Indian J Lepr 2012, 84 : 195-207

http://www.ijl.org.in

Original Article

Efficacy of single-dose chemotherapy (Rifampicin, Ofloxacin and Minocycline-ROM) in PB leprosy patients with 2 to 5 skin lesions, India: Randomised double-blind trial

P Manickam[1], B Nagaraju[1], V Selvaraj[1], S Balasubramanyam[1], VN Mahalingam[1], SM Mehendale[1], VK Pannikar[2], MD Gupte[1], Team of Study Investigators[3]

Received : 02.12.2011 Revised : 19.06.2012 Accepted : 10.07.2012

We conducted randomized double-blind trial for single-dose of Rifampicin, Ofloxacin and Minocycline (ROM) compared to WHO-PB-MDT among paucibacillary (PB) leprosy patients with 2-5 skin lesions. We enrolled 1526 patients from five centres (ROM=762; WHO-PB-MDT=764) and followed them for 36 months post-treatment during 1998-2003. We generated information on clearance of skin lesions and relapse rates per 100 person-years (PY) for all the five centres. At base-line, the patients in the two arms were comparable. Complete clearance of skin lesions was similar (72% vs. 72.1%; p=0.95) in both the arms. Clinical scores declined steadily and equally. Difference in relapse rates was statistically highly significant (ROM=1.13 and WHO-PB-MDT=0.35 per 100 PY; mid-p exact=0.001016). Twenty eight of 38 of these relapses occurred within 18 months. In all, 10 suspected adverse drug reactions were observed (ROM=2; WHO-PB-MDT=8). We extended the follow-up to 48 months for 1082 of 1526 patients from two programme-based centres. No further relapses occurred. Decline in clinical score was not dependent on age, gender, number of lesions or affected body parts. Single dose ROM, though less effective than the standard WHO-PB-MDT regimen conceptually offers an alternative treatment regimen for PB leprosy patients with 2-5 lesions only when careful follow-up for relapse is possible.

Registered at the Clinical Trials Registry of India; Registration number: CTRI/2012/05/002645.

Keywords : Clinical trial, India, Pauci-bacillary leprosy, single-dose chemotherapy

[1] P Manickam, Ph.D, Scientist C
[1] B Nagaraju, DPH, Consultant
[1] V Selvaraj, Ph.D, Scientist B
[1] S Balasubramanyam, MBBS, Scientist-D
[1] VN Mahalingam, M.Sc, Technical Assistant (Research)
[1] SM Mehendale, MPH, Scientist-G and Director
[2] VK Pannikar, MBBS, Formerly Team Leader
[1] MD Gupte, DPH, ICMR Chair in Epidemiology
[3] Team of Study Investigators
[1] National Institute of Epidemiology (ICMR), R127, TNHB, Ayappakkam, Chennai-600 077, Tamil Nadu, India
[2] WHO Regional Office for South-East Asia, New Delhi, India
[3] List enclosed at the end of the manuscript
Correspondence to : MD Gupte email : mohangupted@yahoo.com; mohandgupte@gmail.com

Editor's Note

As also concluded by the authors, the regimen can be considered as an alternative only when proper follow-up is feasible, as such this is not recommended for mass use in NLEP as of now.

Introduction

Globally, leprosy services are currently offered as part of the general health services. Under the general health services, diagnosis and treatment of leprosy is based on number of skin lesions (WHO 1998). Pauci-bacillary (PB) leprosy patients form a substantial proportion [15% in Bhutan, 51% in India and 65% in Myanmar] of the newly diagnosed leprosy patients in South East Asia (WHO 2011).

Difficulty with compliance for long-term therapy is a known hurdle in leprosy programmes (WHO 2004, Heukelbach et al 2011). Further, on the basis of evidence generated from experimental studies, it might be possible to reduce treatment duration for PB leprosy (Ji et al 1996a, Ji et al 1996b). In this context, controlled trials were conducted among PB patients comparing a single-dose combination of rifampicin, ofloxacin and minocycline (ROM) with that of standard WHO-PB-MDT regimen for six-months by our group (Gupte 2000). It was demonstrated that single-dose ROM was almost as effective as the standard WHO-PB-MDT regimen in single lesion cases (Single-Lesion Multicentre Trial Group 1997). Based on these findings, WHO recommended single-dose ROM for single-lesion PB in leprosy control programmes (WHO 1998). Subsequently, single-dose ROM was evaluated in comparison to standard WHO-PB-MDT for PB patients with 2-3 skin lesions, with similar results (2-3 Lesion Multicentre Trial Group 2001). In this trial, the follow-up period was only 18 months and the sample size consisted of only 236 patients. It was considered necessary to generate information for PB leprosy patients with 2 to 5 lesions with adequately large number of patients and long-term follow-up (Gupte 2000).

In this context, we conducted a trial for single-dose ROM compared to standard WHO-PB- MDT among PB leprosy patients with 2 to 5 lesions. Primary objective of the study was to determine efficacy of ROM regimen in terms of complete clearance of lesions. Secondary objective of the study was to compare relapse rates in both the treatment arms. Safety issues for the drug regimens, were considered.

Materials and methods

Study design

It was a two-arm equivalence, randomised, double blind, controlled field trial with randomization at the individual patient level.

Sample size

The conditions for sample size estimation considered were: efficacy level of 50% (± 10%) over 36 months, efficacy measured in terms of complete clearance of skin lesions, power of 80% and type I error of 5%. The required sample size was 600 patients per arm.

Setting

The trial centres were selected on the basis of capacity to recruit eligible patients within six months; having a reasonably equipped base hospital either within the centre or nearby, for admission of patients for complications or adverse drug reactions; good case holding with an annual drop-out rate of less than 5%; experience in administering and implementing WHO-MDT regimens and programmes; and availability of adequately trained staff. Five centres that satisfied the above conditions were chosen for

the study. These centres were: Chennai (Leprosy control unit, Tamil Nadu), Chengalpattu [Central Leprosy Teaching and Research Institute (CLTRI), Chengalpattu, Tamil Nadu], Chittoor and Kadapa district leprosy control units (Andhra Pradesh) and Naini [The Leprosy Mission International (TLMI) Hospital, Uttar Pradesh]. We initially planned for six months of intake, six months of treatment phase and 36 months of post-treatment follow-up. We extended the follow-up period for additional 12 months in two centres (Chittoor and Kadapa). These centres were running large scale control programmes with negligible loss-to-follow-up. These centres were expected to provide information directly relevant to the actual field situation.

Study participants

We essentially used the WHO definition for PB (WHO, 1998) but also considered single nerve lesion as one of the lesions. We defined PB as those with 2-5 skin lesions without any nerve lesion and 1-4 skin lesions with a single nerve lesion. We included PB patients, who were untreated, had negative slit skin smear for acid fast bacilli and who did not have more than one peripheral nerve trunk involvement. The exclusion criteria were (1) children below five years of age (2) patients with reversal reaction and/or neuritis requiring treatment with corticosteroids (3) pregnant women at the time of intake (4) individuals with known allergy to any of the proposed drugs or their derivatives (5) known HIV positive individuals (6) patients with 2 or more peripheral nerve trunk involvement.

Study drugs and treatment schedule

Patients were allocated randomly to either of the two regimens following block randomization. All patients, in both the regimens, were treated for six months, with appropriate pre-coded drugs and identical looking placebo preparations. Standard regimen was WHO-MDT for PB leprosy (WHO-PB-MDT) for six months comprising rifampicin 600 mg once a month and dapsone 100 mg daily for six months. The dosage for children (less than 14 years) was rifampicin 450 mg and dapsone 50 mg. Patients on the standard WHO-PB-MDT arm also received single-dose of ROM-placebo preparation. Patients in the ROM arm received a single-dose of ROM as active drug viz. rifampicin 600 mg, ofloxacin 400 mg and minocycline 100 mg and daily doses of dapsone-placebo (WHO-PB-MDT) and additional monthly dose of rifampicin-placebo. In ROM arm, children below the age of 14 years were given half of the above doses. Trial drugs and identical looking placebos for rifampicin, ofloxacin and dapsone preparations were supplied by WHO.

Data collection

Initial clinical examination included recording numbers and characteristics of skin lesions, nerve lesion and slit skin smears. During the treatment phase, patients were seen and interviewed every month either by the investigator or by trained paramedical workers for any symptoms and signs suggestive of reversal reaction and/or neuritis and any evidence of adverse drug reactions. At the end of the treatment and then at every six months thereafter, a detailed clinical examination was performed and findings were recorded using a prescribed format.

National Institute of Epidemiology (NIE), Indian Council of Medical Research (ICMR), Chennai was the co-ordinating centre for monitoring and ensuring the adherence of trial protocol by the trial centres. Reporting forms were collected; scrutinized and trial database was maintained at NIE. Quality checks were maintained through supervision and monitoring throughout the study period. Medical officers from NIE confirmed special events in cases with appearance of a new skin lesions or nerve involvement.

Operational definitions

Each patient was assessed clinically and a clinical score was recorded for every lesion based on defined criteria (Single-Lesion Multicentre Trial Group 1997) (Table 1).

We defined improvement in terms of complete disappearance of all lesions at the end of follow-up or reduction in clinical score from the base-line. Deterioration or treatment failure was defined as appearance of new active leprosy skin lesion, definite signs/ symptoms of new peripheral nerve trunk damage, confirmed positive slit skin smear at any site observed during the follow-up. The patients showing deterioration were re-examined clinically and bacteriologically. Relapse is defined as occurrence of new active skin lesions with or without positive slit skin smear at any site.

Reactions were classified as type 1 and 2 reactions. Type 1 reactions were defined as occurrence of any of the following manifestations with or without constitutional symptoms such as fever and malaise: (i) existing skin lesions becoming reddish and swollen; (ii) painful, tender and swollen peripheral nerves, including signs of nerve damage such as loss of sensation and muscle weakness. Type 2 reactions were defined as occurrence of short-lived and recurrent crops of tender reddish subcutaneous nodules that may ulcerate with signs of systemic involvement with fever and inflammation in lymph nodes, nerves, eyes, joints, testes, fingers, toes or other organs. Neuritis was defined as appearance of definite new areas of loss of sensation and /or new muscle weakness with or without accompanied tender-ness or pain in the affected nerves.

Management of special events

Special events included relapses, reversal reactions, adverse drug reactions, refusal of treatment, deaths and migrations. We followed WHO guidelines for management of reactions, relapse, neuritis and adverse drug effects (WHO 1998).

On confirmation of a patient with treatment failure or relapse, WHO-MDT regimen was started. In case of doubt between reversal reaction and relapse, we used corticosteroid therapeutic test for 12-24 weeks to differentiate between them (WHO 1998). Mild reversal reactions were managed by prescribing anal-gesics. In case of severe reversal reaction, either the patient was hospitalized or managed with corticosteroids.

In case of suspected adverse drug reactions, physical findings of patient were recorded, along with an indication as to whether the adverse reaction was likely to be attributed to any of the drugs used in the trial. As per the WHO/TDR guidelines and based on available clinical notes, we classified the reported drug reactions into not related, unlikely, possibly related or probably related to the drug. In the event of adverse drug reactions, associated with the drugs used in the trial, the principal investigator at the study centres independently managed the cases as per the protocol.

Data analysis

We described base-line characteristics in terms of frequencies, means and standard deviations for all the study centres. We compared the proportions and obtained exact p-values (two-tailed) using Fisher exact or mid-P exact tests. As per the protocol, we calculated person-year (PY) for study participants from the time of recruitment to observation of primary (clearance of skin lesions) or secondary (relapse) outcomes or lost-to-follow-up due to any adverse drug reaction that necessitated stopping of treatment. Beyond this point, they ceased to contribute to the person-time of observation (right-censored). We calculated relapse rates per 100 PY. We

compared the relapse rates between the two treatment arms using OpenEpi version 2.3.1. We calculated rate ratio (RR) and 95% confidence intervals (95% CI).

In the two centres with additional follow-up, we identified factors associated with clinical scores over the follow-up period using multiple longitudinal regression analysis by generalized estimating equations (GEE) approach (Liang & Zeger 1986). Treatment arm, age at time of examination, sex, number of skin lesions, number of body parts and the time of follow-up were used as important independent variables. Stata 7 (Stat Corp., College Station, Texas) was used for statistical analysis. The analysis was based on intention-to-treat principle.

Human subject protection

The study was approved by ethics committees of NIE (ICMR) and WHO covering all the participating study centres (Registered at the Clinical Trials Registry of India; Registration number: CTRI/2012/05/002645). All the participants in the study were administered informed consent forms in their local languages.

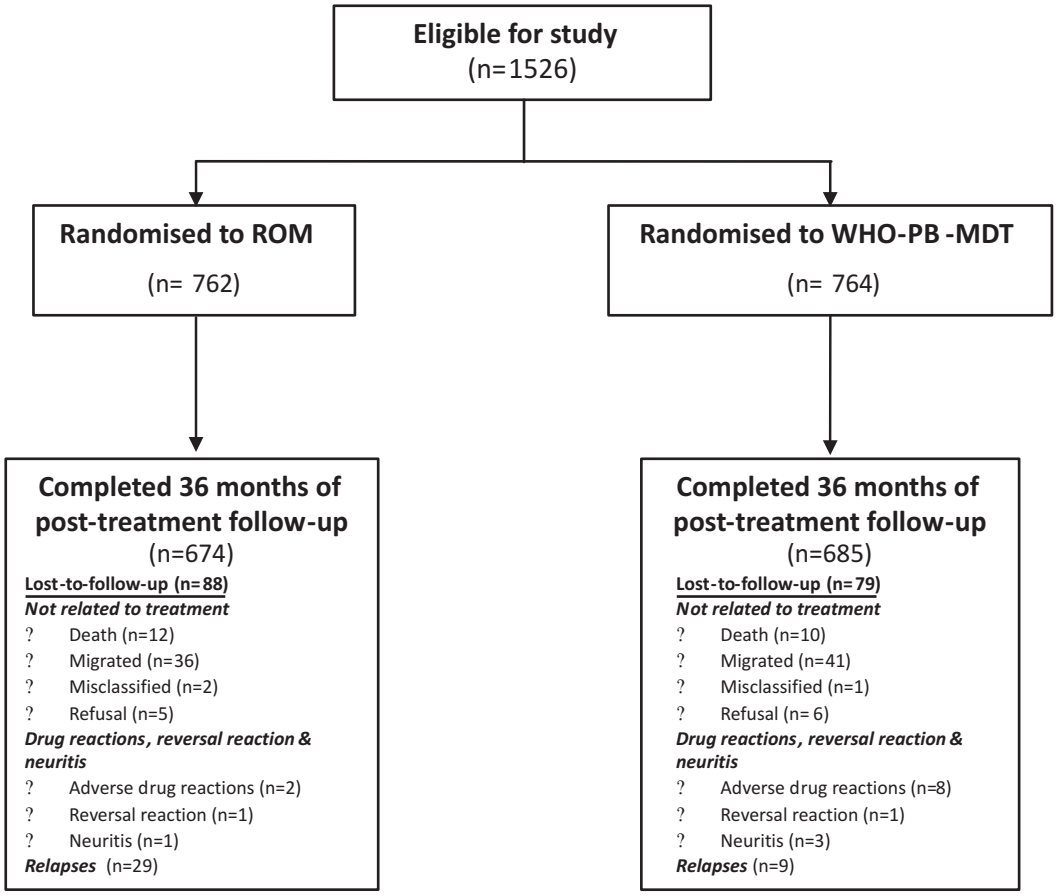

Fig 1 : Intake and follow-up of study participants from all five centres: Randomized controlled trial of single-dose chemotherapy for PB leprosy patients with 2 to 5 skin lesions, India

Table 1 : Operational criteria for assigning clinical scores: Randomized controlled trial of single-dose chemotherapy for PB leprosy patients with 2 to 5 skin lesions, India

Clinical criteria	Assigned score		
	3	2	0
Appearance of Lesion	Clearly visible	Faintly visible	Scar / Complete disappearance
Hypo-pigmentation	Marked	Moderate	Mild
Erythema	Marked	Moderate	Mild
Infiltration	Marked	Moderate	Mild
Anaesthesia	Complete loss	Definite Impairment	Nil

Table 2 : Base-line characteristics of participants by treatment arms: Randomized controlled trial of single-dose chemotherapy for PB leprosy patients with 2 to 5 skin lesions, all five study centres, India

Characteristics	**ROM** (n=762)		**WHO-PB-MDT** (n=764)	
Age (Mean, years)	27		27	
Male gender	369	(48)	360	(47)
Number of lesions				
Single lesion with nerve involvement	57	(8)	37	(5)
2	387	(51)	405	(53)
3	187	(25)	196	(26)
4	100	(13)	86	(11)
5	31	(4)	40	(5)
Number of body parts affected				
1	450	(59)	446	(58)
2	267	(35)	251	(33)
≥ 3	45	(6)	67	(9)
Presence of nerve involvement	149	(20)	156	(20)
Clinical score [Mean (Standard deviation)]	13.7 (5.3)		13.9 (5.2)	

Values in parentheses indicate percentage

Results

Between April 1998 and October 1999, 1526 patients were enrolled in the trial (762 in ROM and 764 in WHO-PB-MDT arms). The base-line characteristics of the patients such as age, gender, number of lesions, number of affected body parts, presence of nerve involvement and clinical scores were similar (Table 2). During the 36 months of post-treatment follow-up, totally 167 (11%) patients were lost-to-follow-up for various reasons (Figure 1; Table 3). Of these, 68% (ROM=55; WHO-PB-MDT=58) were not related

Table 3 : Comparison of lost-to-follow-up by treatment arms : Randomized controlled trial of single-dose chemotherapy for PB leprosy patients with 2 to 5 skin lesions, India

Reasons for lost-to-follow-up	ALL STUDY CENTRES*					TWO STUDY CENTRES* (Chittoor & Kadapa)				
	ROM (n=762)	WHO-PB-MDT (n=764)			mid-p exact	ROM (n=539)	WHO-PB-MDT (n=543)			mid-p exact
	#	Rate/100	#	Rate/100		#	Rate/100	#	Rate/100	
Not related to treatment										
Death	12	1.57	10	1.31	0.83	7	1.30	10	1.31	0.49
Migrated	36	4.72	41	5.37	0.57	40	7.42	39	5.10	0.88
Misclassified	2	0.26	1	0.13	0.62	0	0	1	0.13	0.78
Refusal	5	0.66	6	0.79	0.78	5	0.93	5	0.65	0.99
Drug reactions, reversal reaction & neuritis										
Suspected adverse drug reactions	2	0.26	8	1.05	0.11‡	2	0.37	1	0.13	0.62
Reversal reaction	1	0.13	1	0.13	0.99	0	0	0	0	-
Neuritis	1	0.13	3	0.39	0.63	0	0	2	0.26	0.8
Relapse (per 100 person-years)	29	1.127	9	0.348	0.001‡	17	0.636	8	0.298	0.07

* For 36 months of post-treatment period
† For 48 months of post-treatment period
‡ Fisher exact

to treatment, 10 were suspected adverse drug reactions, 38 were relapses, two reversal reactions and four neuritis.

The proportion of patients who had complete clearance at 36 months of post-treatment follow-up was similar in both the arms [72% in ROM compared to 72.1% in WHO-PB-MDT; mid-p exact=0.95] (Table 4).

With reference to clinical scores, the five-point method of clinical scoring was not followed by all the centres. Naini, Chengalpattu and Chennai centres used the five-point criteria (Table 1). The field investigators in Chittoor and Kadapa centres used two-point criteria (appearance of lesions and anaesthesia) due to its field-oriented operational simplicity. Hence, for the purpose of comparison across the five study centres, we calculated mean clinical score using criteria of appearance of lesions and anaesthesia. We reviewed the contribution of the other three factors, viz., erythema, hypopigmentation and infiltration. For the three centres recording these criteria, clinical scores in the two arms of the study were similar and the decline over 36 months was also similar. During the follow-up, mean clinical scores (on the basis of appearance of skin lesions and anaesthesia) declined substantially from base-line in all the five centres in both the arms (Table 5).

Table 4 : Complete clearance of skin lesions by treatment arms : Randomized controlled trial of single-dose chemotherapy for PB leprosy patients with 2 to 5 skin lesions, India

Follow-up	ALL STUDY CENTRES				TWO STUDY CENTRES (Chittoor & Kadapa)			
	ROM (n=762)		WHO-PB-MDT (n=764)		ROM (n=539)		WHO-PB-MDT (n=543)	
	#	% clearance	#	% clearance	#	% clearance	#	% clearance
During treatment period	735	26.9	735	28.9	521	25.1	529	26.2
Post-treatment period								
6 months	726	38.8	722	39.9	516	37.4	519	38.2
12 months	713	47.3	710	48.5	509	47.3	509	47.2
18 months	693	54.0	705	55.0	500	54.0	505	55.2
24 months	687	58.1	696	58.9	498	59.2	499	60.2
30 months	681	65.1	692	66.8	494	67.2	494	68.3
36 months	674	72.0	685	72.1	492	72.6	494	72.7
48 months	-	-	-	-	468	75.4	477	78.6

Table 5 : Clinical score {Mean [Standard deviation (SD)]} during follow-up: andomized controlled trial of single-dose chemotherapy for PB leprosy patients with 2 to 5 skin lesions, India

Follow-up	ALL STUDY CENTRES				TWO STUDY CENTRES (Chittoor & Kadapa)			
	ROM (n=762)		WHO-PB-MDT (n=764)		ROM (n=539)		WHO-PB-MDT (n=543)	
	#	Mean (SD)	#	Mean (SD)	#	Mean (SD)	#	Mean (SD)
Base-line	762	13.7 (5.3)	764	13.9 (5.2)	539	13.6 (5.4)	543	13.8 (5.3)
During treatment period	735	6.8 (5.2)	735	6.9 (5.1)	521	7.5 (5.3)	529	7.4 (5.0)
Post-treatment period								
6 months	726	5.5 (5.1)	722	5.5 (4.9)	516	6.1 (5.1)	519	6.1 (5.0)
12 months	713	4.7 (4.8)	710	4.7 (4.6)	509	5.2 (4.9)	509	5.3 (4.8)
18 months	693	4.1 (4.6)	705	4.0 (4.4)	500	4.7 (4.8)	505	4.4 (4.5)
24 months	687	3.6 (4.3)	696	3.5 (4.3)	498	4.1 (4.5)	499	3.9 (4.4)
30 months	681	3.3 (4.1)	692	3.1 (4.1)	494	3.7 (4.3)	494	3.5 (4.2)
36 months	674	2.8 (4.0)	685	2.7 (4.0)	492	3.2 (4.2)	494	3.1 (4.1)
48 months	-	-	-	-	468	2.2 (3.5)	477	2.1 (3.4)

Table 6 : Suspected adverse drug reactions reported during treatment phase by treatment arms : Randomized controlled trial of single-dose chemotherapy for PB leprosy patients with 2 to 5 skin lesions, India

#	Treatment arm	Description of the event	Classification of the event
1	ROM	Angular stomatitis; inflammation of the oral cavity	Not related
2	ROM	Swelling and itching on the lesion on right side of the face; no tenderness	Possible
3	WHO	Dermatitis*	Probable
4	WHO	Recovering; treatment stopped (No clinical notes)	Possible
5	WHO	?Mild-moderate; regular MDT without dapsone	Possible
6	WHO	?Mild; treatment stopped (No clinical notes)	Possible
7	WHO	Rashes all over the body; probably due to dapsone allergy*	Probable
8	WHO	Exfoliative dermatitis and jaundice after taking second dose*	Probable
9	WHO	Fever, loss of appetite, jaundice one month after taking treatment	Possible
10	WHO	Angular stomatitis; inflammation of the oral cavity	Not related

*attributable to dapsone

In all, 10 suspected adverse drug reactions were reported in the study. Eight of 10 suspected adverse drug reactions were observed in the WHO-PB-MDT arm (Table 6). Though statistically not significant, the occurrence of more drug reactions in the WHO-PB-MDT arm was of clinical significance. We observed one type 1 reaction in each of the arms. None of the patients were bacteriologically positive at the end of treatment phase or during follow-up.

We compared the incidence of relapses by treatment arms. Totally, 29 relapses occurred in ROM arm (Person years = 2574.16) and 9 relapses occurred in WHO-PB-MDT arm (Person years = 2585.57). The relapse rate per 100 PYs was 1.13 for patients treated with ROM as compared to 0.35 for WHO-PB-MDT, difference being statistically highly significant [mid-P exact = 0.001016; RR:3.2; 95% CI: 1.6-7.2] over 36 months. We observed that majority of the relapses in both the arms occurred within the first 18 months of follow-up (22 of 29 in the ROM and 7 of 9 in the WHO-PB-MDT) from the initiation of active treatment.

Our analysis of data from Chittoor and Kadapa centres included 1082 patients (ROM=539 and WHO-PB-MDT=543). During the 48 months of post-treatment follow-up, totally 137 (13%) patients were right-censored for various reasons. Of these, 65% (ROM=52; WHO-PB-MDT=55) were not related to treatment, 3 were due to suspected drug reactions (2 in ROM and 1 in WHO-PB-MDT), 25 were relapses (ROM=17 and WHO-PB-MDT=8) and 2 cases of neuritis occurred in the WHO-PB-MDT arm (Table 2).

At the end of 48 months of post-treatment follow-up in these centres, there was further increase in complete clearance of lesions and the proportion with complete clearance was similar [75% vs. 79%; ROM vs. WHO-PB-MDT; mid-p exact=0.25] [Table 4]. The clinical scores were declining in similar way compared to what was observed in

Table 7 : Factors associated with clinical score over the follow-up period : Randomized controlled trial of single-dose chemotherapy for PB leprosy patients with 2 to 5 skin lesions, Chittoor and Kadapa centres, India

Characteristics	Model co-efficient*	p value
Baseline clinical score	0.033 (-0.026, 0.091)	0.27
Time of follow-up	- 0.101 (-0.109, -0.094)	0.00
Treatment arm (ROM)	- 0.051 (-0.271, 0.170)	0.69
Age at the time of follow-up	0.011 (0.004, 0.018)	0.002
Male gender	- 0.083 (-0.303, 0.138)	0.46
Number of lesions at baseline	0.149 (-0.178, 0.476)	0.37
Number of body parts affected		
one	Reference category	
two	0.174 (-0.066, 0.414)	0.16
three or more	0.169 (-0.290, 0.628)	0.47
Constant	6.098 (5.667, 6.528)	0.00

*Generalized Estimating Equations with normal link and auto-regression of the order two correlation structure

the combined analysis. The mean clinical scores (SD) at the base-line were 13.6 (5.4) vs. 13.8 (5.3) compared to 2.2 (3.5) vs. 2.1 (3.4) at the end of 48 months in ROM and WHO-PB-MDT arms respectively (Table 5).

Totally, 17 relapses occurred in the ROM arm (Person years=2671.274) whereas 8 relapses occurred in the WHO-PB-MDT arm (Person years=2686.2548). The relapse rate per 100 PY was 0.64 for the ROM as compared to 0.3 for the WHO-PB-MDT arm [mid-P exact=0.07329; RR: 2.1; 95% CI: 0.9-5.2] over 48 months. We observed that majority of the relapses in both the arms occurred within the first 18 months of follow-up (14 of 17 in the ROM and 6 of 8 in the WHO-PB-MDT) from the initiation of active treatment. We did not observe any more relapses or reactions in both the treatment arms during the additional 12 months of follow-up. The GEE analysis indicated that the patient's age (time-dependent variable) and time of follow-up were statistically significant predictors of decline in clinical scores (Table 7) indicating that the clinical score increased with the patient's age and declined with the time of follow-up.

Discussion

We conducted a randomized double-blind controlled trial and documented that single-dose of ROM and observed that complete clearance of skin lesions for PB leprosy patients with 2 to 5 skin lesions was similar to the standard six-month WHO-PB-MDT regimen. However, relapse rate was significantly higher among ROM than WHO-PB-MDT arm.

With integration of leprosy services into the general health services, diagnosis, treatment and follow-up of leprosy patients are entrusted with general health care workers (WHO 2006). Hence, there could be problems with compliance and effectively maintaining leprosy patients on prolonged anti-leprosy drug regimens advocated by WHO. Globally, the need to treat individual PB patients with simpler regimens is being increasingly felt. For instance, uniform six-month WHO-MB-MDT regimen for both PB and MB

patients is being considered as one such promising possibility (Kroger et al 2008). In this context, ROM therapy, a single-dose regimen, conceptually offers an attractive alternative in treating PB patients.

ROM was initially evaluated on PB patients with single skin lesion patients and the follow-up period was for one year (Single-Lesion Multicentre Trial Group 1997). ROM was further evaluated on PB leprosy patients of 2-3 skin lesions, which indicated that treatment with single-dose ROM was as effective as 6 months WHO-PB-MDT (2-3 Lesion Multicentre Trial Group 2001). These studies provided the basis for further studies to evaluate the ROM single-dose regimen for patients with 2 to 5 lesions. In this context, the present study gains significance.

In the present study, a consistent improvement in skin lesions in patients treated with single-dose ROM or WHO-PB-MDT over time was observed, both in terms of complete clearance of skin lesions and reduction of mean clinical score. We documented from the multiple longitudinal analysis of sufficiently longer duration follow-up data from programme-based centres (Chittoor and Kadapa) that the reduction in the clinical mean score was regardless of severity of the disease, number of lesions and number of body parts affected. The multiple regression analysis showed that the patients with lower age responded marginally better to ROM. As duration of follow-up increased, the clinical score decreased significantly.

We observed higher relapse rate among those treated with ROM (3.8%) as compared to WHO-PB-MDT (1.2%). The difference was statistically significant in the overall analysis of 36 months of follow-up. In the two centres with 48 months post-treatment follow-up, the difference was of border-line statistical significance (p=0.07). The observed relapse rate of 1.2% over 36 months with WHO-PB-MDT is comparable to an estimated rate of 1.09% documented by WHO through a multi-country survey (WHO 1995). A more recent data from Tamil Nadu documented a relapse rate of 1.9% during a follow-up of 16 years after release from treatment with WHO-PB-MDT (Ali et al 2005). In the published literature, various studies documented relapse rates of around 2% for duration of follow-up that varies from less than a year to 8 years (Smith and Saunderson 2010).

Primarily, the study size for the present study was intended for testing the equivalence for complete clearance of skin lesions and not for relapse. We observed that 20 of the 29 relapses occurred within 18 months and the remaining 9 within 36 months of completion of treatment. In the additional 12 months of follow-up, no relapses occurred in 1082 patients from Chittoor and Kadapa in both the arms. Overall, we observed that six months of therapy (WHO-PB-MDT) contributed to the reduction in the relapse rate to the tune of 0.78 per 100 PY (1.13 vs. 0.35 per 100 PY). Nevertheless, as practised in the documentation of clinical efficacy of tuberculosis chemotherapy regimen, we need to take into consideration relapses alongwith clinical regression of skin lesions. Observed higher relapse rate among patients receiving single-dose ROM regimen indicated lower levels of efficacy compared to WHO-PB-MDT. The relapses are essentially observed in the first two-years of follow-up. Hence, if single-dose regimen is to be used in treatment regimen, the patients have to be kept under active surveillance for at least two years. This would require training of treating physicians in clinical evaluation of leprosy patients to detect reactions, relapses and treatment failures.

Further, we need to examine suspected adverse drug reactions observed in the WHO-PB-MDT arm

(8 of the 10 drug reactions). Two of the suspected eight drug reactions were of serious nature (exfoliative dermatitis) requiring hospitalization. In the present day context of primary care-based approach to leprosy control and treatment, clinical expertise to identify and manage such drug reactions may be lacking. Hence, on the basis of the observation that a manageable level of relapses occur after completing ROM and possibility of minimal adverse drug reactions, we suggest that single-dose ROM therapy be offered as an alternative approach for PB patients. This regimen could be considered in situations, where patients could understand and physicians could follow them carefully for a minimum period of two years.

We suggest three to six periodic pulse doses (such as once a month supervised ROM administration for PB leprosy with 2 to 5 lesions) can be considered as a possible regimen for further clinical evaluation.

In summary, single-dose regimen ROM was found to be equally efficacious to WHO-PB-MDT regimen in terms of complete clearance of skin lesions in PB leprosy patients with 2 to 5 skin lesions. The observed relapse rates of just over 1 per 100 PY for single-dose ROM may be quite tempting to the leprosy control programmes. A single-dose ROM could be considered conceptually as a treatment option for PB leprosy patients as it appears operationally attractive and practical for both the private and public sectors. However, as an abundant measure of precaution, we suggest that the patients will require counseling and careful post-treatment follow-up for at least two years to watch for signs of relapses.

Team of investigators at study centres

- *Chittoor:* NS Brahmachary, K Sarojamma *(since deceased)* (District Leprosy Officers, Government of Andhra Pradesh)
- *Kadapa:* B Ramachandra Naidu (District Leprosy Officer, Government of Andhra Pradesh)
- *Naini:* Margery Emmanuel, G Rajan Babu [The Leprosy Mission International (TLMI), India]
- *Chengalpattu*: KV Krishnamoorthy, Rao Bhau Rao, E Jayaraman, MK Showkath Ali [Central Leprosy Training and Research Institute (CLTRI), Tamil Nadu]
- *Chennai:* D Andrews Deenabandhu, M Subbaih [Deputy Director of Medical Services (Leprosy), Chennai, Government of Tamil Nadu]

Nie co-ordinating team

MD Gupte, S Balasubramanyam, B Nagaraju, P Manickam, VN Mahalingam.

Writing team

NIE: MD Gupte, P Manickam, B Nagaraju, V Selvaraj, S Balsubramanyam, VN Mahalingam, SM Mehendale; **WHO:** VK Pannikar.

Acknowledgement

We acknowledge with thanks the UNDP/WHO (TDR) Action Programme for the Elimination of Leprosy for involvement in developing the protocol, financial support & co-ordination. We thank the patients for their willing participation and the field teams of all the participating centres. We also thank RS Vallishayee, PA Tamby, V Ramachandran, S Anitha and field staff of NIE for their support during the conduct of the study.

References

1. World Health Organization (2011). Global leprosy situation, 2011. *Wkly Epidemiol Rec.* **86**: 389-400.
2. World Health Organization (2004). Multidrug therapy against leprosy: Development and implementation over the past 25 years. WHO, Geneva.
3. Heukelbach J, André Chichava O, de Oliveira AR et al (2011). Interruption and defaulting of

multidrug therapy against leprosy: population-based study in Brazil's Savannah Region. *PLoS Negl Trop Dis.* **5**: e1031.

4. Ji B, Perani EG, Petinom C et al (1996a). Bactericidal activities of combinations of new drugs against *Mycobacterium leprae* in nude mice. *Antimicrob Agents Chemother.* **40**: 393-399.
5. Ji B, Jamet P, Perani EG et al (1996b). Bactericidal activity of single dose of clarithromycin plus minocycline, with or without ofloxacin, against *Mycobacterium leprae* in patients. *Antimicrob Agents Chemother.* **40**: 2137-2141.
6. Gupte MD (2000). Field trials of a single dose of the combination rifampicin-ofloxacin-minocycline (ROM) for the treatment of paucibacillary leprosy. *Lepr Rev.***71** Suppl: S77-80.
7. Single-lesion Multicentre Trial Group (1997). Efficacy of single dose multidrug therapy for the treatment of single-lesion paucibacillary leprosy. *Indian J Lepr.* **69**: 121-129.
8. World Health Organization (1998). WHO expert committee on leprosy. Seventh report. World Health Organization, Geneva (WHO technical report series no. 874).
9. 2-3 Lesion Multicentre Trial Group (2001). A comparative trial of single dose chemotherapy in paucibacillary leprosy patients with two to three skin lesions. *Indian J Lepr.* **73**: 131-143.
10. Liang KY and Zeger SL (1986). Longitudinal analysis using generalized linear models. *Biometrika.* **73**: 13-22.
11. World Health Organization (2006). Global leprosy situation, 2006. *Wkly Epidemiol Rec.* **81**: 309-16.
12. Ali MK, Thorat DM, Subramanian M et al (2005). A study on trend of relapse in leprosy and factors influencing relapse. *Indian J Lepr.* **77**: 105-115.
13. Kroger A, Pannikar V, Htoon MT et al (2008). International open trial of uniform multi-drug therapy regimen for 6 months for all types of leprosy patients: rationale, design and preliminary results. *Trop Med Int Health*. **13**: 594–602.
14. Smith WC and Saunderson P (2010). Leprosy. *Clin Evid* (Online). Jun 28;pii: 0915. Available: http://clinicalevidence.bmj.com/ceweb/conditions/ind/0915/0915.jsp. [Accessed 25 January 2011].
15. World Health Organization (1995). Risk of relapse in leprosy. The Leprosy Unit, WHO. *Indian J Lepr.* **67**: 13–26.

How to cite this article : Manickam P, Nagaraju B, Selvaraj V, Balasubramanyam S, Mahalingam VN, Mehendale SM, Pannikar VK, Gupte MD and Team of Study Investigators (2012). Efficacy of single-dose chemotherapy (Rifampicin, Ofloxacin and Minocycline-ROM) in PB leprosy patients with 2 to 5 skin lesions, India: Randomised double-blind trial. *Indian J Lepr.* **84** : 195-207.