Risk of relapse among non-lepromatous patients released from treatment after dapsone monotherapy

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Summary   Information on 14,625 non-lepromatous patients released from treatment after dapsone monotherapy and followed up to a maximum of 15 years at the ILEP project, Dharmapuri, India, was analysed to study the pattern of relapses. The overall relapse rate was 5/1000 person years. Males had a higher relapse rate than females. The risk of relapse increased with age, number of lesions and duration of treatment. The risk for relapse remained constant over several years after release from treatment. Even though the absolute risk for relapse after MDT may be different, the pattern of relapses and the factors affecting it may be similar to what has been shown in this study.

Introduction

With the introduction of multidrug therapy the prevalence of leprosy cases requiring treatment has reduced in many endemic districts of India. Paucibacillary cases are being maintained under surveillance for 2 years after treatment, for the early diagnosis of treatment failures, relapses and reactions. There are also a large number of non-lepromatous patients who have been released from treatment after dapsone monotherapy. At present there is very little information on their long term risk for relapse. Further, identification of factors which modify the risk for relapse following dapsone monotherapy, may facilitate the planning of follow-up procedures for patients released after MDT. With this in view a historical cohort study was carried out at the ILEP Leprosy Control project at Dharmapuri, Tamil Nadu, India, to measure the relapse rates among non-lepromatous patients treated with dapsone monotherapy and factors affecting the risk for relapse.

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Background information

The ILEP programme at Dharmapuri was started in 1968 by the Damien Foundation. It was covering a population of 1 million when the project was handed over to the Government of Tamil Nadu in 1985. Throughout this period the unit had maintained a high level of efficiency in leprosy control work and documentation. The population covered by this unit was essentially rural. The control work was based on the guidelines suggested by the National Leprosy Control Programme. Cases were classified into 'N', 'N?L' and 'L', according to the practice prevalent at that time. 'N' included TT and early BT cases and 'N?L' included the more advanced BT and BB. BL and LL cases were put under 'L'. Apart from this, bacteriologically negative cases with macular lesions were classified as 'I'. This probably included a wide range of cases. Polyneuritic cases were classified as 'P'.

Until 1971 dapsone was administered in gradually increasing doses up to a maximum of 300 mg per week for adults; children received half that dose. From 1972 this practice of gradually increasing the dose was given up and the maximum dose was increased to 400 mg per week. From 1975 the dose of dapsone was further increased so that the adults received a maximum of 700 mg per week. Patients were declared inactive when the lesions had disappeared, or when a previously raised lesion had become macular or wrinkled in the absence of any evidence of neuritis.

After inactivity, non-lepromatous patients were maintained on the same dose of dapsone for a period of $1\frac{1}{2}$ to 5 years, wherever possible, before being declared as released from treatment (RFT). These patients were indefinitely followed up during the annual 'known case verification'. The treatment cards contained all the relevant information including details regarding relapses. The criteria for relapse were the following:

(a) Evidence of recurrence of activity in the old lesion;
(b) Appearance of a new lesion;
(c) Evidence of new nerve involvement.

All relapses were seen and confirmed by a medical officer.

Methodology

All non-lepromatous patients released from treatment from 1968 to 1985 were included in the study. Those who were known to have left the area or died were excluded. The individual treatment cards were reviewed carefully and information regarding personal characteristics, nature and extent of the disease, number of weeks of treatment, date of RFT and date of relapse (if relapsed) were extracted. The duration of treatment was calculated from the information on the number of weeks for which treatment was administered to the patients. The information was fed into a computer and analysed using SPSS PC.

Relapse rates were calculated as

$$= \frac{\text{No. of relapses} \times 1000}{\text{No. of person years of follow-up}}.$$

Cases were assumed to have been released from treatment uniformly throughout the year, thus contributing on average half a person year of observation each, during the calender year of RFT. Risk of relapse and cumulative risk for relapse were calculated using the actuarial method. Since cases who had died or left the area were excluded from the study, all the withdrawals were due to censoring caused by the study. Hazard ratios for relapses were calculated based on Cox's proportional hazards model using EGRET.

Results

Of the 14,889 records examined 264 had to be excluded due to incompleteness of information. The remaining 14,625 patients had been followed up for a maximum period of 15 years (mean = 5·2 years; SD = 3·3 years) after RFT. There were 387 relapses during 75,916·5 person years of follow-up giving an overall relapse rate of 5·1/1000 person years.

As shown in Table 1 the relapse rates were lowest for the 'N' type (4·6/1000 per year). 'N?L' and polyneuritic cases had similar relapse rates. Indeterminate cases had the highest relapse rates (24/1000). The differences in relapse rates between 'N' and other types were statistically significant ($P < 0.05$). Relapse rate among males was 80% higher than that among females (Table 2) ($P < 0.001$). Relapse rates appeared to increase with age at diagnosis until 30 years (Table 3). After that the relapse rate showed a fall. A similar trend was noticed when relapse rates were analysed according to age at RFT (Table 4). Relapse rate tended to increase with duration of treatment (Table 5). When the relapse rates were examined according to the three different periods with different treatment schedules, no significant differences were noticed (Table 6).

Relapse rates increased with the number of patches at the time of diagnosis (Table 7).

Table 1. Relapse rates according to type of leprosy

Type	No. of cases	Person years of follow-up	Relapse	Rate/1000 PY
N	13,395	71,620·5	331	4·62
N?L	727	1,509·5	20	13·24
Polyneuritic	459	2,619·5	32	12·21
I	44	167·0	4	23·95
	14,625	75,916·5	387	5·1

Table 2. Relapse rates by sex

Sex	No. of patients	Person years	No. of relapses	Rate/1000 PY	P
Female	7,085	38,092·5	139	3·65 ⎱	<0·001
Male	7,540	37,824·0	248	6·56 ⎰	
	14,625	75,916·5	387	5·1	

Table 3. Relapse rates by age at diagnosis

Age in years	No. of patients	Person years	No. of relapses	Rate/1000
1–10	2,564	15,616	40	2·56
11–20	2,264	12,325	72	5·84
21–30	2,285	11,553·5	86	7·44
31–40	3,203	16,343·5	112	6·85
41 & above	4,309	20,078·5	77	3·83
	14,625	75,916·5	387	5·1

Table 4. Relapse rates by age at RFT

Age at RFT	No. of patients	Person years	No. of relapses	Rate/1000
1–10	480	3,751·0	7	1·87
11–20	3,237	19,508·5	65	3·33
21–30	1,758	8,551·0	62	7·25
31–40	2,605	13,795·5	104	7·54
41 & above	6,545	30,310·5	149	4·92
	14,625	75,916·5	387	

Table 5. Relapse rates by duration of treatment

Duration of treatment in years	No. of patients	Person years	No. of relapses	Rate/1000	P
Up to 3	7,616	43,413·0	174	4·0 ⎫	<0·05
4–5	4,047	19,398·5	107	5·5 ⎬	<0·01
6 & above	2,962	13,105·0	106	8·1 ⎭	
	14,625	75,916·5	387		

Table 6. Relapse rates according to the period of registration

Period of registration	Person years	No. of relapses	Relapse rate	P
1968–1971	49,821·5	255	5·1 ⎫	NS
1972–1974	14,691·0	82	5·6 ⎬	NS
1975–1984	11,404·0	50	4·4 ⎭	
	75,916·5			

Table 7. Relapse rates by number of patches

No. of patches	No. of patients	Person year	No. of relapses	Rate/1000*
1	6,797	38,062·5	127	3·34
2–3	3,872	21,026·0	96	4·57
4–6	1,513	7,089·0	52	7·34
7–10	736	3,094	28	9·05
> 10	1,248	4,025	52	12·92
	14,166†	73,297·0	355	

* χ^2 for trend = 89·3; $P < 0·001$.
† 459 polyneuritic cases were excluded from this analysis.

Graph 1 shows the cumulative risk of relapse according to the number of patches. For patients with more than 10 patches the probability of relapse by the 7th year was 10%.

The annual risk of relapse after RFT was stable at around 5/1000 during the first 7 years. There was a slight decrease in the relapse rate after 7 years (Table 8). This fall is to be expected since there were hardly any cases with more serious forms of disease who had been followed up for more than 7 years.

The effect of the number of patches, duration of treatment and age at diagnosis on the risk for relapse were examined by doing survival analysis using Cox's proportional hazards model for males and females separately (Appendix I & II). The relative risk for relapse increased with the number of patches and duration of treatment as seen in the univariate analysis. However, the relative reduction in the risk for relapse after age 30, seen in the univariate analysis, disappears when adjustments are made for the number of patches and duration of treatment. Thus the risk for relapse tends to increase with the age of the patient at detection. The pattern was similar when age at RFT was entered into the model instead of age at detection.

Table 8. Risk of relapse by year of follow-up

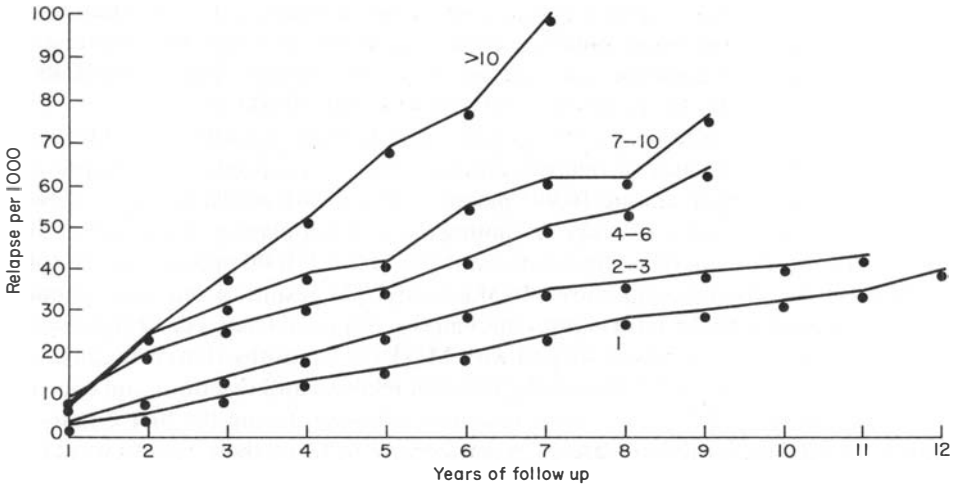| Years after RFT	No. starting the period	Relapse	Withdrawals during the year	Risk/1000	Cumulative probability of relapse/1000
1	14,625	64	1,385	4·59	4·6
2	13,176	78	1,393	6·25	10·8
3	11,705	66	1,476	6·02	16·7
4	10,163	50	1,361	5·27	21·9
5	8,752	40	1,891	5·12	26·9
6	6,821	33	1,581	5·47	32·3
7	5,207	27	1,085	5·79	37·9
8	4,095	11	1,072	3·091	40·9
9	3,012	9	563	3·30	44·1
10	2,440	4	485	1·82	45·9
11	1,951	3	1,085	2·13	47·9
12	863	2	511	3·30	51·0
13	350	—	285	—	—
14	65	—	61	—	—
15	4	—	—	—	—

Figure 1. Cumulative risk of relapse (per 1000) according to year of follow-up by number of patches.

Discussion

The annual risk of relapse following RFT appears to remain steady for 7–9 years at about 5 per 1000. Jesudasan[1] studied relapse rates according to the time after RFT and reported the relapse rates to be about 13/1000 for the first 2 years and about 5/1000 subsequently. The design of that study varied from the present one, in that, there was a one time special verification of all RFT cases. Neelan[2] had reported that relapse after RFT remained the same over the first $4\frac{1}{2}$ years of follow-up. This study suggests that the phenomenon of relapse occurs relentlessly for fairly long periods after releasing from treatment which is incompatible with the concept of median incubation period of $3\frac{1}{2}$ years suggested by Pattyn.[3]

The finding that the males had a higher rate of relapse was similar to what has been reported by Jesudasan. One possible reason for this could be differential surveillance. On the other hand this finding is consistent with the reduced risk of disease and higher rate of remission[2] that women seem to enjoy.

The striking association between the risk for relapse and the number of patches is consistent with the findings from other studies.[1,2]

The effect of age on the relapse rate could be a function of the severity of the disease, since with increasing age at detection the severity also increases incipiently. Similarly the duration of treatment could be a surrogate for severity of disease. Patients whose lesions took a longer time to resolve could have received longer duration of treatment. Thus it appears possible that the duration of time taken for the resolution of lesions may be related to the risk of relapse.

The overall absolute risk for relapse per year is only about 5/1000 in this group and could be considered a conservative estimate. Maintaining all patients under active surveillance may not be cost effective. On the other hand it may be worthwhile following up individuals with multiple lesions since the risk of relapse is quite high even if they have had prolonged treatment.

Though, these results are based on the analysis of secondary data, they should reflect the load of relapses that occur during routine field work. It is difficult to estimate the proportion of dapsone-resistant cases among them. An average control unit of 400,000 population in a hyperendemic district may have about 10,000 known cases of non-lepromatous leprosy, released after treatment with dapsone monotherapy. One should expect to get about 50 cases of relapses annually from this population. Chopra *et al.*[4] reported 21 relapses from among 10,995 patients treated with paucibacillary regime and followed up to a maximum of 4 years. Assuming that this population yielded about 21,000 person years of follow-up the relapse rate would be about 1/1000 person years of follow-up, which is lower than the one shown by this study. The results of our study cannot be directly compared with the information on relapses, obtained from a careful prospective follow-up of paucibacillary cases treated with MDT for 6 months. This is because of the difficulties one may face in distinguishing between relapses and reactions and because of the well-known fact that risk for these reactions is higher during the first 2 years after initiation of treatment. In the case of monotherapy most of these events would have occurred during therapy and not after release from treatment. Similarly, frequent and careful follow-up may yield a larger number of events related to changes in the nature and extent of the patches which, probably would be missed, during routine surveillance.

Even though there is a problem of comparing absolute rates of relapses between a historical cohort study and a concurrent cohort study, the pattern of relapses and the factors that modify the risk of relapse are likely to be similar for both those treated with monotherapy and MDT. Further, as shown in this study, the risk of relapse may remain constant over a long period of time after releasing from treatment.

Acknowledgments

References

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Appendix I

Effect of age, number of patches and duration of treatment on risk for relapse (Cox's proportional hazards model)—males

Term	Hazard ratio	95% Confidence bounds	
Age			
0–10	1·000*	—	—
11–20	1·142	1·059	1·231
21–30	1·251	1·154	1·357
31–40	1·306	1·209	1·410
> 40	1,440	1·340	1·547
NOP			
1	1·000*	—	—
2–3	1·007	0·9511	1·067
4–6	1·162	1·071	1·261
7–10	1·270	1·142	1·411
> 10	1·710	1·566	1·868
Treatment			
< 3 years	1·000*	—	—
4–5 years	1·357	1·281	1·438
> 6 years	1·391	1·299	1·490

* Reference category; NOP: Number of patches.

Appendix II

Effect of age, number of patches and duration of treatment on risk for relapse (Cox's proportional hazards model)—females

Term	Hazard ratio	95% Confidence bounds	
Age			
0–10 years	1·000*	—	—
11–20 years	1·181	1·079	1·294
21–30 years	1·253	1·152	1·363
31–40 years	1·232	1·142	1·328
> 40 years	1·363	1·267	1·467
NOP			
1	1·000*	—	—
2–3	1·020	0·9646	1·079
4–6	1·139	1·050	1·236
7–10	1·200	1·063	1·355
> 10	1·568	1·415	1·737
Treatment			
< 3 years	1·000*	—	—
4–5 years	1·508	1·422	1·600
> 6 years	1·580	1·468	1·700

* Reference category; NOP: Number of patches.

Risque de recidives chez les patients non-lepromateux chez qui le traitement a ete arrete apres une monotherapie par la dapsone

T D PANDIAN, JAYAPRAKASH MULIYIL ET CLAIRE VELLUT

Résume   Les données relatives à 14·625 patients non-lépromateux chez qui le traitement a été arrêté après une monothérapie à la dapsone et suivis pendant un maximum de 15 ans dans le cadre du projet ELEP à Dharmapuri en Inde, furent examinées pour déterminer le profil des récidives. Le nombre total des récidives était de 5/1·000 personnes par an. Le nombre de récidives chez les hommes était plus élevé que chez les femmes. Le risque de récidive augmentait avec l'âge, le nombre de lésions et la durée du traitement. Le risque de récidive restait constant plusieurs années après la fin du traitement. Quoique le risque absolu de récidive après *MDT* puisse être différent, le profil des récidives et les facteurs déterminants peuvent être semblables à ceux mentionnés dans cette étude.

Riesgo de recaída en los pacientes no lepromatosos liberados del tratamiento de monoterapia con dapsona

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Resumen   La información de 14·625 pacientes no lepromatosos liberados del tratamiento de monoterapia con dapsona y seguidos hasta un máximo de 15 años fue analizada en el proyecto ELEP, en Dharmapuri, India, para estudiar el modo de desarrollo de las recaídas. La tasa de recaída en conjunto fue de 5/1000 años personas. Los hombres tuvieron una tasa de recaída más alta que las mujeres. El riesgo a la recaída aumentó con la edad, número de lesiones y duración del tratamiento. El riesgo de recaida permaneció constante durante varios años después de la liberación del tratamiento. Aún cuando el riesgo de recaída absoluto después de *MDT* puede ser diferente, el modo de recaídas y los factores que lo afectan pueden ser similares a los que se han mostrado en este estudio.