphology and nerve involvement, patients were classified in the Ridley-Jopling spectrum as tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB), borderline lepromatous (BL) and lepromatous (LL). In addition some patients were also classified as indeterminate (I) or pure neuritic leprosy (PNL) wherever applicable. All patients with a positive SSS for AFB, having more than five skin lesions, with involvement of two or more distant body parts, more than one involved peripheral nerve trunk (excluding the draining nerve) or falling in BB, BL and LL spectrum were classified as multibacillary (MB) and treated with 12 months of WHO MDT MBR. We always tried to correlate the histopathological diagnosis with clinical diagnosis and in case of discrepancy lower spectrum of the disease was taken as the working diagnosis for the benefit of the patient.

Information about incidence, type, severity and time of onset of reaction in different clinical forms and their correlation with bacterial load or other parameters was noted and analysed. Type 1 reaction was diagnosed if the patient had redness, swelling or tenderness of pre-existing lesions, with or without appearance of new lesions, presence of edema of hands, feet or face or had tenderness of one or more nerves with or without nerve function impairment (NFI).[10] Type 2 reaction was diagnosed if the patient had multiple, small, tender, evanescent nodules/ plaques, with or without constitutional symptoms such as fever, malaise, lymphadenitis and myalgia.[10] Deformities were classified according to standard WHO grading system.[11] In all cases after release from treatment (RFT) diagnosis of relapse was as per the criteria of Becx –Bleumink[12] which includes: appearance of new skin lesions, new activity in previously existing skin lesions, increase of bacteriological index (BI) 2 + or more in two sets of skin smears, BI becoming positive in a previously negative patient, new nerve function loss, histological evidence of relapse in skin or nerve biopsy, and lepromatous or related hypersensitivity activity in eye(s).

All patients were administered the MDT MBR as per the recommendation of WHO. Monthly dose was given supervised. No patients were given more than 2 months MDT MBR and none of them received accompanying MDT. After release from treatment (RFT), patients were followed up from a minimum of 9 months upto a maximum of 10 years, till the time of analysis. For the initial 2 years of follow-up, all patients were reviewed monthly; later the patients were followed up every 6 months or less frequently at the leprosy clinic of our institute. In addition patients were also advised to report whenever they experienced symptoms suggestive of reactions/nerve function impairment.

The data was filed and processed using Microsoft Excel software, 2007 version and variables were correlated using SPSS v. 7·5 software. Chi-square test was applied with a confidence interval of 95% wherever necessary.

Results and follow up

Among 1210 patients reviewed, 480 (39·6%) were paucibacillary (PB) and 730 (60·3%) had MB disease. Analysis done for 730 MB patients is reported.

Among 730 MB patients, 545(74·6%) were men and 185 (25·3%) were women with a mean age at presentation being 35·33 ± 16·01 years for men and 36·46 ± 16·13 years for women. Nearly 67% of the patients (488/730) were in the age group of 21–50 years (Table 1).

Table 1. Demographic and clinical profile of study population (MB patients)

	≤20		21–30		31–40		41–50		51–60		≥61		
Age (years)	M	F	M	F	M	F	M	F	M	F	M	F	Total
BT	42	15	40	10	34	16	38	12	10	8	10	10	245 (33·5%)
BB	0	0	5	1	4	2	3	4	6	1	3	0	29 (3·9%)
BL	26	7	70	22	30	12	16	8	7	2	2	0	202 (27·6%)
LL	17	1	50	20	42	10	14	5	23	8	39	5	234 (32·0%)
PNL	0	0	5	2	8	4	1	0	0	0	0	0	20 (2·7%)

M = males, F = females

Only 270 (37%) patients were local residents of Chandigarh and rest 460 (63%) were from other neighbouring Northern states of India like Uttar-Pradesh 139 (30·2%) and Bihar 85 (18·5%). Only 81(11%) patients gave a definite history of contact with a leprosy patient in the form of a family member suffering from leprosy. The disease duration at the time of presentation was less than 6 months in 213 (29·2%), 6 months to 1 year in 168 (22·9%) and more than 1 year in rest of the patients.

CLINICAL PROFILE

Patients clinically diagnosed as BT were classified as MB when lesions were $>$ 5 in number, lesions located on two or more distant sites, $>$ one enlarged nerve trunk or a positive SSS. Out of these 730 patients, 245 BT cases were classified as MB based on these criteria (vide supra). Percentage of patients according to the type of leprosy is shown in Table 1. Majority of the patients belonged to the borderline group (65·2%) followed by LL (32%).

REACTIONS

Four hundred and one patients (54·9%) experienced lepra reaction (Type 1 and Type 2) either at the time of initial presentation to our clinic, during treatment or in the post treatment follow up (Table 2).

Type 1 reaction: Two hundred and forty three (33·3%) patients suffered from Type 1 reaction. Nearly 70% (170/243) of them presented to us with reaction in their first visit and 53 patients developed reactions within the first 6 months of starting MDT MBR. The incidence was higher in males (156 Vs 87). Only skin lesions were affected in 78·1% (190/243) patients and the remaining had involvement of both skin and nerves. Recurrent Type 1 reaction was noted in only 12 patients during the post treatment follow up (1–4 years).

Table 2. Time of onset of reactional episodes

	BT (245)		BB (29)		BL (202)		LL (234)	
	No.	%	No.	%	No.	%	No.	%
Type 1 reaction								
At registration	95	38·7	11	37·9	59	29·2	5	2·1
0–6 months	28	11·4	3	10·3	20	9·9	2	1·3
7–12 months	6	2·4	–	–	1	3	1	0·42
2nd year	4	1·6	–	–	2	–	–	–
≥3 years	2	0·8	–	–	3	–	1	–
Total	135		14		85		9*	
Type 2 reaction								
At registration	–	–	–	–	8	4	30	12·8
0–6 months	–	–	–	–	4	2	14	6
7–12 months	–	–	–	–	1	0·5	17	7·3
2nd year	–	–	–	–	12	5·9	50	21·4
3–5 years	–	–	–	–	6	3	7	3
≥ 5 years					2	1	7	3
Total	–	–	–	–	33		125	

*LL subpolar

All these patients were males with an initial BI $\geq 2+$. All episodes of Type 1 reaction including the recurrent reactions started declining as the therapy continued and had ceased to occur by 4 years of post-treatment follow-up. The longest time period for recurrent Type 1 reaction was $3\frac{1}{2}$ years seen in two, three, and one patient with BT, BL, subpolar LL respectively. Two patients with BT who suffered from recurrent Type 1 reaction had multiple lesions (≥ 9 lesions) and the most markedly infiltrated lesions were still persisting even after completing 12 months of MDT MBR.

Type 2 reactions: One hundred and fifty eight (21·6%) patients experienced Type 2 reactions during the period of study from registration to follow up. These reactions were primarily seen in the BL and LL spectrum. Thirty eight (16·8%) patients manifested reactions at the time of presentation. The reactions continued to occur during the first 2 years of therapy though with reduced frequency but it was at the end of 2 years of stopping MDT MBR that a surprising number of 62(39·2%) patients presented with reaction for the first time. Only skin was involved in 118 (74·7%) patients and the remaining 40 (25·3%) had involvement of both skin and nerves. The incidence of Type 2 reactions was higher in females (90 Vs 68). Recurrent ENLs were seen in 14 patients who had a high initial BI $\geq 3+$ and half of these cases continued to present to us with recurrent ENLs even after 5 years of stopping the treatment though with lesser frequency and severity.

DEFORMITIES

WHO Grade 2 deformity was present in 265patients (36·3%) and 107(14·7%) had Grade 1 deformity. Among these 372 patients with deformities, 242patients (65%) had deformities at the time of registration and remaining 20% and 15% developed it during treatment and post-treatment follow-up respectively. On analysing the type of visible deformities, it was seen that 53/372 (14·2%) had partial claw hand, followed by foot drop (5·9%), complete claw hand (4·3%), wrist drop (0·8%), and clawing of toes (0·3%). Wasting of thenar or hypothenar muscles was noted in 101 patients (27·2%), and 28 (7·5%) had trophic ulcers of hands or feet or both. Forty one patients (11%) had a combination of complete claw hand with trophic ulcers of foot and or foot drop. There was higher frequency of deformities in patients with age more than 40 years (50% vs. 46%) and male gender (50% vs. 40%). This difference, however could attain statistical significance only in case of male gender ($P = 0{\cdot}007$). Ninety three patients with Grade 1 deformity experienced worsening of their sensory/ motor functions during the episodes of recurrent Type 1 reaction and five patients developed worsening from mobile claw hand to a fixed claw hand.

BACILLARY (BI) AND MORPHOLOGICAL INDEX (MI)

Three hundred and thirteen patients (42·9%) had a high BI $\geq 3+$, followed by 297 (40·7%) and 100 patients (13·7%) with BI $2+$ and $1+$ respectively before starting MDT. In the remaining 20 patients belonging to the PNL group, SSS was negative.

Analysing the BI at the end of treatment revealed a standard decrease in the bacillary load in all but 25 patients. On close follow-up of these patients, 14 of them persisted to have a higher BI in SSS even after 3 years of completion of treatment which subsequently declined gradually and by 5 years had become negative in all except six patients. All these six patients suffered from recurrent Type 2 reactions and all of them had relapsed with the disease by the third year of the surveillance period.

Table 3. Clinico-histopathological correlation

Spectrum	Number of patients with clinical diagnosis	Histopathological consistent diagnosis. Number (%)
BT	245	150 (61·2)
BB	29	6 (20)
BL	202	72 (35·7)
LL	234	133 (56·7)

Nearly 33% (103/313) patients had a higher MI of 20% and in the remaining patients MI ranged between 2% to 10%. No solid staining bacilli bacteria could be seen (MI = 0) by the end of 6 months in all but four patients. These four patients had a higher initial MI (20%), which continued to be positive even after completion of 12 months MDT MBR. The clinical examination in these four patients revealed that most of the initial lesions were still active in the form of infiltrated patches and even new lesions had appeared during the course of treatment. All these patients were later started on alternative treatment with minocycline and ofloxacin following which the MI became zero and the lesions regressed by 1 year and completely subsided by 2 years of starting alternative therapy.

HISTOPATHOLOGICAL CORRELATION

The overall clinicopathological correlation was observed in 49·5% of all cases. The percentage of cases for which histopathological diagnosis coincided with the clinical diagnosis is shown in Table 3.

At the end of treatment, histological examination of biopsy specimens showed an overall regression in the inflammation and reduction in the size of granulomas in all except 16·7% (122/730) patients. Fourteen of these patients suffered from recurrent ENLs, four patients were still MI positive at the end of therapy period and two of them relapsed 3 years after RFT. Follow-up of the remaining patients was uneventful

CLINICAL EVALUATION

In the follow-up period (9 months – 10 years), total clearance of lesions were observed in majority (96%) of lesions except minimal hypopigmentation in some patients. In the remaining 4%, the lesions took a longer time to heal and by 4 years of RFT the lesions had regressed but never actually disappeared. Four patients who were started on alternative therapy with ofloxacin and minocycline showed clinical improvement in form of reduction in infiltration in the plaques by 18 months of therapy.

Very few patients (1·2%) presented with vague neuropathic pain during the surveillance period.

RELAPSE

Relapse of the disease was observed in only 13 patients (1·7%). These relapses were noted after 3 years of RFT, all of whom were males who had an initial BI $\geq 3+$ and belonged to the LL spectrum of the disease. All these patients presenting as clinical relapse, had the

appearance of new patches and infiltrated plaques and increase in the area of sensory loss. Their BI was higher when compared to the status of BI at RFT. Histologically features of relapse were seen in eight of these patients in the form of new epithelioid cell granuloma formation and positive solid staining acid fast bacilli on modified FiteFaraco staining. Six of these patients had experienced recurrent ENLs. All patients were restarted on MDT MBR and showed both clinical and histopathological improvement on completion of 12 months MDT.

Discussion

The world has now reached a status of leprosy elimination with the help of effective national leprosy control programmes and WHO MDT. However, the current global leprosy prevalence status as on August 2012 is 181941 cases of which a large proportion (83,187 cases) is from India.[13] The appropriate duration of MDT for MB patients is the time required to reduce the size of viable bacterial population to such an extent that the rifampicin (RMP) resistant mutants are completely eliminated and the great majority of drug susceptible organisms are killed.[14] RMP kills *M. leprae* very fast (99·9% with a single dose) and the patient becomes sterile/non-infectious in less than 4 weeks. Working on the duration of time taken to kill RMP resistant bacilli if any, Ji *et al.*[15] and Girdhar *et al.*[16] found that it takes 3–9 months for biopsy inoculums to become negative for bacteria when treated with only dapsone and clofazamine. This indicates that a minimal period of 9 months would be required for MB therapy. Considering this bactericidal efficacy of RMP combined with clofazamine and dapsone, and the encouraging observations of good response even in defaulters who had taken WHO MDT MBR for less than a year, WHO had rightfully reduced the duration of MDT from 24 months to 12 months.[3] The decision to reduce the duration of therapy has had almost universal approval.

Prolonged and regular follow-up of leprosy patients has been a major problem in many of the reported studies. Among the 730 patients after RFT, follow-up periods ranged from 9 months to as long as 10 years. Patients initially came for follow-up once every month for a year subsequently they were followed up once in 3 months and later on every 6 months and subsequently even little less frequently.

Similar to general epidemiological trends as in previous reports,[17] the incidence of disease in our patients was higher in males (74·6%) in comparison to the females (25·3%) and majority (67%) were in the 21–50 year age group.

The definition of MB leprosy has been changing ever since the WHO MDT regimen was implemented in 1982. These modifications during the past decades have resulted in more and more patients being classified as MB disease. The proportion of MB disease among newly detected cases of leprosy has risen from 20·8% in 1985 around the world to as high as 61·7% among the African regions in 2010.[13] The load of MB cases in our study was high (59·5%) compared to the paucibacillary group (40·5%). This data is comparable to that reported from other tertiary care centres around the world.[18–28]A recent WHO report shows an MB population of 74·1% from India for the year 2010–2011. The high incidence of MB cases in tertiary care centres is also expected as patients generally report when they have a widespread disease or develop signs and symptoms of neuropathy or reaction.

This delay in reporting may also explain the higher proportion (36·3%) of patients with Grade 2 deformities at the time of presentation to us. A field based study from China has reported even higher rates (57%) for deformities and disabilities, which were significantly higher in MB cases (81·2%) compared to PB cases (53%).[29] Sow *et al.* identified risk factors for deformities as: male sex, advanced age and MB disease[30] however in our study, it was statistically significant only for male sex ($P = 0{\cdot}007$). We have however not compared the rate of deformities in PB and MB. Ninety three patients with Grade 1 deformities reported a worsening of their sensory/motor weakness. It is well known that the deformities may continue to occur during the course of disease either as a result of reactions or continued nerve damage.

Clinicopathological correlation varied from as low as 20% in BB spectrum to 61% in BT types of leprosy similar to the observations by various workers.[31–35] Leprosy expresses itself in different clinico-pathological forms depending on the immune status of the host at any given time (which is a continuum) but the expression in the form of morphology of skin lesions may take longer to manifest. So much of the diversity seen in both clinical and histological features depends on the time the lesion is biopsied during the evolving process.

Nearly 55% of our MB patients suffered from reactions either at the time of presentation, during treatment or on follow-up. Sixty one percent of patients developed Type 1 reaction in comparison to only 39·4% who had Type 2 reactions. The majority (59·3%) presented to the clinic for the first time with a reactional episode. This figure is higher compared to that reported by Kumar *et al.*[21] from the same centre in which 30·9% of their patients presented for the first time with reaction. Incidence of Type 1 reactions fell dramatically over years of follow-up and none occurred after 4 years of RFT. This observation is similar to that reported earlier.[21] Type 1 reaction was more commonly seen in the BT spectrum of the disease and Type 2 reactions were more often seen in the lepromatous spectrum. Unexplainably 39·2% of BL & LL patients developed ENL for the first time after 2 years of the start of treatment. Fourteen LL patients had recurrent ENLs which continued till 5 years on follow-up. All these patients had a high BI $\geq 3+$. This figure is half of that reported by Kumar *et al.*.[21] This may be explained by the changing definition of MB leprosy with parallel fall in the incidence of the disease, less intense publicity campaign or reduced awareness advocating self-reporting.

In addition to the general morbidity produced by the reactions of both types the more serious effect was the progression of mobile claw hand to fixed claw hand in five patients. Fortunately, no changes occurred in patients with trophic ulcer/ foot drop.

After starting of treatment, all patients had a standard decrease in BI which was also seen during RFT follow-up except for 14 patients who demonstrated a slower fall in BI. These patients suffered from recurrent ENLs approximately every 12 weeks during the surveillance period.

Neuropathic pain was noted in very few patients during the surveillance period. Most of the affected were males in age group of 40 years and above.

Relapse of leprosy was noted in only 13(1·7%) of our patients. The figure for relapse with 12 months MDT MBR was comparable to that reported by Kaur *et al.*[36] but lower than that of Katoch *et al.*[37] even though they had combined 12 month WHO/MDT/MB regimen plus *Mycobacterium w*. vaccine and 12 month WHO/MDT/MB regimen plus once a month minocycline and ofloxacin, respectively.

All patients in our study were assessed for relapse as per Becx-Bleumink criteria. The relapse rates reported in other studies have been summarised in table–4. Relapses occurred only in LL patients with a baseline BI of $\geq 3+$. This manifested in all patients after 3 years

Table 4. Relapse rates in MB cases after 12 months of MDT MBR in various studies

S.No.	Study	Number of patients	Follow up duration	Relapse (%)
1	Kaur I *et al.* (2002)	136	2–3 years	2·2
2	Desikan *et al.* (2008)	660	Few months to 12 years	0·76
3	Kyaw *et al.* (2008)	200	Few months to 8 years	0·5
4	Katoch *et al.* (2008)	100	9–10 years	5·7
5	Present study	730	9 months to 10 years	1·7

of completing MDT MBR and during the follow-up period which was as long as 10 years. A clinical trial using four different multidrug regimens in the treatment of MB leprosy also reported that relapses occurred late, beginning at 5 years after the initiation of the therapy.[38]

Conclusion

On evaluating the efficacy of MDT MBR for 12 months in our study, we observed a low relapse rate comparable to that reported with longer duration of therapy. As the percentage of patients likely to relapse is very small ($<2\%$), giving longer treatment to all MB patients may not be justified. Also, at the start of therapy, one cannot identify with certainty the patients who will relapse especially in field conditions where facilities for SSS and histopathology are not available. Therefore, categorisation of patients in low risk and high risk groups is not easy in field conditions. But in ideal circumstances, surveillance of those patients with a high BI ($\geq 3+$), with more than one nerve trunk involvement, wide spread disease and with multiple lesions is advisable. Administering immunotherapy in this group of patients should be considered.

Summarising the observations in our study:

- Lesions in majority of the patients had healed at the end of the therapy.
- Nearly half of the patients presented with lepra reaction. Type 1 reactions were more often seen as compared to Type 2 reactions. Both types of reactions became less frequent after the introduction of MDT MBR and finally ceased. However, it took longer in case of Type 2 reactions.
- WHO Grade 2 deformity was observed in 265patients (36·3%) and 107(14·7%) had Grade 1 deformity at the time of presentation. Deformities worsened in a considerable number of patients after RFT treatment and follow-up due to reactions and continued nerve damage.
- Clinico-histological correlation was seen in only 49·5% of the patients.
- Patients who relapsed had a higher initial BI of $\geq 3+$, high MI up to 20% and most of them manifested recurrent ENLs. Only 1·7% of the total treated population of patients relapsed.
- All patients had tolerated the MDT MBR treatment without any significant adverse reactions.

Thus, the recommendation for 12 months MDT MBR for all MB patients is robust and an operationally practical decision, which seems logical. It will positively help in further reducing the overall prevalence, annual NCDR, and reducing the rate of new cases with Grade 2 deformities as envisaged in the enhanced global strategy (plan period 2011–2015).

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