INTERNATIONAL JOURNAL OF LEPROSY

Volume 52, Number 3
Printed in the U.S.A.

Relapse Rates Among Nonlepromatous Patients Released from Control[1]

Kumar Jesudasan, Melville Christian, and David Bradley[2]

This study is a follow-up of 1701 nonlepromatous patients on dapsone monotherapy who were released from control and was done with data collected from the Schieffelin Leprosy Research and Training Centre, Leprosy Control Area of Gudiyatham Taluk, India. This area has been previously described by Karat, *et al.* ([8]).

A summary of the literature on relapse rates (RR) in patients with nonlepromatous leprosy (NL) treated with sulfones is given in Table 1. Choudhury, *et al.* ([3]) and Parikh, *et al.* ([11]) discussed the various criteria used for releasing patients from control. The World Health Organization (WHO) ([16–18]) also has given guidelines on release from control of patients on dapsone monotherapy.

MATERIALS AND METHODS

Since 1975, NL patients with indeterminate (Ind), tuberculoid (TT), and borderline tuberculoid (BT) leprosy have been assessed for inactivity using the same criteria as WHO ([16]). (Borderline borderline and borderline lepromatous patients were not included in this study.) After inactivity, dapsone (DDS) monotherapy (same dosage of dapsone) was continued for an additional two years or a total recommended minimum period of treatment of 4½ years (234 weeks of dapsone therapy), whichever was greater. The patients were then released from control (RFC), providing the disease had shown no signs of activity over the period of maintenance therapy and at the time of RFC. The Mitsuda lepromin test was done but the results did not influence the decision on RFC. A lepromin reading of more than 5 mm after four weeks was considered as positive. A skin smear was also done at the time of RFC and only skin-smear negative patients were released from control.

Patients who had been released from control were re-examined during the period September 1979 to March 1980, and a skin smear was taken at that time. Patients who had relapsed were classified using the Ridley and Jopling ([12, 13]) classification with the inclusion of indeterminate (Ind) leprosy as suggested by Job and Chacko ([6]). The classification used was primarily clinical and bacteriological; histopathology was only used if there was a doubt in the diagnosis or classification of relapse.

Statistical tests used for analysis. For comparision of frequencies in 2 × 2 tables the ordinary Chi-square test and the Fisher exact test were used ([1]). For comparison of rates, using person years of risk, the Chi-square test for person years of risk and an "exact" test using the binomial distribution were used. In order to test the statistical significance of observed trends, the Chi-square test for trends was used (P. Smith and T. Marshall, 1982, personal communication).

RESULTS

There were 2027 patients who had been released from control (RFC) at the beginning of the study. During the follow-up it was found that 57 patients (2.8%) had died and 179 (8.8%) had permanently left the area. Of the remaining 1791 patients, 89 were still living in the area but could not be seen because they were temporarily away. One patient refused to be examined. The remaining 1701 patients, who comprised 95% of those who could possibly be seen, were re-examined. They contributed a total of 5254 person years of risk (PYR). There were 51 patients who had relapsed (3%),

[1] Received for publication on 31 October 1983; accepted for publication on 31 January 1984.

[2] K. Jesudasan, M.B.B.S., D.T.P.H., Ph.D., Epidemiologist; M. Christian, M.B.B.S., D.T.M.&.H., Dip. Epid. (Prague), Head, Department of Epidemiology and Leprosy Control, Schieffelin Leprosy Research and Training Centre, Karigiri, Tamil Nadu 632106, South India. D. Bradley, M.A., D.M., M.R.C.Path., F.I.Biol., F.F.M.L., Director, Ross Institute, London School of Hygiene and Tropical Medicine, London WC1E, 7HT, U.K.

TABLE 1. *Summary of literature on relapse rates among nonlepromatous leprosy patients.*

Year	Author (Ref. no.)	No. patients in group	No. followed	Type of leprosy	Overall % relapses	Relapse rate/1000 PYR
1958	Davey (4)	631		NL[a]	6	
1965	Browne (2)			TT[b]	0.9	
				AC[c]	5	
1968	Kandasamy (7)	10,000		NL	4	
1974	Ramu (11)		170	BOR[d]	7.6	
1978	Vellut (15)		7700	TT	0.5–2.5	
1979	Touw-Langendijk (14)	678	105	TT	14	
				BT	15	
1979	Neelan (9)	209	174	NL		39
1979	Ekambaram (5)	4990	1879	NL 1 pat.[e]	1.6	
				NL mul.[f]	2.5	

[a] NL = nonlepromatous.
[b] TT = tuberculoid.
[c] AC = all classifications.
[d] BOR = borderline.
[e] NL with one patch.
[f] NL with multiple patches.

giving an overall relapse rate (RR) of 9.7 per 1000 PYR. (All relapse rates are given per 1000 person years at risk.)

Relapse rates by age, sex, and classification of patients (Table 2). The age used in these calculations was the age at the time of RFC; the age-specific relapse rates did not significantly differ. TT patients had a RR of 8.2, Ind patients had a RR of 11.9, and BT patients had a RR of 17.4 per 1000 PYR. Lepromin-positive TT patients had a significantly lower RR than lepromin-negative Ind, lepromin-negative TT, and lepromin-negative BT patients. Lepromin-positive BT patients had a significantly lower RR than lepromin-negative TT patients. Male patients had a higher RR as compared with females (11 vs 8, Table 3). Lepromin-positive females overall had a significantly lower relapse rate than lepromin-negative females and lepromin-negative males.

Lepromin-negative females in the age group 16–25 had significantly higher RR than females in all the other age groups. This is probably related to pregnancy and childbirth. Indirect standardization was done for age, sex, and classification, however it did not significantly influence the results.

TABLE 2. *Relapse rates by type of leprosy and lepromin.*

Lepromin		Type of leprosy			Total
		Ind.	TT	BT	
Positive	No. relapses	2	13	3	18
	No. RFC patients	179	711	71	961
	Person years at risk	543	2033	201	2777
	Relapse rates/1000 PYR	3.6	6.4	14.9	6.4
Negative	No. relapses	9	19	4	28
	No. RFC patients	125	355	54	534
	Person years at risk	427	1257	169	1853
	Relapse rates/1000 PYR	21.1	15.1	23.7	15.0
Total[a]	No. relapses	13	30	7	50
	No. RFC patients	341	1182	136	1659
	Person years at risk	1191	3673	403	5167
	Relapse rates/1000 PYR	11.9	8.2	17.4	9.7

[a] Includes patients whose lepromin status is not available.

TABLE 3. *Relapse rates by age, sex, and lepromin status.*

Age group		Male		Female		Total
		L−[a]	L+[b]	L−	L+	
11–15	No. relapses	3	1	2	0	7
	No. RFC patients	44	65	22	43	203
	Person years at risk	154	177	73	95	592
	Relapse rates/1000 PYR	19.5	5.6	27.4	0	11.8
16–25	No. relapses	5	5	4	1	17
	No. RFC patients	64	109	28	56	347
	Person years at risk	216	497	99	133	1080
	Relapse rates/1000 PYR	23	10	40	7.5	15.7
≥25	No. relapses	8	7	7	4	27
	No. RFC patients	173	328	212	319	1129
	Person years at risk	578	962	737	932	3819
	Relapse rates/1000 PYR	13.8	7.2	9.5	4.2	7.6
Totals L−, L+	No. relapses	16	13	13	5	
	No. RFC patients	284	572	266	409	
	Person years at risk	957	1662	920	1162	
	Relapse rates/1000 PYR	16.7	7.8	14	4.3	
Totals[c] Male, Female	No. relapses	32		19		51
	No. RFC patients	942		759		1701
	Person years at risk	2891		2363		5254
	Relapse rates/1000 PYR	11		8		9.7

[a] Lepromin negative.
[b] Lepromin positive.
[c] Includes patients whose lepromin status is not available. Details of the ages of 22 patients are missing.

Time trends in relapse rates (Table 4). The overall relapse rate increased up to a maximum of 13.6 in the second year and then tended to taper off. Of the patients who relapsed, 96% did so within three years of RFC. The fall in the RR of lepromin-negative patients reached statistical significance at the 5% level.

Relapse rates by percentage of attendance during whole course of treatment (Table 5). As the percentage of overall attendance increased, the RR decreased. Lepromin-negative patients with an attendance of less than 51% had a significantly higher relapse rate than: a) the lepromin-positive patients with an attendance of less than 51%, b) those with an attendance between 51–75%, and c) those with an attendance of over 75%.

Relapse rate by deformity grade (Table 6). Using the deformity grade as formulated by WHO ([16]), it was seen that each patient

TABLE 4. *Relapse rates by lepromin status and time trends.*

Lepromin	Year of follow-up (rate)					Total
	1	2	3	4	5–7	
Positive	8/981[a] (8.2)[b]	7/813 (8.6)	2/587 (3.4)	0/355 (0)	1/88 (11.4)	18/2824 (6.4)
Negative	12/550 (21.8)	11/517 (21.3)	5/454 (11.0)	1/313 (3.2)	0/43 (0)	29/1877 (15.5)
Totals[c]	22/1701 (12.9)	20/1476 (13.6)	7/1148 (6.1)	1/751 (1.3)	1/178 (5.6)	51/5254 (9.7)

[a] Number of relapses/person years at risk.
[b] Relapse rate/1000 person years at risk.
[c] Includes patients whose lepromin status is not available.

TABLE 5. *Relapse rates by percentage of attendance and lepromin status.*

Lepromin	% attend.	No. relapses	No. in group	PYR	RR/ 1000 PYR
Positive	0–50	7	394	1163	6.0
	51–74	6	284	811	7.4
	75–100	5	303	850	5.9
Negative	0–50	14	185	622	22.5
	51–74	9	175	608	14.8
	75–100	6	190	647	9.3
Total[a]	0–50	25	653	2034	12.3
	51–74	15	507	1568	9.6
	75–100	11	541	1652	6.7

[a] Includes patients whose lepromin status is not available.

TABLE 6. *Relapse rates by deformity grade.*

Deformity grade[a]	No. relapses	No. patients	PYR	RR/ 1000 PYR
0	40	1405	4377	9.0
1	2	51	161	12.4
2–15	9	245	716	12.6

[a] WHO deformity grade (see text).

could have a maximum deformity grade of 15 (3 × the five regions). In this analysis the deformity grades from the different regions were added up and re-grouped. The first group consisted of patients with no deformity, the second group had only sensory loss in any one region (total cumulative grade of 1), and the third group consisted of patients with a cumulative total between 2 and 15. Overall, patients with deformities did not have a significantly higher RR than did patients with no deformities.

Relapse rate by number of patches at time of registration and lepromin status (Table 7). The RR increased with the number of patches. Lepromin-positive patients with a single patch had a statistically significantly lower relapse rate than: a) patients with 2–4 patches ($p < 0.05$); b) lepromin-negative patients with 2–4 patches ($p < 0.05$); and c) lepromin-negative patients with 5 or more patches ($p < 0.05$).

Relapse rates by duration of treatment (Table 8). Some patients had been on treatment since 1962, and 112 (6.6%) of the patients had had only 4–4½ years of treatment by method one (see below). Thus, at the time of RFC the patients had been on treatment for between 4–18 years. The duration of treatment was calculated in two ways: The first method gives the actual duration of treatment received, which is the number of weeks of treatment the patient actually received. In the second method, the duration of treatment was calculated as the period between the date of registration of the patient and the date of RFC. The duration of treatment varied a great deal. However, the differences in the relapse rates were not statistically significant.

Analysis of smears taken at follow-up examination. Of the 1701 patients in the study, the skin smear results were available for 1317 patients (77.4%). This included all of the 51 patients who relapsed. Only ten of the patients (all relapses) were skin-smear positive for acid-fast bacilli at the time of follow-up, and these ten patients were lepromin negative at the time of RFC. Only one of these ten patients (who had a bacterial index of 1) did not show any clinical evidence of relapse and was diagnosed to have relapsed on bacteriological evidence alone. All of the other patients who relapsed were diagnosed on clinical grounds.

Analysis of 326 patients not seen. The data on these groups were analyzed separately in order to study the possible biases that not seeing them would create. Detailed analysis failed to show any such bias.

DISCUSSION

The results showed that some of the observed differences in the relapse rates in the study were statistically significant (p was less than or equal to 0.05). Many of the differences in the relapse rates were substantial. For example, BT patients had more than double the relapse rate as compared with TT patients (8.2 vs 17.4 per 1000 PYR), but this difference was not statistically significant. The reason for this is the small sample size in the various subgroups.

Lepromin-positive TT patients (lepromin done at time of RFC, lepromin test was not done at registration) had a significantly lower RR when compared with lepromin-negative TT, Ind, and BT patients ($p < 0.05$). Thirteen TT patients who were lep-

TABLE 7. *Relapse rates by lepromin status and number of patches.*

Lepromin status		Number of patches		
		1	2–4	≥5
Positive	No. relapses	5	7	4
	No. RFC patients	393	252	115
	Person years at risk	1122	734	331
	Relapse rates/1000 PYR	4.5	9.5	12.1
Negative	No. relapses	7	11	4
	No. RFC patients	195	153	65
	Person years at risk	671	535	217
	Relapse rates/1000 PYR	10.4	20.6	18.4
Total[a]	No. relapses	13	19	9
	No. RFC patients	663	447	197
	Person years at risk	2048	1405	598
	Relapse rates/1000 PYR	6.3	13.5	15.0

[a] Includes patients whose lepromin status is not available.

romin positive relapsed, but none of the 120 patients with a lepromin reading of over 10 mm or in whom the lepromin test ulcerated, relapsed. Thirty-three percent of TT patients were found to be lepromin negative. Polar TT patients are supposed to always be lepromin positive. If this is so, then the patients who were lepromin negative are more likely to be Ind or BT patients, wrongly classified clinically as TT, and the 700 lepromin-positive TT patients can be considered as the true polar TT patients. The problems of clinical classification under field conditions, changes in the criteria for classifications over time, and biases involved are other possible explanations. Thus, a lepromin test done at the time of registration will probably help in a more acurate classification and will serve as a better predictor of the risk of relapse.

These findings suggest that a period of follow-up of three years could result in detection of over 80% of the relapse cases that occur in the first seven years. It is unlikely that a special follow-up program is necessary. At the time of RFC, all patients should be educated about the risk of relapse and the need to report back if any new lesions develop. Patients who have a higher risk of relapse, such as those with an attendance of 50% or less, whose lepromin was negative, and those patients with multiple patches, could be selectively followed up if thought necessary.

Patients with deformities can continue to be released from control so long as the patients continue to receive care. "RFC does not mean release from *care,* and many patients with deformity will continue to need long-term supportive care, especially in the field of disability limitation, foot wear, and rehabilitation" (E. P. Fritschi, personal communication).

The relapse rates increased proportion-

TABLE 8. *Relapse rates by method and duration of treatment.*

Years of treatment	Method 1—RR by actual duration of treatment				Method 2—RR by total duration of treatment			
	No. relapses	No. in group	PYR	RR/ 1000 PYR	No. relapses	No. in group	PYR	RR/ 1000 PYR
4–4.5	3	116	367	8.2				
4.5–5.5	14	437	1275	11.0	0	74	197	0
5.5–8.5	28	920	2959	9.5	17	655	2028	8.4
>8.5	6	227	651	9.2				
8.5–10.5					26	705	2311	11.3
>10.5					8	267	718	11.1

ally to the increase in the number of patches. This suggests that the greater the number of patches, the more serious the disease process. The findings also suggest that duration of therapy between 4.5 to over 10.5 years with dapsone did not significantly influence the relapse rate.

The relapse rates in the NL patients studied were significantly influenced by the lepromin reaction, the number of patches, and attendance. In planning criteria for the RFC of patients, obviously, if possible, one should aim at a zero relapse rate. However, in large-scale leprosy control programs, one has to consider the costs and benefits of continuing therapy against the benefits of releasing patients from control, decreasing the total patient load, and better care for those under treatment. WHO ([17, 18]), in its recommendations for the release from control of NL patients on dapsone monotherapy, takes into consideration only the classification of the patient and recommends different durations of treatment for the various types. The present study indicates that the duration of therapy (>4½ years) per se will not significantly influence the relapse rates, and that clinical classification under field conditions tends to be unreliable. Based on the findings of this study, classification along with the lepromin status, the number of patches, and the regularity of attendance are probably better indicators of the risk of relapse in NL patients, and should be taken into consideration in determining chemotherapeutic regimens, including those with multiple drugs.

These results also indicate that in NL patients dapsone is an excellent drug which gives relatively few relapses (3% overall). One is aware that shortening considerably the period of chemotherapy (as suggested by WHO[19]) for NL patients could result in the saving of a lot of time, energy, and resources in the field of leprosy. However, carefully planned studies are necessary to evaluate the best schedule of treatment, using short-term chemotherapy with multiple drugs. Much of the confusion in the literature regarding the use of dapsone is because of the lack of adequate data to evaluate the efficacy of dapsone monotherapy, even though it has been used for over 30 years. These studies should be carefully done in selected centers at first. Their results should be evaluated before widespread use of multiple drugs in the treatment of nonlepromatous leprosy can be recommended for routine use.

SUMMARY

A total of 1701 nonlepromatous patients treated with dapsone monotherapy for at least 4½ years and released from control were followed up and examined for evidence of relapse. They contributed a total of 5254 person years of risk, and there were 51 relapses (3%), giving an overall relapse rate of 9.7/1000 person years of risk. This paper examines the effect of various factors on the risk of relapses, such as age, sex, and classification of the disease; duration and regularity of treatment; percentage of attendance; deformity grade; number of patches and lepromin status. Some of the factors studied, such as age, sex, classification, percentage of attendance, and the number of patches in association with the lepromin status, were found to significantly influence the risk of relapse in these patients. Therapy in nonlepromatous leprosy is discussed in light of these findings.

RESUMEN

Se hizo el seguimiento clínico de 1701 pacientes no lepromatosos tratados solo con dapsona por 4½ años y después liberados del tratamiento, para establecer la incidencia de recaídas. Ocurrieron 51 recaídas (3%), dando una incidencia global dentro de la población en riesgo, de 9.7/1000 personas año. En el trabajo se examina el efecto sobre el riesgo, de factores tales como la edad, el sexo, la clasificación de la enfermedad, la duración y regularidad del tratamiento, el porcentaje de asistencia a las instituciones de salúd, el grado de deformación, el número de manchas y la reactividad a la lepromina. Alqunos de los factores estudiados (edad, sexo, clasificación, porcentaje de asistencia al médico, número de manchas y reactividad a la lepromina) influyeron significativamente en el riesgo de recaída en estos pacientes. En base a los hallazgos se discute la terapia de los pacientes con lepra no lepromatosa.

RÉSUMÉ

On a suivi et examiné en vue de mettre en évidence des récidives, un total de 1701 malades nonlépromateux traités par la monothérapie à la dapsone pendant au moins 4½ ans, et libérés des contrôles. Ce groupe représente un total de 5254 personne-années de risque. On a observé 51 récidives (3%), ce qui donne un taux de récidive global de 9.7/1000 personne-années de risque. Cet article examine l'effet de divers facteurs sur le risque de récidive, tel que l'âge, le sexe, le type de la maladie; la durée et la régularité du traitement; l'as-

siduité au traitement; le degré des mutilations; le nombre de macules et le status lépromínique. Certains des facteurs étudiés, comme l'âge, le sexe, le type de la maladie, le pourcentage d'assiduité, et le nombre de macules associé au statut lépromínique, influençaient significativement le risque de récidive chez ces malades. La thérapeutique de la lèpre nonlépromateuse est discutée à la lumière de ces observations.

Acknowledgments. We wish to express our thanks to Dr. E. P. Fritschi and all the staff at the Schieffelin Leprosy Research and Training Centre who helped in this project. Our thanks to Mr. Kanagaraj, the team of paramedical workers, and especially all the staff of the Department of Epidemiology and Leprosy Control for helping in this project. Our sincere thanks to Mr. A. K. Askew and The Leprosy Mission for all of their help and financial support. Our thanks to Professor Muthukrishnan, Mr. Srinivasan, Mr. Kannan, and Mr. Gnanaraj of the Indian Institute of Technology at Madras, who helped in the data processing and analysis. We express our sincere appreciation to Dr. P. E. Fine who helped in the planning of the study and the analysis of the data. We wish to thank all the staff of the Ross Institute, especially Mrs. J. Clarkson, and the staff of the Tropical Epidemiology Unit, especially Dr. P. G. Smith, Mrs. D. Carson, and Mr. T. Marshall, for their assistance with the analysis of the data. We also wish to thank Mr. N. Christopher and Mr. Lewis Kumar for the secretarial help.

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