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Relapse Rate and Incidence of Dapsone Resistance in Lepromatous Leprosy Patients in Addis Ababa: Risk Factors and Effect of Short-term Supplementary Treatment[1]

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Previous studies in the Addis Ababa, Ethiopia, area carried out in the period 1973–1974 reported a probable incidence of 3% secondary dapsone resistance per year. If resistance continued to develop at the same rate, this would have led to a prevalence of about 30% by 1980. In such a situation the efficacy of dapsone, even in combinations with other drugs, would be doubtful ([11, 12]). Measures to decrease the emergence of dapsone-resistant bacilli were, therefore, considered. In lepromatous patients already on dapsone treatment, the effect of the short-term addition of one or more drugs was investigated in a clinical trial, designed and initiated in 1976 by J. M. H. Pearson* and co-workers of the Medical Research Council (MRC) of London. After the closure of the MRC project in 1978, the trial was carried on by the staff of the All Africa Leprosy and Rehabilitation Training Center (ALERT).

This paper focuses mainly on the data obtained during the five-year follow up after the discontinuation of the supplementary treatment.

MATERIALS AND METHODS

All of the patients aged 12 years or more with lepromatous leprosy attending ALERT's outpatient clinic were included in the trial. The entry was spread over six months, from September 1976 until March 1977. About half of the 806 patients (58%) were taken into the trial before 1 January 1977. In the evaluation, this date was therefore considered as the starting point of the trial treatment.

The patients, all continuing dapsone treatment, were each randomly assigned to one of four treatment groups. The first group (A) served as a control group, the second (B) received 150 mg thiacetazone daily for 12 months, the third (C) received thiacetazone daily for 12 months plus 600 mg rifampin daily during months 1 and 7, and the fourth group (D) received rifampin daily during months 1 and 7 but no thiacetazone. Thiacetazone was given in the form of "Thiazina" tablets (150 mg thiacetazone

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plus 300 mg isoniazid) since thiacetazone tablets were difficult to obtain. All treatment was self administered. After the 12-month trial treatment, the patients continued with dapsone 100 mg daily.

The patients' compliance with the prescribed treatment was assessed on the occasion of a clinic visit in the 12th month of the trial and six months after the trial in a random sample of 73 and 63 patients, respectively, by Ellard and co-workers ([7]). A study of the dapsone compliance was repeated at four years after the discontinuation of trial treatment in 94 patients (H. Huikeshoven, personal communication, 1983). The degree of irregularity in those surveys was assessed according to the same criteria ([7]).

Urinary concentrations of dapsone and creatinine were determined by modifications of the Bratton and Marshall ([3]) and alkaline picrate procedures ([5]). Urine samples collected during the trial from patients prescribed Thiazina (groups B and C) were also tested for the presence of isoniazid metabolites ([6]).

The patients were reviewed at six-month intervals by an ALERT clinician. Details of the patients' complaints, state of health, and drug treatment were recorded. Examination included inspection of the skin, palpation of nerves, assessment of nerve function, and slit-skin smears. Patients developing signs of relapse ([10, 19]), such as the reappearance of new leprosy skin lesions or an increase in the bacillary concentrations of a minimum of 2 points on Ridley's log scale of the bacterial index (BI), were transferred to a special clinic for examination and follow up. They were started on supervised dapsone therapy, 100 mg daily orally or 375 mg weekly intramuscularly, until worsening of the leprosy status confirmed dapsone resistance ([19]). In addition, mouse foot pad tests were carried out whenever facilities were available.

The tests were performed using routine methods ([15–17]). Five thousand *Mycobacterium leprae* were inoculated in both hind foot pads of groups of mice, each group receiving a different concentration of dapsone in its diet (0.01%, 0.001%, and 0.0001% w/w). Growth of *M. leprae* in mice treated with dapsone, resulting in a yield of more than tenfold the inoculated number of bacilli, was taken to indicate the presence of *M. leprae* resistant to dapsone at the concentration used. If no growth occurred in even the untreated control mice, the inoculum was considered not to have contained a sufficient number of viable bacilli and the test was regarded as a failure.

The patients' hospital case records were examined and data abstracted regarding age, sex, classification, treatment, clinical and bacteriological evolution of the disease, and frequency and types of reactions.

RESULTS

At the conclusion of the trial, the average duration of patient follow up was five years. From the 806 patients who started trial treatment, 8.4% discontinued the trial treatment before the end of the year. During the five years of follow up, 3.1% of the patients were transferred or died, and 5.7% defaulted. Thus, the results of trial treatment for 667 patients were available for analysis (Table 1).

Comparison of trial groups (Table 2). The male : female ratio over the total group of 667 patients studied was 62:38. Females seemed to be slightly overpresented in group D—45% females and 55% males.

The age distribution over the four groups was not significantly different. Female patients at the start of the trial were younger than the males; 59% of the females as compared to 47% of the males were 35 years or younger ($p < 0.01$). This difference seems related to the development of their disease at an earlier age than men; 33% of the females started antileprosy treatment at 18 years or younger compared to 17% of the male patients ($p < 0.001$). Information on pregnancies was often not recorded in the hospital files and appeared difficult to obtain in retrospect. The distribution of females of child-bearing age was similar over the female study groups. It is, therefore, likely that the frequency of pregnancies in the female groups has not been significantly different.

The duration of treatment prior to the trial was about equal for males and females, ranging from only a few months to 23 years, with a median of 8–9 years in all groups. Seventy-five percent of the patients in all groups, males as well as females, were treated for a minimum of six years and, there-

TABLE 1. *Number of patients lost to follow up.*

	Trial group				Total
	A	B	C	D	
No. patients at intake	221	206	191	288	806
Lost during trial treatment	11.8%	6.8%	8.4%	6.4%	8.4%
Lost during 5-year follow up	9.0%	5.3%	11%	10%	8.8%
No. patients left for analysis	175	181	154	157	667

fore, at risk of developing a relapse caused by dapsone-resistant *M. leprae.*

The patient classification was abstracted from the hospital records, but criteria for differentiation between BL and LL were not always clear in retrospect. Some patients were simply diagnosed as L, whereas LL seemed to have been overdiagnosed. BL leprosy was diagnosed in 20% of the total study population, without significant difference from this percentage in the four groups.

About 30% of the patients in all groups were bacteriologically positive at the start of the trial.

Reversal reaction had been diagnosed during the course of the disease in 8% and 10%, respectively, of male and female patients. Thirty-four percent of the males and 41% of the females had suffered from one or more attacks of erythema nodosum leprosum (ENL). The frequencies of these complications in the four groups were not significantly different.

In 17% of the studied population, antileprosy drugs other than dapsone had been administered prior to the trial. Streptomycin and Thiazina had been given to 6.4% of patients because of concomitant tuberculosis, while thiambutosine and clofazimine had been administered in most cases be-

TABLE 2. *Variables of four groups of lepromatous patients in a clinical trial of short-term supplementary treatment.*

	Trial group				Total
	A	B	C	D	
Supplementary treatment		Thiazina	Thiazina + rifampin	Rifampin	
No. patients	175	181	154	157	667
Females	35%	39%	33%	45%	38%
Age 18–35 years[a]					
Males	50%	41%	49%	49%	47%
Females	59%	64%	61%	54%	59%[b]
Start treatment ≤18 years					
Males	20%	17%	17%	13%	17%
Females	36%	24%	35%	37%	33%[c]
Treatment prior to trial ≥6 years					
Males	75%	76%	68%	76%	73%
Females	85%	79%	67%	76%	77%
Skin smear positive[a]					
Males	31%	28%	29%	31%	29%
Females	21%	33%	39%	28%	30%
BL classification					
Males	29%	17%	19%	20%	21%
Females	20%	10%	20%	20%	17%

[a] At start of trial treatment.
[b] Significantly higher than percent males, $p < 0.01$, chi-square with Yates' correction.
[c] Significantly higher than percent males, $p < 0.001$, chi-square with Yates' correction.

TABLE 3. *Variables of the group of relapsed patients and of the total study population.*

	Relapsed patients		Total study population	
	Male	Female	Male	Female
No. patients	23	22	414	253
Median age (yr)[a]	36	28	36	33
Median duration of treatment (yr)[a]	8–9	8–9	8–9	8–9
Age 18–35 years[a]	11	19[b]	195	149[c]
Start treatment ≤18 years	4	12[b]	71	82[d]
Treatment prior to trial ≥6 years	14	18	302	195
Skin smear negative[a]	8	11	294	177

[a] At start of trial treatment.
[b] Significantly more than total female study population and more than relapsed males, $p < 0.05$, chi-square with Yates' correction.
[c] Significantly more than males, $p < 0.01$, chi-square with Yates' correction.
[d] Significantly more than males, $p < 0.001$, chi-square with Yates' correction.

cause of recurrent ENL. In this respect, no significant differences were observed in the four groups.

Also, no significant differences were found among the groups in regard to treatment compliance (personal communications: G. A. Ellard, 1982, and H. Huikeshoven, 1983). However, over the years the percentage of patients taking their treatment as prescribed appeared to decrease. While 93% of the urine samples was found positive for dapsone at the end of the supplementary treatment and 82% at six months after its discontinuation, a mere 56% of samples taken 3.5 years later contained dapsone ([7] and personal communication, H. Huikeshoven, 1983). The remaining 44% of the samples were from patients considered to be "grossly irregular" ([7]). In particular the self administration of Thiazina was not adhered to well. Of the 45 patients who had been prescribed Thiazina, only 30% were found with isoniazid metabolites in the urine ([7]). This poor compliance was possibly due to the adverse effects of Thiazina—34% of the males and 45% of the females in group B plus group C reported with all sorts of complaints which they attributed to their taking of Thiazina, whereas in groups A and D only 1% and 4%, respectively, had such complaints (data from hospital records).

Group of relapsed patients. Relapses which became obvious before the year of trial treatment was completed (four in each of the groups A and B) were removed from the study and not considered further. Dur-

TABLE 4. *Number of relapsed patients during the five years after one-year supplementary treatment.*

Trial group	No. patients		Total no. relapses		Annual incidence relapses		DDS-resistant relapses		Annual incidence resistant relapses	
A										
Males	114	175	12 (10.5%)	11.4%[a]	2.1%	2.3%[a]	3 (2.6%)	3.4%[a]	0.5%	0.7%[a]
Females	61		8 (13.1%)		2.6%		3 (4.9%)		1.0%	
B										
Males	111	181	5 (4.5%)	7.2%	0.9%	1.4%	1 (0.9%)	2.8%	0.2%	0.6%
Females	70		8 (11.4%)		2.2%		4 (5.7%)		1.1%	
C										
Males	103	154	4 (3.9%)	4.5%	0.8%	0.8%	0	0.6%	0	0.1%
Females	51		3 (5.8%)		0.8%		1 (2.0%)		0.4%	
D										
Males	86	157	2 (2.2%)	3.2%	0.4%	0.6%	0		0	
Females	71		3 (4.2%)		0.8%		0		0	
Total										
Males	414	667	23 (5.5%)	6.7%	1.1%	1.3%	4 (1.0%)	1.8%	0.2%	0.4%
Females	253		22 (8.7%)		1.7%		8 (3.2%)		0.6%	

[a] Percentage of patients in trial group.

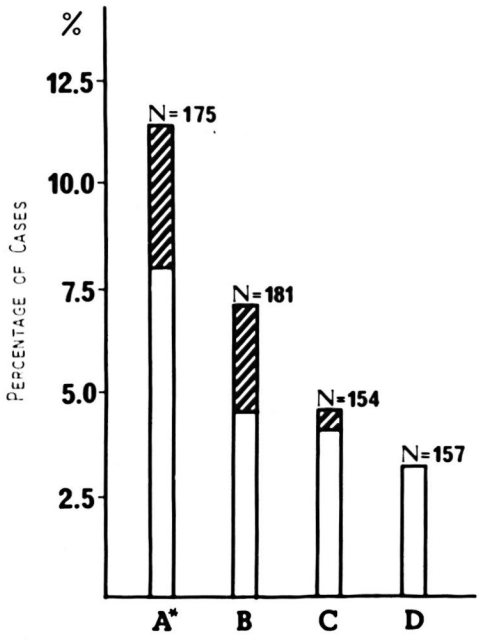

FIG. 1. Percentage of overall relapses and dapsone-resistant relapses over a five-year period after one year of supplementary treatment. A = control, B = Thiazina, C = Thiazina plus rifampin, D = rifampin supplementation, ▨ = percent relapses, □ = percent DDS-resistant relapses.

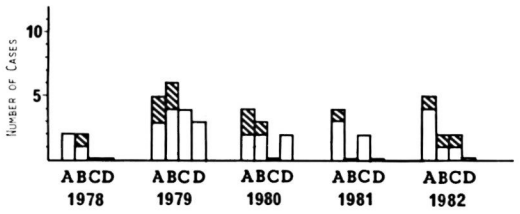

FIG. 2. Numbers of relapses during the five years after one-year supplementary treatment. A = control, B = Thiazina, C = Thiazina plus rifampin, D = rifampin supplementation, ▨ = relapse responding to DDS, □ = clinically DDS-resistant relapse.

ing the five years of follow up, a total of 45 patients, or 6.7% of the studied population, presented with a relapse while they were continuing dapsone therapy. The diagnosis was based on both clinical and bacteriological criteria in 41 cases. Two patients were diagnosed as relapses because of a BI increase of 3 points and the reappearance of solidly stained bacilli in their skin smears. They did not, however, show visible new skin lesions. The remaining two patients developed BT/BB skin lesions, and their relapses were histopathologically confirmed. The mean duration of dapsone therapy prior to relapse was 10.5 years for both males and females. Twelve out of the 45 patients failed to respond to supervised full-dosage dapsone and were clinically diagnosed as having a dapsone-resistant infection. Drug sensitivity tests in mice could only be carried out in 8 of these 12 patients; they failed in 2 and showed some degree of dapsone resistance in 6 cases.

Data from the group of relapsed patients were compared to data of the total study population (Table 3). No differences were found regarding classification, duration of treatment prior to the trial, or percentage of patients experiencing reactions. The proportion of females was 49% as compared to 38% in the total study population, but this is not significantly different.

A significantly higher proportion of relapsed female patients was 18–35 years of age at the start of the study; 86% as compared to 58% of the total female study population ($p < 0.05$). Six of the 22 female relapses were diagnosed during pregnancy or soon after delivery. The relatively younger age of the relapsed female patients was due to their starting antileprosy treatment at a younger age. Such a preponderance of relapses in young patients was not seen in the male patients.

At the start of the study, we observed bacteriological negativity in 19 (42%) of the 45 patients who would later relapse, with no significant difference between males and females. Over the total study population, 70% of both male and female patients were found to have negative skin smears.

Distribution of relapses and dapsone resistance. The distribution of relapsed cases over the four groups can be seen in Figure 1 and Table 4. Figure 2 indicates the time of occurrence of the relapses. The relapse rate was highest in the control group—20 patients or 11.4%, of whom six (3.4%) appeared clinically to be dapsone resistant. This results in an average annual incidence of 2.3% relapses and 0.7% dapsone-resistant leprosy in the control group.

The addition of Thiazina (group B) had a slight, but not a significant, effect on the relapse rate—7.2% as compared to 11.4% in the control group. Five patients (2.8%) subsequently failed to respond to super-

vised full-dosage dapsone therapy and were considered dapsone resistant. The annual incidence of relapse was, therefore, 1.4% and that of dapsone-resistant relapses was 0.6%. The proportion of relapses in the male patients of group B was lower than the female patients, 4.5% as compared to 11.4%, but not statistically significant. The relapse rate was not significantly different from the relapse rate in the male control patients.

The overall relapse rate in patients who received supplementary treatment with rifampin (groups C and D taken together) was 3.9%. This was significantly lower compared to the rate in the control group ($p < 0.01$). Relapses did not occur during the year of trial treatment or the first two years after the last course of rifampin therapy. Thereafter, the annual incidence was found to be lower than in the control group. Only one of the relapsed patients, diagnosed during the last year of the study, did not improve on supervised dapsone treatment. *M. leprae* obtained from this patient were found to have intermediate dapsone resistance in the mouse foot pad test.

A total of six mouse foot pad studies were successfully carried out in the 12 clinically confirmed, dapsone-resistant cases. They showed partial dapsone resistance (to 0.0001% w/w dapsone in the mouse diet) in the patient of group B who relapsed in 1978, and intermediate dapsone resistance (to 0.001% w/w dapsone) in the group C patient mentioned above. Four strains, three from group A patients and one from a group B patient, were found fully resistant (to 0.01% w/w dietary dapsone).

DISCUSSION

The four groups seemed to be equal in all relevant aspects. Risk factors which have been identified in relation to relapse and emergence of dapsone-resistant strains, such as duration and irregularity of dapsone therapy and the bacteriological status [1, 8, 13, 16, 18], were equally represented in each of the four groups. The proportion of females of child-bearing age was about equal in the trial groups, and we therefore assume no significant difference in the number of pregnancies in the females in the respective groups.

During the five-year follow up, 46 patients (5.7% of the total number of patients taken into the trial) were lost to follow up for unknown reasons. At their last visit, none of the defaulting patients showed any sign of clinical activity. Five patients had positive skin smears but without solid forms. The average BI exceeded 2 in two cases only, and those patients were treated for less than three years prior to defaulting. It therefore seems unlikely that dissatisfaction with the prescribed treatment due to relapse of the disease was the reason for discontinuation of treatment.

Effect of the supplementary treatment. The addition of thiacetazone, in combination with isoniazid, had a slight but insignificant effect on the relapse rate among group B patients. No effect could be demonstrated on the incidence of dapsone resistance.

Thiazina compliance in the 45 patients tested was only 30%, and this may well be the cause of the disappointing effect of the addition of Thiazina to dapsone therapy. Unfortunately, information on sex-associated compliance is lacking. In view of the relatively lower proportion of males complaining about adverse effects of this drug (34% as compared to 45% of females), a better compliance with Thiazina in the male patients might be considered as an explanation for the slightly better efficacy of this drug in males.

The effect of the addition of rifampin was significant in both group C and group D. The first relapse occurred two years after the last course of rifampin and at a lower rate as compared to the control group. The mean annual relapse rate over both groups C and D taken together was 0.7%, and all cases except one continue to respond to full-dosage, supervised dapsone therapy. Apparently two months of unsupervised daily intake of rifampin has been very effective in reducing the viable bacterial population, resulting in a decrease of the relapse rate and a decrease in the incidence of dapsone-resistant infections.

Precipitating factors. The proportion of females of child-bearing age at the start of the trial treatment was significantly higher in the group of relapsed patients compared to the total female study population. This observation seems to support the conclu-

sion drawn from an earlier study by Duncan and co-workers that pregnant patients are a high-risk group for relapse of the disease and are at high risk for the development of dapsone-resistant leprosy ([4]). In their study, failure of compliance with treatment and suppression of cell-mediated immunity during pregnancy were offered as possible explanations. On the basis of increased immunological instability during pregnancies, reversal reactions could also be expected to occur at a higher frequency in females than in males. Our data do not bear this out.

We noted that the women in our study population were younger and appeared to have developed the disease at an earlier age than men. Similar patterns of incidence rates for lepromatous leprosy have been reported from Burma and South India ([2, 14]).

It has been observed that young patients are less regular in their attendance (unpublished data and [9]). It is tempting to consider this irregularity of treatment to be the cause of a higher relapse rate in young males. However, a similar observation could not be made in the male study populations.

The cause for an increased relapse rate in young females is probably multifactorial. In our study, a relapse of the disease did not often appear to be associated with pregnancy, but our number of female relapsed patients is small. Further comparative studies of relevant variables in male and female patients are obviously needed to clarify the type of association between relapse of the disease and sex, particularly regarding the influence of pregnancy on relapse.

The median duration of dapsone therapy at the start of trial treatment in the group of relapsed patients was 8–9 years; this was not different from that in the total population. No difference in the duration of dapsone therapy prior to the relapse between male and female relapsed patients was observed. Duration of treatment does not seem in itself to be an important determining factor in the development of relapses.

Forty-two percent of the 45 relapsed patients were smear negative at the start of trial treatment and 13% had already been negative for over five years. A similar observation was reported from Malaysia ([20]). This shows that attainment of bacteriological negativity does not seem to be a test of cure of lepromatous patients.

Control group. The average annual relapse rate in the control group over the five-year follow up appeared to be 2.3%, and the incidence of dapsone-resistant leprosy in this group was 0.7% per year, a considerably lower incidence than the estimated 3% annual incidence over the five years prior to our study. The decrease in both relapse rate and incidence of dapsone-resistant leprosy could very well be due to the (re)introduction in 1974 of full-dosage dapsone therapy, uninterrupted during reactions, whereas in the previous decade, treatment with low-dosage dapsone was practiced in Ethiopia. The long half-life of dapsone and its high therapeutic ratio does apparently allow for irregularity of intake of as much as 20–40%, as found in our study population, without serious impairment of its efficacy. The conclusion that dapsone, particularly if administered in a dosage of 100 mg daily, is still a valuable antileprosy drug seems justified.

SUMMARY

A clinical trial was initiated at ALERT, Addis Ababa, Ethiopia, to study the effect of one-year supplementary treatment on the incidence of dapsone-resistant leprosy in lepromatous patients already on dapsone monotherapy. A total of 806 patients on dapsone therapy were assigned to one of four groups. The first group served as a control group, the second received a combination tablet of thiacetazone and INH (Thiazina) daily for 12 months, the third group received Thiazina daily for 12 months plus rifampin daily during months 1 and 7, and the fourth group received rifampin daily during months 1 and 7 but no Thiazina.

Eighty-three percent of the patients were followed for five years after discontinuation of the supplementary treatment. The annual incidence of relapses and dapsone-resistant leprosy in the control group appeared to be 2.3% and 0.7%, respectively. The Thiazina treatment had no significant effect on either the overall relapse rate or the incidence of dapsone-resistant leprosy. The rifampin treatment, on the other hand, did significantly lower the relapse rate and only a single case of dapsone resistance was detected. A high incidence of relapse was found in young female patients.

Nineteen of the 45 relapsed patients were bacteriologically negative at the start of the

supplementary treatment and six had already been negative for over five years.

RESUMEN

Se inició un estudio clínico en ALERT, Addis Ababa, Etiopía, sobre el efecto (a un año) de la terapia suplementaria en la incidencia de lepra resistente a la dapsona en pacientes lepromatosos ya en tratamiento con dapsona. Un total de 806 pacientes bajo terapia con dapsona fueron asignados a uno de 4 grupos. El primer grupo sirvió como control, el segundo recibió una combinación de tiacetazona e INH (tiazina) diariamente durante 12 meses, el tercer grupo recibió diariamente tiazina por 12 meses más rifampina diaria durante los meses 1 y 7, y el cuarto grupo recibió rifampina diariamente durante los meses 1 y 7, pero no tiazina.

El 83% de los pacientes se siguió durante 5 años después de suspender el tratamiento suplementario. La incidencia anual de recaídas y de casos de lepra resistentes a la dapsona en el grupo control fue de 2.3% y 0.7%, respectivamente. El tratamiento con tiazina no tuvo efectos significantes sobre el grado de recaídas ni sobre la incidencia de resistencia a la dapsona. El tratamiento con rifampina, por otro lado, bajó significativamente la incidencia de recaídas y soló se presentó un caso de resistencia a la dapsona en este grupo. La mayor incidencia de recaídas se encontró en pacientes femeninos jóvenes.

De los 45 pacientes que mostraron recaídas, 19 fueron bacteriológicamente negativos al comienzo del tratamiento suplementario y 6 ya tenían cuando menos 5 años de negatividad.

RÉSUMÉ

Dans le centre ALERT, à Addis-Abeba, en Ethiopie, on a entrepris un essai clinique ayant pour but d'évaluer l'effet d'un traitement complémentaire d'une durée d'un an sur l'incidence de la lèpre résistante à la dapsone chez les malades lépromateux déjà traités par la monothérapie à la dapsone. On a réparti 806 malades traités par la dapsone en quatre groupes. Le premier groupe a servi de groupe témoin, le second a reçu quotidiennement une tablette combinant de la thiacétazone et de l'INH (Thiazine) pendant 12 mois; le troisième groupe s'est vu administrer de la thiazine journellement pendant 12 mois, accompagnée de rifampine chaque jour au cours du premier et du septième mois; quant au quatrième groupe, il a reçu de la rifampine quotidienne au cours du premier et du septième mois, mais pas de thiazine.

Quatre-vingt trois pour cent des malades ont été suivis pendant cinq ans après l'interruption du traitement de complément. L'incidence annuelle de récidives et de lèpre résistant à la dapsone dans le groupe témoin s'est élevée respectivement à 2,3% et à 0,7%. Le traitement pas la thiazine n'a eu aucun effet significatif, tant sur le taux global de récidives que sur l'incidence de lèpre résistante à la dapsone. Par ailleurs, le traitement par la rifampine n'a pas significativement réduit les taux de récidive; un seul cas de résistance à la dapsone a été détecté. Une incidence élevée de récidive a été observée chez les malades jeunes de sexe fëminin.

Sur les 45 malades ayant présenté des récidives, dix-neuf étaient bactériologiquement négatifs au début du traitement de complément, et six avaient été négatifs de façon persistante pendant plus de 5 ans.

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