

INTERNATIONAL JOURNAL OF LEPROSY

and Other Mycobacterial Diseases

VOLUME 72, NUMBER 1

MARCH 2004

Relapses in Multibacillary Patients Treated with Multi-drug Therapy until Smear Negativity: Findings after Twenty Years¹

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ABSTRACT

The Schieffelin Leprosy Research and Training Center at Karigiri, India participated in several of the World Health Organization (WHO) trials. The first trial on combined therapy in multi-bacillary leprosy was initiated in 1981. The main objectives of this field trial were to evaluate the efficacy of WHO recommended regimens in preventing relapses, especially drug resistance relapses. This paper reports on the relapses twenty years after patients were inducted into the WHO field trial.

Between 1981 and 1982, 1067 borderline lepromatous and lepromatous patients were inducted into the WHO field trial for combined therapy in multi-bacillary leprosy trial. Among them, 357 patients were skin smear positive. During the follow-up in 2002, only 173 of them could be traced and assessed. The mean duration of follow-up was 16.4 ± 1.83 years. Two patients relapsed 14 and 15 years after being released from treatment, the relapse rate being 0.07 per 100 person years follow-up. Drug susceptibility tests done on one of the relapsed patients revealed drug sensitive organisms to all multi-drug therapy drugs.

RÉSUMÉ

Le centre de recherche et de formation de Schieffelin à Karigiri aux Indes a participé à plusieurs études cliniques sponsorisées par l'Organisation Mondiale de la Santé (OMS). La première étude clinique sur la thérapie multiple contre la lèpre multi-bacillaire y fut initiée en 1981. L'objectif principal de cette étude de terrain était d'évaluer l'efficacité des prescriptions recommandées par l'OMS à prévenir les rechutes, en particulier les rechutes avec souches résistantes. Cet article rapporte les rechutes 20 ans après que les patients ont été enrôlés dans l'étude de terrain de l'OMS.

Entre 1981 et 1982, 1067 patients lépromateux et lépromateux borderline furent enrôlés dans l'étude clinique de terrain de polychimiothérapie au sein de l'étude de lèpre multi-bacillaire. Parmi ces derniers, 357 patients présentaient un résultat positif au test bactérioscopique du suc dermique. Durant le suivi de 2002, seuls 173 d'entre eux ont pu être retrouvés et évalués. La durée moyenne de suivi était de $16,4 \pm 1,84$ années. Deux patients ont

¹Received for publication 9 October 2003. Accepted for publication 30 October 2003.

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rechutés 14 et 15 années après la fin du traitement, le taux de rechute étant de 0,07 pour 100 personne-années de suivi. Des tests de susceptibilité aux médicaments, effectués sur l'un des patients qui avait rechuté, a révélé des organismes sensibles à tous les médicaments utilisés dans la polychimiothérapie.

RESUMEN

El centro Schieffelin de entrenamiento e investigación contra la lepra en Karigiri, India, ha participado en varios estudios de campo de la Organización mundial de la Salud (OMS). El primer estudio sobre terapia combinada en casos de lepra multibacilar se inició en 1981. El principal objetivo de este estudio fue la evaluación de la eficacia de los regímenes de tratamiento recomendados por la OMS en la prevención de recaídas, especialmente las recaídas en la resistencia a las drogas antileprosas. En este artículo se informa sobre la incidencia de recaídas 20 años después de haberse realizado el estudio de la OMS.

Entre 1981 y 1982, 1067 pacientes con lepra lepromatosa y lepra lepromatosa subpolar se incluyeron en un estudio de campo de la OMS para recibir tratamiento antileproso combinado. Trescientos cincuenta y siete de estos pacientes resultaron positivos para bacilos en linfa cutánea. Durante el seguimiento en 2002, sólo 173 de los pacientes pudieron ser localizados y evaluados. El tiempo promedio de seguimiento fue de 16.4 ± 1.83 años. Dos pacientes tuvieron recaídas a los 14 y 15 años, respectivamente, después de haber completado el tratamiento, siendo la tasa de recaída de 0.07 por 100 persona/años de seguimiento. Las pruebas de susceptibilidad realizadas en uno de los pacientes revelaron que los microorganismos fueron sensibles a todas las drogas de la poliquimioterapia.

World Health Organization (WHO) field trials on Multi-drug therapy (MDT) regimens strongly recommend their use worldwide and are reported to be highly successful⁽⁴⁾. Several studies have reported very low relapse rates after the completion of MDT, which must be interpreted with caution, as the duration of follow up in a majority of studies was relatively short⁽¹²⁾. Relapses in leprosy following treatment with rifampicin-containing regimens are known to occur at least 5 ± 2 years after stopping treatment⁽¹⁵⁾. As a consequence, it has been recommended that a follow-up of 10 years or more is required for drawing final conclusions on relapse rates after MDT^(4,11). The Schieffelin Leprosy Research and Training Center, Karigiri, was one of the centers to field test the WHO MDT regimens (Ref). An earlier paper reported no relapses after following up a subset of new, previously untreated patients for 13.7 ± 1.4 yrs.⁽¹⁶⁾ This paper presents the latest data on relapses twenty years after they were inducted into the WHO field trial.

MATERIALS AND METHODS

The Schieffelin Leprosy Research and Training Center (SLRTC), Karigiri in India participated in several of the WHO MDT field trials, the first trial on combined therapy in multibacillary (MB) leprosy in De-

cember, 1981. The objectives of this field trial were to evaluate the efficacy of WHO recommended regimens in preventing relapses, especially drug resistant relapse.

Of the 1067 multi-bacillary patients inducted into the trial during 1981 to 1983, only 357 patients were smear positive and were classified as either borderline lepromatous (BL) or lepromatous (LL) based on the Ridley-Jopling classification⁽¹⁾. According to their area of residence, patients were allocated to either of the two regimens being tested in the trial. Patients living in geographical divisions I and II were given Regimen A (THELEP) and those living in divisions III and IV were given Regimen B (Study Group). The regimens given are as follows:

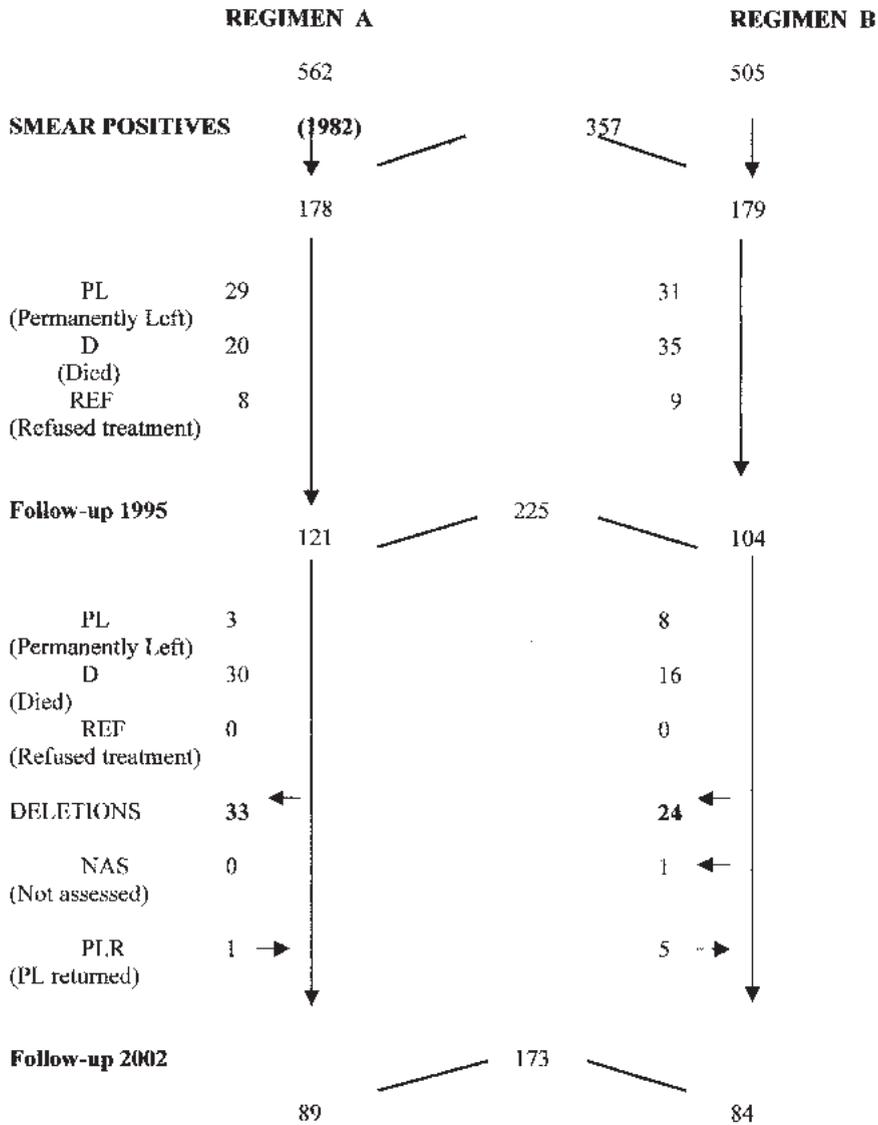
Regimen A (THELEP regimen)

Rifampicin 600 mg on two consecutive days monthly—supervised +
Clofazimine 600 mg on two consecutive days monthly—supervised +

Inj. Acedapsone (DADDS) 225 mg intramuscular once every two months +
Dapsone 100 mg daily self-administered

Regimen B (Study Group regimen)

Rifampicin 600 mg once a month supervised +



FLOW CHART

Clofazimine 300 mg once a month supervised +
 Dapsone 100 mg once a month supervised +
 Clofazimine 50 mg self-administered +
 Dapsone 100 mg self-administered

The patients received the supervised dose at the clinic and compliance of the unsupervised drugs was monitored both by tablet count and the Dapsone:Creatinine ratio (D:C ratio) in urine. Smear positive patients

were treated for a minimum period of 2 yrs or until smear negativity, whichever occurred later and then released from treatment (RFT). All patients recruited into the study were followed up annually with a clinical and bacteriological examination and a motor/sensory assessment. In 1995, only 225 of the original 357 smear positive patients could be followed up, after which annual follow-up and examination was discontinued.

In 2002, an attempt was made to follow-

TABLE 1. Mean age, male:female ratio, clinical type.

Year assessed	Mean age in years	Male:female ratio	Clinical type			
			BL		LL	
			No.	%	No.	%
1982	40	3.2:1	118	33.1	239	66.9
2002	65.2	2.3:1	67	38.5	106	61.5

up all living patients from the 357 smear positive patients belonging to the original 1982 cohort. All patients who could be traced underwent a clinical and bacteriological examination and a motor/sensory assessment. Any history of symptoms and signs of reactions were noted. For those patients who had died, a detailed verbal autopsy was done to establish the cause of death.

Relapse was diagnosed if two of the following three criteria were met: (i) occurrence of definite new skin lesion(s); (ii) increase of the BI of >2+ or over the previous value from any site; (iii) demonstration of viable *M. leprae*, by mouse footpad inoculation.

RESULTS

Of the 357 smear positive MB patients inducted into the trial in 1982, only 173 patients were available for follow-up in 2002 (vide flow chart). Eighty-nine patients belonged to Regimen A and 84 to Regimen B. The mean duration of follow-up of the 173 patients was 16.4 ± 1.83 yrs. Among those followed up, 75.1% were above 30 yrs of age, 70.5% were males, 61.3% were classified as LL and 12.1% had a BI of 3+ or more. Among the 184 patients not available for assessment, 101 (54.9%) had died, 65 (35.3%) had migrated and 18 (9.8%) were uncooperative. When compared to those not followed up, in the follow-up group there were significantly more males (81.5%; $p = 0.02$), LL (72.3%; $p = 0.035$) and patients with BI 3+ or more (45.7%; $p < 0.001$).

Among 173 patients assessed in 2002, the mean age was 57.2 yrs (S.D. = 10.4) (Table 1). There was no significant difference in the age and cause of death between patients treated with the two regimens. Since no significant differences were found in the characteristics of patients treated with

TABLE 2. Duration of treatment with monotherapy and MDT.

Duration in months	Monotherapy		MDT	
	No.	%	No.	%
<6	29	16.8	—	—
6–12	17	9.8	—	—
13–24	16	9.2	78	45.1
25–60	51	29.5	90	52.0
>60	60	34.7	5	2.9

the two regimens, they have been combined as one group for further analysis.

Table 2 shows the duration of treatment with dapsone monotherapy and MDT. The majority of patients had received dapsone monotherapy prior to MDT. The duration of dapsone monotherapy ranged between less than 8 weeks to more than 10 yrs. All patients were treated with MDT for a minimum of 2 yrs or till smear negativity. Seventy eight patients (45%) had received MDT for 2 yrs, 90 (52%) for 3 to 5 yrs, and 5 (3%) for more than 5 yrs. The longest duration of treatment was for 2 patients who were given MDT for 8 yrs. It is observed that there is no significant association between the duration of monotherapy received prior to MDT and the duration of MDT subsequently required by patients to reach smear negativity ($p = 0.13$).

Among the 173 patients assessed in 2002, two patients were diagnosed as relapse; a relapse rate of 0.07 per 100 person years follow-up. Both patients were males, who had Dapsone monotherapy prior to MDT and had received Regimen B.

The first patient relapsed 15 yrs after RFT. He was diagnosed as LL in 1976 and was initiated on monotherapy, which he took regularly until 1982. In 1982, he was inducted into the WHO MDT trial. His initial bacterial index (BI) in 1976 was 3.50+ and his BI just prior to initiation of MDT had come down to 2.0+. Subsequent to treatment with MDT, he became negative after 4 yrs of MDT in 1986. He was RFT in 1987 and was followed up annually for 9 yrs, until 1996. He remained negative till then. During the follow-up in 2002, he was found to have new skin lesions that showed signs of activity and on smear examination had an average BI = 1.3+ at routine sites and 4.0+ at selective sites. He was diagnosed as

TABLE 3. Relapses.

S.No.	Sex	Initial type	Initial BI	Duration of mono	Duration MDT	Time of relapse after RFT	BI at relapse
1	M	LL	3.50	6	5	15 years	Routine 1.0 Selective 4.0
2	M	LL	3.25	15	2	14 years	Routine 1.0 Selective 5.0

relapse and restarted on MDT. The mouse footpad inoculation detected viable bacilli in T900_r mice and they were sensitive to all MDT drugs.

The second patient relapsed 14 yrs after RFT. He was diagnosed as LL in 1967 when he was 9 years old, and was initiated on Dapsone monotherapy, which he took regularly for 15 yrs. His initial BI prior to monotherapy was 3.25, which came down to 0.8 in 1982, when he was inducted into the WHO MDT trial. Two years after MDT, he became smear negative in 1984 and was RFT. Annual assessments were done for 11 yrs after RFT until 1995. In 1998, he voluntarily presented with active skin lesions and a smear examination revealed an average BI of 1.0+ in routine sites and 5.0+ at selective sites. Mouse footpad inoculation was not done on this patient. He was diagnosed as relapsed and restarted on MDT. He became smear negative after 2 yrs.

DISCUSSION

As in the case of other infectious diseases, the relapse rate is a crucial parameter in assessing the long-term efficacy of chemotherapy. The relapse rate after WHO recommended MDT regimens is generally accepted to be low. A WHO questionnaire survey reported that the cumulative risk of relapse was 0.77% for multi-bacillary (MB) leprosy patients, 9 yrs after stopping MDT (²²). Other follow-up studies have reported relapse rates varying from less than 1% to 20.0% (^{5, 12, 15}). The AMFES study reported no relapses after a mean duration of follow-up of 5 yrs (⁹), and a more recent paper reported no relapses after a follow-up of 13 yrs. (¹⁶).

In this study, 173 smear positive patients were followed up, twenty years after they were initiated on MDT. The mean duration of follow-up was 16.4 ± 1.83 yrs after RFT, which perhaps is the longest follow-up of a

cohort of MB patients reported. The relapse rate in this study is 0.07 per 100 person years follow-up, which is lower than the acceptable relapse rate of 1.0 per 100 person years and relapse rates reported in other studies (¹⁵). Nevertheless, three important aspects need to be considered while interpreting these findings. Firstly, the two patients who relapsed had 6 and 15 yrs of monotherapy prior to being initiated on MDT. Secondly, patients in this trial were treated for a minimum period of 2 yrs or until smear negativity, whichever occurred later. Thirdly, the patients not followed up, were significantly different from those followed up, in terms of more males, LL and higher BI at induction. Thus this cohort may not represent the untreated new patients currently being treated with WHO-MDT recommended regimens.

It is known that the rate of relapse is governed by two factors; namely, the high initial bacterial load and the long period of follow-up (⁷). The initial bacterial load before and at RFT is noted to be closely correlated to the risk of relapse. Among patients with an initial BI of $\geq 4.00+$, the relapse rate was reportedly 38.9% as compared to no relapses among those with an average BI of $< 4.00+$ (¹²). In another study of patients treated up till smear negativity, a higher relapse rate of 1.27 per 100 person years was observed among patients with a initial BI of $\geq 4.00+$ as compared to 0.46 per 100 person years among patients with a initial BI of $< 4.00+$ (¹⁰). In the present study, patients who relapsed had a high initial BI of 3.25 and 3.50 prior to monotherapy. They continued to be positive with BI = 0.8+ and 2.0+ when they were recruited into the trial. In contrast, only a few relapses have been reported among patients with a high initial bacterial index treated with fixed duration therapy (FDT) (^{9, 14, 17}). However, the low relapse rates among these patients with a high bacterial index

could be attributed to the relatively short duration of follow-up.

Relapses after treatment with rifampicin containing regimens are said to occur late, usually more than 5 yrs after RFT^(8, 12, 15, 19), and therefore it is considered necessary that patients should be followed for a minimum of 7 to 10 yrs after completion of treatment^(4, 8). This contrasts with information from certain authors that 75% of relapses occurred during the first 4 yrs after completion of treatment and also that annual risk of relapse does not increase with time⁽⁶⁾.

The patients who relapsed in this cohort had a long duration of follow-up after MDT before being diagnosed as having a relapse. An earlier paper reported no relapses after following a subset of patients from the same cohort for 13.7 ± 1.4 yrs⁽¹⁶⁾. Both relapses reported in the present study had dapsone monotherapy prior to MDT and hence were not reported in the above paper. Relapses may be either due to persisters or reinfection⁽¹⁹⁾. In the absence of any method to prove reinfection, it is reasonable to assume that both the relapses reported are due to persisters; however, reinfection in these patients cannot be ruled out.

Relapse was diagnosed in both the patients 15 and 14 yrs after RFT underlining the importance of continued surveillance after RFT, at least in those patients with an initial high bacillary index. However, in spite of a field program wherein long-term surveillance after RFT was possible, more than 50% of the initial cohort was lost to follow-up due to deaths and migration. Thus long-term follow-up may not be cost-effective or feasible and education of the patient to report soon after appearance of new skin lesions may perhaps be the best option in the integrated setting.

Acknowledgment. The authors gratefully acknowledge the contributions made by the late Dr. Melville Christian, late Dr. Kumar Jesudasan, Dr. V. Pannikar, Dr. Vijaykumaran, and Dr. Manimozhi. The authors thank Dr. P. S. S. Sundarao and Dr. Abraham Joseph for their encouragement and support. The authors appreciate the untiring efforts of Mr. P. Samuel, Mr. Raja Samuel, Mr. S. Vincent, Mr. P. Dorairaj, and other field staff. The field trials of Combined therapy in lepromatous leprosy received financial support from the UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases.

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