Original Article

A randomized controlled trial to compare cure and relapse rate of paucibacillary multidrug therapy with monthly rifampicin, ofloxacin, and minocycline among paucibacillary leprosy patients in Agra District, India

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ABSTRACT

Objectives: To study cure rate and relapse rate of standard World Health Organization paucibacillary multidrug therapy (PB-MDT) with monthly rifampicin, ofloxacin, and minocycline for six months (ROM-6) among paucibacillary leprosy patients. **Methods:** A total of 268 patients, detected during active search in Agra district during 2001–2004, who had paucibacillary (PB) leprosy having 1–5 skin lesions and/or one nerve thickening/tenderness, were allocated, using random number tables, to two treatment groups; PB-MDT and ROM-6. On the first day of the month, dose of PB-MDT and of the ROM were given under supervision for 6 months. After completion of drug therapy, patients were followed every 6 months for first 5 years and later annually for next 3 years for monitoring disease status, cure rates, reactions and relapses. Chi square test was used to compare relapse rates. **Results:** The cure rate at 2 years was 99% in ROM-6 and 97.0% in PB-MDT group, of those who completed treatment and the difference was statistically not significant. At 5 years, only 88 patients in PB-MDT group and 90 patients in ROM-6 group could be followed; all were observed to be cured. However, during the period of 5-8 years, 3 of 67 patients in PB-MDT group and 1 of 73 in ROM-6 group were observed to have relapsed. In all, 10 relapses were noted (3 in ROM-6 and 7 in PB-MDT group) giving a relapse rate of 1.10/100 person years in PB-MDT and 0.435/100 person years in ROM groups ($P = 0.053$; statistically not significant). Of the 10 relapses, 5 occurred within 5 years (3 in PB-MDT group and 2 in ROM-6), 4 during 5–8 years (3 in PB-MDT and 1 in ROM-6), and 1 occurred in MDT group after 8 years. **Limitation:** A number of patients were lost to follow up after release from treatment and thus actual number of relapses in the study could not be assessed. Additionally, diagnosis was purely clinical and histology could not be done for reasons related to functional difficulties in the field. **Conclusion:** The study shows that PB-MDT and ROM-6 have almost similar acceptability, cure rate and relapse rate.

Key words: Minocycline, multidrug therapy, ofloxacin, paucibacillary leprosy, rifampicin

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INTRODUCTION

There has been a perceptible decline in the prevalence of leprosy in the world, particularly in the countries of South East Asia region where leprosy was earlier highly endemic. Even though leprosy control program has changed strategies, as many as 189,018 new cases of leprosy were registered

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globally in the beginning of 2013 of which two thirds were reported in India alone.[1] Recent leprosy data gathered by the national health system in India reveal that about half the cases registered were of multibacillary (MB) type.[2] In contrast, active field surveys have shown that less than 20% of patients in the community are of multibacillary type while the rest are of paucibacillary (PB) type.[3]

Among the paucibacillary cases, a significant proportion of new patients have a single lesion.[4] A small proportion of early cases may self-heal,[5] but the risk of progressive disease in the remaining patients if left untreated is not small. As there are no clinical and laboratory parameters to identify this group of individuals who may worsen, it is the norm to institute treatment in all patients to prevent the possible risk of severe disease, deformities and reduce the spread of infection.

For the success of any mass treatment program, easy, short, effective and safe treatment that could be given under supervision is considered suitable. The paucibacillary (PB) regimen, as recommended by the World Health Organization (WHO), is given world over for this subgroup of patients. It is important to note that paucibacillary multidrug therapy (PB MDT) has been in use since 1982 and identification of alternative effective chemotherapeutic regimen may be useful in those who may need it.

Single monthly dose therapy, consisting of rifampicin, ofloxacin, and minocycline (ROM) was thus felt useful by WHO in 1998 to be tested in these (single skin lesion) patients as an option against the standard 6 months PB regimen. In a multicentric trial in south India[6] and later by other workers,[7,8] the 6-month multidrug therapy (MDT) regimen was found useful with cure rates of 54.7% at 18 months follow-up. However, there were concerns related to length of unsupervised therapy with dapsone, difficulties in measuring regularity in taking treatment and its limited beneficial effect in paucibacillary cases with 2–3 skin lesions.[9] One limitation of this study[9] was that cases without nerve thickening were treated; however, up to 60% of cases in the PB spectrum may show this.

Moreover, for complete information on relapses, a long-term follow up is necessary.[7,9] The present work was, therefore, planned to test the effectiveness of ROM-6 against WHO PB-MDT, since a single dose of ROM in PB leprosy had been found to be less effective as compared to WHO PB-MDT.[9,10]

METHODS

This was a randomized field trial and was mainly aimed at comparing cure and relapse in paucibacillary leprosy patients treated with standard WHO PB-MDT and those treated with 6 monthly doses of ROM.

Inclusion/exclusion criteria of patients for the study

Newly detected leprosy patients diagnosed clinically as paucibacillary leprosy were included. These included patients with 1–5 skin lesions, either erythematous or hypopigmented, with definite impairment or loss of sensation (tested with ball point pen) and having one thickened nerve. None of the patients had taken leprosy treatment. Children aged below 5, adults above 70, those with asthma, and pregnant, and lactating women were excluded.

Sample size, case detection and treatment allocation

Based on the findings of a previous study comparing ROM with MDT suggesting 53.4% efficacy at 18 months[3] in paucibacillary leprosy with 2-3 lesions,[7] it was assumed that cure rate was likely to improve from 53.4% to 70% at 24 months after release from treatment (RFT). Using Type-1 error as 0.05 and power of the test as 0.80 and a likely drop out of around 5%, it was calculated[8] that 134 patients would be required in each of the two arms of the study. Suspected cases recruited by field workers during the active field survey of the population were initially checked by trained and experienced paramedical workers (PMW) with 5–15 years of experience working in leprosy, and then by an experienced medical doctor. The authors have long experience working in leprosy (AK [15 years], AG [33 years], BKG [35 years]). After thorough clinical examination and confirmation of diagnosis, patients were allocated randomly to either of the two treatment groups[9] till 268 patients were recruited. For allocation of patients to the two treatment groups, 268 three-digit random numbers from the table were written in the patient registers in advance. Patients with even numbers were given PB-MDT and those with odd numbers were given ROM. Blinding to treatment was not undertaken. The recruitment of patients was started on 2 June, 2001 and completed on 3 July, 2004.

Skin slit smears from earlobes and the edge of the skin lesions were taken in patients who consented to the procedure. In all, 220 (82.1%) smears were collected from 268 patients, 126 in the PB-MDT group and 94 in the ROM-6 group [Table 1].

Ethical permission and informed consent of patients

Permission of the Human Ethics Committee of the Institute was obtained, for treatment and for smear examination. At the time of starting treatment, all patients were informed about the disease, its implications, treatment, possible side effects and benefits. Once consent was obtained, they were given treatment as per the random allocation. In case of children, consent of their parents was taken. This study is now registered on Clinical Trial Registry of India vide REF/2013/11/005995 dated 22 November, 2013.

Treatment

ROM and MDT packs supplied by WHO were used for the study in both the groups. Children aged 5–14 years were given one pack (rifampicin 300 mg, ofloxacin 200 mg, and minocycline 50 mg) and adults (aged >14 years) were given two packs in the ROM group. In the PB-MDT group, the child and adult MDT packs were used. Monthly ROM was given under supervision. For PB-MDT, one daily dose of rifampicin and dapsone was given under supervision and for the remaining days, patients were advised to take dapsone daily on their own. Treatment was continued for 6 months.

Patient counseling

Patients were counseled at the time of taking consent for starting treatment. They were informed about possible mild discomfort, such as intolerance of drugs resulting in loose motions, vomiting or mild weakness, and were advised to take sugar-salt or oral rehydration salts [ORS]) solution if diarrhea or vomiting occurred, and to contact the health worker in case of any serious side effects. A paramedical worker or doctor was to visit the patient if needed.

Follow-up and assessment

Patients were visited by a trained paramedical worker every month for supervised drug administration, to check the clinical condition and monitor side effects, if any. However, formal assessment after completion of treatment for each patient was done once in 6 months. Lesion activity, erythema, infiltration, size, any new lesion and/or new nerve thickening or deformity was monitored and recorded. Cure of the disease was defined as complete resolution of the lesion or patch becoming flat, hypopigmented and with decrease in size of the lesion and/or regaining of sensation. The reasons for default were noted among those who did not complete the prescribed treatment.

Defining relapse

The appearance of new lesion(s) or a definite increase in size of the lesion, observed by the patient or detected by us, or appearance of nerve thickening, were taken to indicate relapse of disease. This definition is the same as used in the single lesion study.[9] Any sudden redness and/or swelling of the lesion (with or without a new lesion) especially in the first 6–12 months of follow up was considered a late reaction. All such patients were treated with 20 mg prednisolone equivalent per day. If there was no obvious change in the inflammation in lesions after 4 weeks of corticosteroid treatment, the patients were considered to have relapsed. Relapse was defined based purely on clinical signs, after ruling out reactions.

Follow-up

The study was conducted between June 2001 and November 2010. Although the initial objective of the study was to follow patients for 5 years, 140 patients were actually followed up for a total period of 8 years, including an interim observation at 2 years after release from treatment (RFT). Since the intake of patients took nearly 36 months, the longer follow up beyond 5 years was possible in a proportion of cases in both groups. Of 134 in each group at entry, there were 100 patients in the PB-MDT group and 103 in the ROM-6 group available for follow up at the end of 2 years; 88 in PB-MDT and 90 in ROM-6 groups at the end of 5 years; and 67 in PB-MDT and 73 in ROM-6 groups at the end of 8 years.

Statistical methods

Pearson $\chi 2$ was used to compare proportions and Mantel–Haenszel test the relapse rate by person years.[12] Cox regression analysis was done to check the effect of confounders on treatment outcome. Since no effect was found, these results are not presented.

RESULTS

Characteristics of patients

Table 2 presents details of patients in the two groups at inclusion. The age distribution of cases suggests

that patients were comparable (mean 36.4 years in the PB-MDT group vs. 40.2 years in ROM group, $P = 0.059$). There were more women (62.3%) in the study because they stay at home and are more likely to be detected during active household surveys.

The mean duration of disease at detection was also not significantly different (32.0 months in ROM vs. 35.8 months in MDT), ($t = 1.09$, $P = 0.29$). As seen from Table 2, 40.6% of patients in the ROM arm had untreated disease of shorter duration (<12 months) as compared with 31.3% in the PB-MDT arm.

In both groups of the study, about a third of patients had a single lesion on the skin and about 10% presented with 4–5 skin lesions. All the nerves were palpated in each patient but about one-third of patients (33.6% in the PB-MDT group and 31.3% in the ROM group) did not have any nerve thickening while 67.5% (66.4% in the PB-MDT group and 68.7% in the ROM group) had1 thickened nerve [Table 1]. Skin smears could be done in 82% of the patients of whom all but two were negative. Both the positive patients had low BI (1+) and were continued on PB-MDT treatment by default as the smear results were available late, by which time the patients had taken treatment for two months and were responding.

Table 1: Clinical and treatment status of patients

Clinical/treatment status	% (n) in 6 monthly MDT group (*N*=134)	% (n) in 6 monthly ROM-6 group (*N*=134)	Total (*N*=268)
Patches			
0-1	31.3 (42)	37.3 (50)	34.3
2-3	58.2 (78)	53.7 (72)	56.0
4-5	10.5 (14)	9.0 (12)	9.7
Nerves			
0	33.6 (45)	31.3 (42)	32.5
1	66.4 (89)	68.7 (92)	67.5
Smear status			
−ve	92.5 (124)	70.2 (94)	81.3
+ve	1.5 (02)	0	0.75
Could not be done	6.0 (08)	29.8 (40)	17.9
Grade 2 deformity	2.2 (03)	0.73 (01)	1.5
Treatment completion rate	79.9 (107)	85.8 (115)	82.8
Default rate	20.1 (27)	14.2 (19)	17.2
Default at month			
1	9.2 (12)	8.2 (11)	8.6
2	6.7 (09)	2.2 (03)	4.5
3	3.0 (04)	3.2 (04)	3.0
4	0	0.7 (01)	0.4
5	1.5 (02)	0	0.7
Clinical status at RFT			
Cured	51.5 (69)	50.7 (68)	51.1
Partial cured	24.6 (33)	29.1 (39)	26.9
No improvement	3.0 (04)	0.8 (01)	01.8
Reaction	0.7 (01)	0	0.04
Treatment stopped/ migrated	20.1 (27)	14.2 (19)	17.2
Lost to follow up	0	5.2 (07)	2.6

MDT: Multidrug therapy, ROM: Rifampicin, ofloxacin, and minocycline, RFT: Release from treatment

Effect of confounders

The Cox regression analysis was done using age, sex, duration of disease, and treatment regimen but none of these factors was found to affect cure rates significantly ($P > 0.05$). Thus it was assumed that these did not act as confounders to affect the cure rate by the respective treatment.

Status at release from treatment

In this study, it was observed that 107 (79.9%) patients in the PB-MDT group and 115 (85.8%) patients in the ROM-6 group had completed their treatment and the rest discontinued (defaulted) at various stages. Of the 46 cases who discontinued treatment, 35 (76.1%) did so in the

Table 2: Characteristics of patients included in the study (ROM vs. MDT)

	% in 6 monthly MDT Arm (*N*=134)	% in 6 monthly ROM Arm (*N*=134)	Total (268)
Age			
5-14	9.7	6.0	7.8
15-24	11.9	14.9	13.4
25-34	20.9	17.9	19.4
35-44	21.6	17.2	19.4
45-54	20.1	17.9	19.0
>54	15.7	26.1	20.9
Mean (SD)	36.4 (15.3)	40.2(17.4)	38.3 (16.4)
Median	37.5	40	39.5
Sex			
Male	35.1	40.3	37.7
Female	64.9	59.7	62.3
Disease duration			
At detection (months)			
1-6	13.4	18.8	17.0
7-12	17.9	21.8	21.2
13-24	23.1	18.8	19.9
>24	45.5	40.6	41.9
Mean (SD)	35.8 (30.0)	32.0 (30.6)	33.8 (30.3)
Median	24.0	24.0	24.0

SD: Standard deviation, MDT: Multidrug therapy, ROM: Rifampicin, ofloxacin, and minocycline

first 2 months itself, and then the number of defaulters declined as the treatment schedule progressed [Table 1]. The reasons for default or discontinuation of treatment as reported by patients included a feeling of weakness/intolerance following intake of drugs, swelling of feet, vomiting/diarrhea, feeling that they were cured and discontinuation due to pregnancy or lost to treatment. One patient felt stigmatized in taking drugs and refused to continue treatment [Table 3].

At the time of completion of 6 months therapy, that is, on release from treatment (RFT), the clinical status of the patients suggested that 69 (51.5%) in the PB-MDT group and 68 (50.7%) in the ROM-6 group had complete healing of their lesion(s), whereas 33 (24.6%) in the PB-MDT group and 39 (29.1%) in the ROM-6 group had partial healing of lesions or showed no improvement. One patient in the PB-MDT group developed type 1 reaction at release from treatment (RFT). A total of 7 (5.2%) patients were lost to follow up in the ROM-6 group and could not be located after the last dose was given to them, the remaining number is accounted for by defaulters; 27 (20.1%) in PB-MDT and 19 (14.2%) in ROM-6 group. Four (3%) patients in the PB-MDT group did not show any improvement at release from treatment (RFT) as compared with 1 (0.8%) in the ROM-6 group [Table 1]. None of these differences were statistically significant.

Treatment and observations

Observations at the end of 2 years: At the end of 2 years, 100 patients in the PB-MDT group and 103 in the ROM-6 group were followed up. In the PB-MDT group, 97 (97%) were cured for the disease, 1% still continued with active disease, two cases of reaction, and one relapse were observed. Whereas in ROM group, of the 103 patients that were followed up, 99% were cured of the disease, 1% still continued with active disease, no reactions but 2 relapses were observed. This difference was statistically not significant

Table 3: Reasons of default in two treatment arms of PB leprosy

Complaint	6 monthly MDT arm (134)	6 monthly ROM arm (134)	Total (268)
Weakness/intolerance	16	10	26 (9.7)
Swelling of feet	07	0	07 (2.6)
Vomitting/diarrhea	01	05	06 (2.2)
Felt cured/leprosy stigma	01	04	05 (1.89)
Pregnancy	01	0	01 (0.4)
Lost to treatment	01	0	01 (0.4)
Default (rate)	27 (20.1%)	19 (14.2%)	46 (17.2%)
X^2_1 , *P* value	1.68, *P*=0.195		

MDT: Multidrug therapy, ROM: Rifampicin, ofloxacin, PB: Paucibacillary

Observations at the end of 5 years: At the end of 5 years, only 88 patients of MDT group and 90 of ROM group could be followed up. In MDT group, all the patients were observed to be cured of the disease. Although two cases of reaction were seen within the first 6 months in this MDT group, no more reactions were observed during the 2–5 years period. However, 3 relapses were detected during this period. In ROM-6 group, all the 90 (100%) were cured of the disease, no new reaction or relapse, except for the 2 relapses detected earlier, were observed.

Observations at the end of 8 years and beyond: At the end of 8 years, 67 patients from the MDT group and 73 in the ROM-6 group were followed up. In the MDT group, 95.5% were observed to be cured of the disease, and 6 relapses (3 more than during the 5–8 year period) were observed. In the ROM group, of the 73 patients, 72 (98.6%) were cured of the disease and 3 relapsed (1 more than during the 5–8 year period).

A small group of patients (17 in the PB-MDT and 16 in ROM-6 groups) were also observed beyond 8 years. All the patients in the ROM-6 group were observed to be cured, and there were no further relapses or reactions. However, in the MDT group, 94.1% were cured, with one new relapse.

The overall cure rates were observed to be 93.3% (97/104) in the MDT group and 97.2% (105/108) in the ROM-6 group. Although ROM cured more patients, the difference was not statistically significant.

The mean duration of follow up was 6.25(SD = 2.1) years; 6.12 (SD = 1.97) years in the MDT and 6.37 (SD = 2.30) years in the ROM-6 groups respectively.

For a comparison of the overall frequency of relapses in the two groups, 3 relapses in ROM-6 group for an observation period of 688.1 patient years (PY), gives a relapse rate of 0.445/100PY and 7 relapses in the MDT group occurred in 636.4 PY with a relapse rate 1.10/100 PY. The difference in the two groups was not statistically significant ($X^2_{MH} = 3.76$, $P = 0.053$) [Table 4].

Cure rates in defaulters

An attempt was made to contact the defaulters and monitor their clinical progress at the end of the study.

Among 19 defaulters in the ROM-6 group, 9 (47.4%) could be traced, 8 (88.8%) of whom were found to have been completely cured at the time of last visit. One person continued to have active disease, and also developed grade 2 disability. Of the 27 defaulters in PB-MDT group, 23 (85.2%) could be traced and 19 (82.6%) were found to have been cured but 4 (17.4%) still had active disease.

DISCUSSION

In an attempt to explore alternative leprosy treatment, single dose therapy for early leprosy had been field tested and one dose of ROM was reportedto be "almost as effective "as standard 6 months WHO-PB regimen in treatment of single lesion PB leprosy.[6] The cure rates at the end of the study at 18 months were 54.7% in the MDT arm and 46.9% in ROM arm respectively, which was not significantly different. Clinical improvement at 18 months was seen in over 99% patients in both the groups. A recent study has also clearly revealed that efficacy of ROM therapy was as high as 93% at 2 years in curing single lesion PB leprosy.[11] However, a systematic review to examine the role of single dose ROM has suggested that it was less effective in curing paucibacillary leprosy than the conventional WHO-MDT given for 6 months, and emphasized the need for trials comparing effectiveness of multidose ROM versus standard 6 monthly WHO-MDT in paucibacillary and multibacillary leprosy.[13]

In the present study, observations at the end of 5 years suggested a 100% cure in the PB-MDT group with 3 relapses, in comparison with a 100% cure and 2 relapses in the ROM-6 group. However, at the end of 8 years, relapses in the PB-MDT group doubled to 6 with a cure rate of 95.5% among those followed up, in comparison with 3 relapses in the ROM-6 group and a 98.6% cure rate.

In the studies mentioned earlier, disease regression had been the main outcome criteria.[6-8] However, of late, reports of relapses in patients treated with a single dose of ROM have been published.[14-16] In a report by WHO, a relapse rate of 3/1000 person years at risks (PYAR) has been mentioned.[17] In Bangladesh, a relapse rate of 5.09/1000 person years at risks was observed in patients treated with ROM and followed up for 4.5 years.[16]

In view of the high relapse rate even in patients with a single skin lesion, we considered that repeating monthly ROM for 6 months could be a better option, especially considering the fact that our study included all PB cases with upto 5 lesions with/without 1 main nerve. This enabled us to compare a totally supervised regimen with a treatment schedule that is partly self-administered. The drugs included in the once-monthly regimen have all been shown to

Table 4: Comparison of relapse rate in two treatment groups

Treatment	Number of patients	Person-years of follow up	Number of relapses	Relapses/ 100 person years	*P* value
MDT	104	636.4	07	1.100	X^2_{MH}=3.76
ROM	108	688.1	03	0.436	*P*=0.053
Total	212	1324.5	10	0.755	

MDT: Multidrug therapy, ROM: Rifampicin, ofloxacin, and minocycline

Table 5: Events rates in those completed treatment by treatment arms of PB leprosy

Follow up (months)	MDT Arm (*N*=107)					ROM Arm (*N*=115)				
	No. at FU	Cure (%)	Not cured (%)	Reac-tion (*n*)	Relapse (*n*)	No. at FU	Cure (%)	Not cured (%)	Reaction (*n*)	Relapse (*n*)
RFT	104	66.3	33.7	1	0	108	63.0	37.0	0	0
6	104	73.1	25.0	1	1	108	78.7	19.4	0	2
12	103	90.3	9.7	0	0	107	90.7	9.3	0	0
18	103	93.2	4.9	0	0	103	94.2	5.8	0	0
24	100	97.0	1.0	0	0	103	99.0	0	0	0
36	99	98.9	0	0	1	97	100.0	0	0	0
48	89	98.9	0	0	1	97	100.0	0	0	0
60	88	100.0	0	0	0	90	100.0	0	0	0
61-96	67	95.5	0	0	3*	73	98.6	0	0	1
>96	17	94.1	0	0	1*	16	100.0	0	0	0
Total		93.3		2	7		97.2		0	03

*1 out of 3 also developed Grade 1 disability during 61-96 months and 1 after 96 months. MDT: Multidrug therapy, ROM: Rifampicin, ofloxacin, and minocycline, RFT: Release from treatment, PB: Paucibacillary

have potent bactericidal action on *Mycobacterium leprae* both in footpad of mice and in human patients. The patients in this study have been observed for over 5 years to compare the long-term outcome of the two treatment regimens.

In the present study, a few cases of Type 1 reactions were observed. It could be possible that some reactions might have been treated by other practitioners for reaction and not reported due to follow up being recorded only at 6 month intervals.

The present study has shown that the cure rates in patients who completed treatment in the two groups continued to improve at 6, 12 and 18 months after therapy reaching an overall cure rate of 93.3% in the PB-MDT and 97.2% in ROM-6 groups [Table 5]. The number of patients showing clinical response in the ROM-6 group indicates the efficacy of 6 monthly doses of ROM in paucibacillary patients. The cure rate with ROM-6 was similar to that of PB-MDT. The relapse rates, although more in number in the PB-MDT group than in the ROM-6 group, were not statistically significantly different. Thus, the study results clearly demonstrate that ROM-6 is an acceptable supervised therapy for PB leprosy which could be an effective alternative to PB-MDT.

The study has limitations. A good number of patients were lost to follow up after release from treatment and thus actual number of relapses in the study could not be assessed. Additionally, diagnosis was purely clinical and histology could not be done for reasons related to functional difficulties in the field.

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