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A randomised controlled trial assessing the effect of adding clarithromycin to Rifampicin, ofloxacin and minocycline in the treatment of single lesion paucibacillary leprosy in Agra District, India

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Summary
Aim: To assess if there is any additional short and long term effect of adding clarithromycin to rifampicin, ofloxacin and minocycline (ROM), the combination here after called C-ROM, in treating single lesion PB leprosy detected in the field.
Methods: 300 patients, detected on active search in Agra district, who had single lesion leprosy but no nerve thickening, were randomly allocated (using random number table) to two treatment groups, 151 to ROM and 149 to C-ROM. All the patients were given single dose of ROM or C-ROM and followed up every 6 months for disease status, cure rate, reaction and relapse. Survival analysis was used to compare relapse rate.
Results: The cure rate at 2 years was 93·1% in ROM and 91·4% in C-ROM group. By this time three relapses had occurred in the ROM group while two patients were found to have relapsed in the C-ROM group. Thus, there was no statistical difference in relapse rates (2·1% vs. 1·41%, $P = 0{\cdot}287$) in the two groups. Long term observations over 3–5 years revealed nine relapses (five in ROM, four in C-ROM) giving relapse rate of 1·05/100 Person years in ROM and 0·90/100 person years in C-ROM group – again no significant difference was observed ($P = 0{\cdot}87$).
Conclusion: The study shows that addition of clarithromycin to ROM does not significantly improve the efficacy as measured in terms of cure rates and relapse rates in single skin lesion leprosy patients.

Introduction

During the last decade there has been a perceptible decline in the prevalence of leprosy the world over, in particular South East Asia. However, almost half a million new cases of

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leprosy continue to be registered every year. With increasing awareness, and easy availability of services, a significant proportion of new patients detected on active search are patients with single lesions.[1] Though earlier work had shown that a large proportion of them may self heal,[2] the risk of progressive disease in the remaining patients is not small, if left untreated. As there are no clinical and laboratory parameters to identify which individuals may worsen among the large pool of single lesion cases, leprosy workers agreed to institute treatment in all patients to prevent the possible risk of severe disease and deformities and to contain the spread of infection.

To ensure the success of any mass treatment programme, easy, short, effective and safe treatments that can be given under supervision are considered suitable. The Pauci-bacillary (PB) regimen, as recommended by the World Health Organization (WHO) for this subgroup of patients has all the components, but is considered too long. Single dose therapy, consisting of rifampicin, ofloxacin and minocycline (ROM) was tested in these patients and compared with the standard 6 months PB regimen in a multi-centric trial in south India[3] and later by other workers.[4,5] Though found useful, its efficacy, as measured in cure rates at 18 months follow-up was less than that observed in the group given 6 months PB treatment (46·9% in ROM arm vs. 54·7% in the PB-MDT arm). This study assessed whether the addition of another effective drug – clarithromycin, increases the efficacy of ROM treatment in single lesion patients both in the short and the long term. Clarithromycin was chosen as an additional drug because of its potent bactericidal action against *M. lepae* – acting by inhibiting protein synthesis.[6] A randomised controlled trial design was used to test this hypothesis.

Study Design and Methods

This was a randomised field trial and was mainly aimed at studying the additional efficacy (if any) of clarithromycin in single lesion leprosy treatment with ROM (Figure 1).

SAMPLE SIZE

Based on single lesion trial findings suggesting about 47% efficacy (complete cure at 18 months), it was assumed that the addition of clarithromycin to ROM should improve the efficacy of cure by about 15 percentage points (47% to 62%) at 24 months. Assumption of 15 percentage points additional efficacy was made due to 6 months additional time and addition of clarithromycin. Using Type-1 error as 0·05 and power of the test as 0·95 and a likely drop out of around 5% at 2 years follow up, it was estimated that 299 patients were required for the study and thus it was decided to take 150 patients in each of the two treatment groups.[7]

INCLUSION CRITERIA FOR THE STUDY

The study was conducted in patients detected in the field survey in Agra district. The Case definition for single lesion leprosy was the presence of single skin lesion, either erythmatous or hypo-pigmented with definite impairment or loss of sensation (tested with ball point pen) and with no nerve thickening. All patients were newly detected leprosy cases, and none had previously taken leprosy treatment. Patients were skin smear negative.

Exclusion Criteria: Children below the age of five and individuals aged over 65 years were not included in the study, nor were pregnant and lactating women.

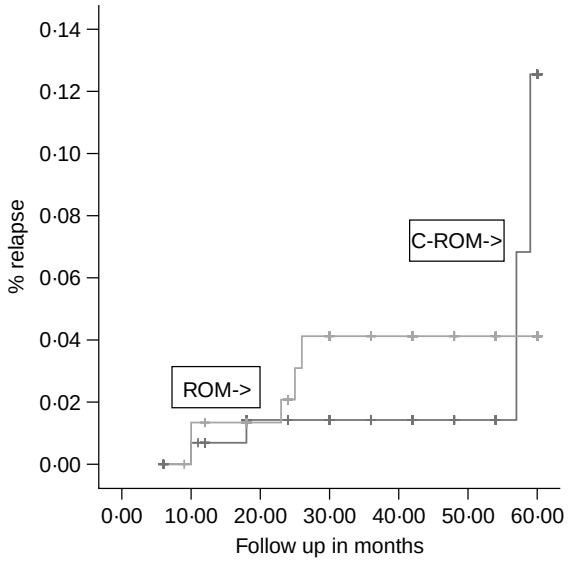


Figure 1. Relapse rate in Single Lesion Leprosy.

Clinical Examination: The clinical examination was done to assess disease activity on skin lesions to test for sensation using a ball point pen. Nerve thickening was assessed by palpating nerves like the ulnal, radial, lateral popliteal, great oriculor, post tibial and muscular cutaneous. However no formal VMT/ST testing was done.

Treatment allocation: The patients were allocated to the two treatment groups, using a three digit Random Number Table. Patients falling on odd numbers were allocated to the ROM (placebo) group and those at even numbers were given clarithromycin plus ROM (C-ROM) (experimental group). The intake of patients started on 06/06/2001 and ended on 26/02/2005 in the field areas.

ETHICAL PERMISSION AND INFORMED CONSENT OF PATIENTS

The permission of the Ethical committee of the Institute was obtained. At the time of starting treatment, all the patients were informed about the disease, its implications, treatment, possible side effects and benefits. Once they had consented, they were put on the respective treatments. In the case of children, the consent of their parents was taken.

TREATMENT

WHO supplied ROM packs were used for the study in both groups. In the second group clarithromycin (MACLAR®- Gracewell Division of Glenmark Pharmaceutical, Mumbai (India) Batch No. G0920D, Jan 2000 and No. C-1481009, August 2003) obtained from the local market was given in addition to ROM. The ROM group was taken as the 'control group". Children aged 5–15 were given one pack (rifampicin 300 mg, oflxacin 200 mg and minocycline 100 mg) and adults in the ROM group were given two packets. In the C-ROM group, the patients received, in addition, 250 mg of clarithromycin – a single dose given to child patients and 500 mg to adults under supervision.

FOLLOW-UP AND ASSESSMENT

Formal assessment of each patient was made every 6 months. Lesion activity erythema, infiltration and size, any new lesion and/or new nerve thickening was recorded. The nerves palpated were: ulnar, radial, lateral popliteal, greater oriculor and muscular cutaneous and post tibial. Cure of the disease was defined as the complete healing of the lesion, the patch becoming flat hypopigmented with decrease in size of the lesion and/or restoration of sensation. No formal VMT/ST testing was done.

DEFINING RELAPSE

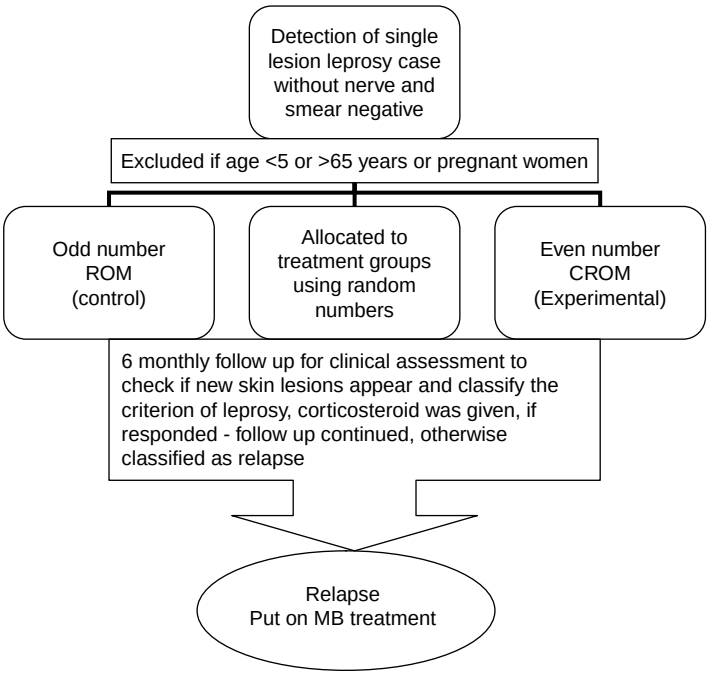
The appearance of new lesion(s) or a definite increase in size of the lesion and/or appearance of nerve thickening were taken as relapse. Any sudden redness, swelling of the lesion (with or without a new lesion) especially in the first 6–12 months follow up, was considered as a late reaction. All such patients were put on corticosteroids (20 mg prednisolone equivalent per day). If there was no obvious change in the morphology of lesions (inflammation) in four weeks, the patients were considered to have relapsed. Relapses were defined based on clinical presentation, and no biopsy was done.

DURATION OF STUDY

The study was planned for 5 years follow up, but with an evaluation at 2 years after the intake was over.

STATISTICAL METHODS

The Fisher exact test was used to compare the efficacy (proportion cured) of the two regimens. Kaplan-Mier survival analysis and Log-rank tests were applied to compare the pattern of relapses.[7]



Results

Of the 300 patients taken in the study, over 90% have completed 24 months follow-up, while around 60% have been observed for over 36 months following the intake of drugs (mean 36·76 ± 14·8). As is seen from Table 1, 15% of the patients were children and almost 60% were females.

In about a third of the patients, the disease was of recent onset (less than 6 months) while the mean duration of illness was 19·5 ± 18·8 months (median 12 months). In 80% of the patients, the lesion was small (up to 20 cm^2) with mean of 15·8 + 23·2 cm^2 with median 8·0 cm^2 in size (taken as length × breath). In almost 85% of patients the lesion was present on exposed areas.

Table 1. Characteristics of the Patients in treatment arms (ROM vs. CROM)

	% in ROM-arm ($N_1 = 151$)	% in CROM-arm ($N_2 = 149$)	% in Total ($N = 300$)
Age			
5–14	19·2	11·4	15·3
15–24	29·1	19·5	24·3
25–34	16·6	20·8	18·7
35–44	17·2	21·5	19·3
45–54	7·9	14·1	11·0
> 54	9·9	12·8	11·3
Mean (SD)	28·1 (15·8)	33·6 (16·1)	30·9 (16·2)
Median	25·0	34·0	30·0
Sex			
Male	38·4	43·6	41·0
Female	61·6	56·4	59·0
Duration of Disease (months)			
1–6	37·6	33·6	35·6
7–12	21·5	24·2	22·8
13–24	18·8	24·8	21·8
> 24	22·1	17·4	19·8
Mean (SD)	19·3 (18·8)	19·8 (18·8)	19·5 (18·8)
Median	12·0	12·0	12·0
Size of Lesion (CM^2)			
Up to 2·0	18·0	19·4	18·7
2·1–4·0	18·8	13·4	16·1
4·1–8·0	14·3	17·2	15·7
8·1–12·0	12·8	11·2	12·0
12·1–20·0	15·0	18·7	16·9
20·1–40·0	14·3	9·7	12·0
> 40·0	6·8	10·4	8·6
Mean (SD)	15·2 (23·0)	16·4 (23·5)	15·8 (23·2)
Site of lesion			
Face or Neck	17·8	24·1	20·9
Hand or Shoulder	54·1	56·0	55·1
Leg or Foot	14·4	9·9	12·2
Stomach or Back	8·9	6·4	7·7
Thigh or Buttock	4·8	3·5	4·2
% Followed up at			
6 months	100·0	100·0	100·0
12 months	100·0	100·0	100·0
18 months	98·0	97·3	97·7
24 months	89·4	94·0	91·7

Table 2 shows that the cure rate in the two treatment groups ROM and C-ROM at the end of 6, 12, 18, and 24 months were similar: healing of the lesion was seen in 73% and 78% patients in the groups respectively at the end of 6 months. Over 90% of patients, in both the groups, were observed to have healed lesions within 24 months of single dose treatment (the difference at both the time intervals was not statistically significant).

The comparison of relapse rates in the two groups has been made at all intervals. As is seen from Table 2, the cumulative relapse rate at 2 years was 2·1% (three relapses in 135 patients) in the ROM group as against 1·41% (two relapses in 140 patients) in the C-ROM patients. Despite the larger number of relapses in the ROM treated patients, the difference was not significantly different (Log rank test $=$ 1·13, $P = 0{\cdot}287$) at 2 years follow-up.

All the patients have been kept under review. A proportion of them have been followed for 5 years with a mean observation of around 3 years (37·8 $\pm$ 14·5 months in the ROM and 35·7 $\pm$ 15·0 months in the C-ROM group). During the subsequent follow-up, two patients in the ROM and two in the C-ROM group were observed to have worsened. Both the patients in ROM group relapsed during the third year. However, relapse in two patients in the C-ROM group occurred late – nearly 5 years after the single dose treatment. Thus a total of nine relapses were seen, three patients relapsed within a year of intake of either ROM or C-ROM. Comparing the overall frequency of relapses in the two groups, five relapses were seen in the ROM group in an observation period of 475·6 patient years (PY), giving a relapse rate of 1·05/100 PY. In the C-ROM treated patients, a total of four relapses occurred in 443·4 PY, relapse rate being 0·90/100 PY. The difference in the two groups was not statistically significant ($P = 0{\cdot}874$).

The clinical details of relapses are given in Table 3. All the relapsed cases, except one were adults.

The child who relapsed was little over 5 years old and was a family contact of three MB cases within the family. It is seen that in almost all of them, the appearance of new lesions was the common presentation of relapse.

Table 2. Comparative Efficacy of Two treatment regimens at Follow-up (FU)

	ROM					C-ROM				
FU in months	N	% Cured	% Partial/ No Cured	Re-lapse Cases	LFU %	N	% Cured (n)	% Partial/ No Cured	Re-lapse Cases	LFU %
6	151	72·8	26·4	0	0	149	78·5	21·5	0	0
12	151	89·4	8·6	2	0	149	89·3	6·7	1	2·7
18	148	94·6	4·1	0	1·4	145	91·7	0·7	1	5·5
24	135	93·1	0	1	6·3	140	91·4	0·7	0	7·8
30	100	96·8	0	2	1·0	99	91·9	0	0	8·0
36	90	97·0	0	0	3·2	83	95·2	0	0	4·8
42	86	96·5	0	0	3·5	76	96·1	0	0	3·9
48	43	93·0	0	0	7·0	40	95·0	0	0	5·0
54	35	94·3	0	0	5·7	32	87·5	0	0	12·5
60	28	92·9	0	0	7·1	24	70·8	0	2	20·9
Total				05					04	
Mean FU (SD)		37·8 (14·5)					35·7 (15·0)			
Median		42·0					36·0			

LFU include migrated and dead.

Table 3. Clinical presentation at relapse

S.No.	Age/Sex of patient	Treatment type	Duration (months) of disease at detection	Initial size of lesion (Sq-CM) and site	Time at relapse (months)	Clinical presentation at relapse (new lesions)
1	25/F	ROM	12	Dry lesion, Face	25	>20
2	35/M	ROM	12·0	38·0, Buttock	10	>15
3	65/M	ROM	36·0	195·0, Knee	10	1
4	27/F	ROM	24·0	18·0, Arm	27	2
5	05/M	ROM	6·0	1·0, Back	24	1, contact of 3 MB cases*
6	30/F	C-ROM	24·0	18·0, Hand	10	1
7	30/M	C-ROM	3·0	45·0, Arm	10	2 + increase of size in earlier lesion
8	45/F	C-ROM	12·0	22·0, Face	59	1
9	36/F	C-ROM	24·0	22·0, Face	57	1 + reactivation of earlier lesion

* The child was a contact case of 3 MB patients in the family, Grand father was BI of 6 + , Grand mother MB and father also MB case.

Discussion

In an attempt to reduce the length of treatment, single dose therapy for early leprosy (single lesion and later up to five lesions[5]) had been field tested. One dose of ROM was reported[3] to be "almost as effective as standard 6 months WHO – PB regimen in treatment of single lesion PB leprosy. In this report,[3] the cure rate at the end of the study at 18 months was nearly equal (46·9% in the ROM arm and 54·7% in the WHO (PB) arm respectively. Clinical improvement at 18 months was seen in over 99% of patients in both the groups. This indicated utility of the single dose treatment of such patients.

In the above studies, the disease regression was the main outcome criteria.[3–5] However, reports of relapses in patients treated with a single dose of ROM have started appearing.[8–10] In a report by WHO, a relapse rate of 3/1000 person years at risks (PYAR) has been mentioned.[11] Workers in Bangladesh have followed patients treated with ROM, for longer periods and have reported a relapse rate of 5·09/1000 person years (PYAR) in an observation period of 4·5 years.[10] This was slightly more than a relapse rate of 3/1000 PYAR among patients given WHO MDT.[10]

One of the possible reasons for lower cure rates, as observed in the above multi-centre trial at 6 months and the reported relapses on follow-up in the ensuing years in other studies using single-dose treatment, could be that the regimen is not robust enough to kill all the organisms and allow early healing to occur. With this possibility, we have added clarithromycin to the ROM – thus making the regimen more robust and have undertaken this trial since clarithromycin has a potent bactericidal action against *M. leprae.*[12,13] Further, the drug has been shown to have synergistic activity with minocycline both in toxoplasma infection[14] and against *M. leprae.*[6] This is possibly because of the sequential protein synthesis block with these two drugs. A similar possibility of enhanced activity when co-administered with rifampicin adds to its usefulness. In addition, higher levels of the drug within the cells (*M. leprae*) makes the drug useful in the treatment of leprosy.

The present study has shown that cure rates do not seem to be affected by the addition of clarithromycin, as almost a similar proportion of patients in the two groups improved at

6, 12 and 18 months after therapy. The cure rates observed in the present study are a little higher at 6 months than reported by the Single Lesion Study Group.[3] This is possibly on account of early disease, as almost 58% of patients in both the groups had disease of less than 6 months duration. This may also be related to the relatively small size of the lesions. Ensuring that none of the patients had any nerve thickening, and thus had localised disease, could be another reason. Comparing the relapse rates, only two patients relapsed in the C-ROM regimen in contrast to five in ROM group in the first 2·5 years following the single treatment dose. Although the number is more in the ROM group the difference is not significant. However, on long term follow-up occurrence of relapse in two other patients in the former (C-ROM) group indicates that the addition of clarithromycin only delayed but did not prevent reactivation of the disease. This may possibly be because of small numbers of *M. leprae* that were not killed and took longer to result in relapse. Thus the addition of clarithromycin to a single dose of ROM does not seem to improve on the efficacy of ROM at least in the short term. As is likely with single dose ROM therapy, the presence of clarithromycin may not affect the organisms which are not in dividing phase or are metabolically inactive. It will be interesting to see how the patients in the two groups behave on longer follow up.[15] In view of late relapses, it is possible that a second dose of ROM given 12 or 24 months later may help to reduce the late relapses considerably.

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Contributors Statement:

Dr. Anil Kumar has been responsible for planning and undertaking field activities, data analysis and preparing the manuscript. Dr. Anita Girdhar has been responsible for the conduct of the trial and clinical evaluation of the patients, and Dr. BK Girdhar for the overall supervision, clinical monitoring and report preparation.

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