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# Comparative Study of Two Regimens of Combined Chemotherapy of One Year Duration in Multibacillary Leprosy. Results After Four and Five Years' Follow-up[1]

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The necessity for combined chemotherapy in multibacillary leprosy is now universally recognized and has heen discussed in a number of papers ([7, 9, 18]). However, the optimal combination of drugs, the frequency of their administration and, above all, the duration of therapy are unknown, and can only be revealed by controlled clinical trials. Another complicating factor is that, in general, it is believed that after stopping treatment very long follow-up periods are necessary.

We present here our observations on two groups of patients who were both treated for one year and followed thereafter for periods of 4–5 years.

## PATIENTS AND METHODS

**Patients and pre-treatment investigations.** Forty adult multibacillary leprosy patients, not suffering from concomitant tuberculosis and with active disease as revealed by the presence of papules, nodules, plaques, and areas of infiltrated skin, giving a history of not having been treated previously and having given their consent were selected. There were two exceptions concerning the absence of previous treatment: one patient in Regimen B was a relapse case who had abandoned dapsone therapy seven years earlier; another patient in Regimen B had had some dapsone treatment during the previous six months.

Routine clinical and neurological examinations were performed; smears from one earlobe, five skin sites, and the nasal mucosa were examined for acid-fast bacilli (AFB). A skin biopsy was taken for histopathology and for bacillary counts before the start of treatment and at intervals later. A Mitsuda test was performed with locally prepared lepromin. Patients were examined, and if necessary treated, for other cutaneous, intestinal, or urinary parasitoses before being started on antileprosy treatment.

**Therapeutic regimens and patient allocation.** The two regimens were:

Regimen A: 26 RMP 600 2/7, 52 DDS 100 7/7. Rifampin 600 mg, twice a week, for six months; dapsone 100 mg, daily, for one year.

Regimen B: 26 RMP 600 2/7, 26 PRO 500 7/7, 52 DDS 100 7/7. Rifam-

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pin 600 mg, twice a week, for six months; prothionamide 500 mg, daily, for six months; dapsone 100 mg, daily, for one year.

Due to a misunderstanding, the patients were not randomized between the two treatment regimens, but a first group of 20 patients was treated with Regimen A from June 1977 to 1978, and the second and third groups of patients were treated with Regimen B from September 1977 to 1978, and from February 1978 to 1979, respectively.

Patients were not selected for inclusion in either group but were allocated to these in the order of their arrival at the Institut Marchoux.

**Patient management.** Patients resided in houses at the Institut Marchoux, eventually with their families, and came every morning to the institute to take their supervised treatment. At the end of the specific treatment, placebo tablets were administered.

During treatment, patients were examined clinically and bacteriologically at 3, 6, and 12 months and thereafter at least once a year, many of them every six months. At irregular intervals, urine was examined for the presence of dapsone by the dapsone/creatine ratio method ([3]). At the beginning of treatment and at six- and 12-month intervals thereafter, bacterial counts were performed on homogenates of skin biopsies in some of the patients. At two intervals some skin biopsies were sent on wet ice to Antwerp for mouse foot pad inoculation.

TABLE 1. *Characteristics of the two patient treatment groups.*

| Characteristics | Group | |
|---|---|---|
| | A | B |
| Number at intake | 20 | 20 |
| Male/female | 18/2 | 15/5 |
| Age | | |
| Mean | 26.3 | 26.3 |
| Median | 25 | 25 |
| Range | 18–45 | 15–39 |
| Bodyweight | | |
| Mean | 56 | 52.6 |
| Median | 55 | 46 |
| Range | 50–62 | 48–70 |
| BL/LL | 11/9 | 12/8 |
| BI (mean) | 4.5 | 4.3 |
| Excluded | | |
| Before treatment (BT) | — | 1 |
| During treatment | | |
| ENL-clofazimine treatment | 2 | — |
| Gynecol. diseases | — | 1 |
| Left Institut Marchoux | 3 | 4 |
| Remaining for analysis | 15[a] | 14[b] |

[a] Males = 13, females = 2.
[b] Males = 10, females = 4.

## RESULTS

Table 1 shows the main characteristics of the two patient groups. Age and body weight were identical in the two groups, as were the bacterial load and the proportion of patients classified as borderline lepromatous (BL) or lepromatous (LL). There were, however, more women in group B ($p = 0.05$, Fisher's exact test) at intake.

One patient from group B was excluded because of misdiagnosis: histopathology showed borderline tuberculoid (BT) lesions and a homogenate of a 10 mg skin biopsy revealed only three AFB. Another group B patient who developed severe gynecological problems after three months had to be transferred to another hospital. Two patients from group A were removed from the trial; one because treatment was switched to clofazimine after 4½ months because of erythema nodosum leprosum (ENL) and the second was also treated with clofazimine and surgery after two months because of ulnar neuritis. Three patients from group A and four patients from group B interrupted their treatment and left the institute.

Clinically, the patients improved rapidly. The cutaneous lesions shrank and became wrinkled after time intervals which varied with the individual patient. The lesions in one patient in the A group were slower to regress and he was even suspected of relapse two years after the start of treatment. This was not confirmed by later examinations. He has now a bacterial index (BI) of 1. Seventy-two months and 66 months after the start of treatment, the patients showed only the usual sequellae of the disease.

Table 2 shows the evolution of the bacterial load based on homogenates of skin biopsies from 17 group A and 10 group B patients from whom fresh skin biopsies could be examined at the start and after six and 12 months of treatment. There was a gradual shift to lower numbers, amounting to approximately 1 log after 12 months.

TABLE 2. *Evolution of the AFB load in skin biopsy homogenates of 17 group A and 10 group B patients.*

| Patient treatment group | Biopsies (mo.) | No. AFB/g skin homogenate | | | | Mean |
|---|---|---|---|---|---|---|
| | | $<10^7$ | $10^7$–$10^8$ | $10^8$–$10^9$ | $>10^9$ | |
| A | 0 | | 3 | 10 | 4 | $2.9 \times 10^8$ |
| | +6 | 1 | 7 | 9 | | $5.0 \times 10^7$ |
| | +12 | 3 | 10 | 4 | | $2.0 \times 10^7$ |
| B | 0 | 2 | | 5 | 3 | $3.5 \times 10^8$ |
| | +6 | 2 | 4 | 2 | 2 | $2.2 \times 10^8$ |
| | +12 | 5 | 3 | 2 | | $2.0 \times 10^7$ |

Table 3 shows the evolution of the mean BI in the skin and the nasal mucosa. The continuing fall of the indices after stopping treatment is evident. One patient in group A was skin-smear negative at 48 months; two patients were negative at 54 and 60 months, respectively. The BI of the nasal mucosa of two patients was negative at 36 months, and it was negative in all 15 patients at 48 months.

In group B, three patients were skin-smear negative at 54 months. In the nasal mucosa, the BI became negative at 12 months in 1 patient (he had a BI = 3 at the start); at 24 months in 4 patients; at 36 months in 6 patients; and by 48 months in all 14 patients.

On several occasions (Table 5) skin homogenates were inoculated into the foot pads of mice. The mice were examined after one year and no multiplication of *Mycobacterium leprae* was observed.

Erythema nodosum leprosum (ENL) was a frequent complication. In Table 4 the total number of episodes of ENL requiring treatment for each patient is presented. The ENL was treated with aspirin and/or thalidomide. Many patients had recurrent ENL for 2–3 months followed by a symptom-free interval of one or several months. Nearly half of the patients in group A and more than half in group B developed ENL during treatment. (The difference was not significant, $p = 0.19$, Fisher's exact test.) In both groups the earliest attacks of ENL were seen after three months (one in group A, two in group B). During the follow-up period, 14 out of 15 patients in group A and 10 out of 14 patients in group B developed ENL (the difference was not significant, $p = 0.12$, Fisher's exact test). Two patients in group A were quite exceptional in that they had a total of 13 months and 21 months of treatment for ENL (separated by treatment-free intervals). The latest ENL episodes in group A were observed 54 months after chemotherapy was started.

TABLE 3. *Evolution of the mean BI in skin and nasal mucosa and the number of patients whose BI became negative. N = 15 for group A; N = 14 for group B.*

| Patient treatment group | | Months after treatment started | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 6 | 12 | 24 | 36 | 48 | 54 | 60 |
| A | Skin BI | 4.5 | 4.2 | 4.6 | 4.4 | 4.1 | 3.2 | 2.2 | 1.4 |
| | Neg.[a] | — | — | — | — | — | 1 | 2 | 2 |
| | Nasal mucosa BI | 3.8 | 3.8 | 3.2 | 2 | 1.2 | 0 | 0 | 0 |
| | Neg.[a] | — | — | — | — | 2 | 15 | 15 | 15 |
| B | Skin BI | 4.3 | 4.3 | 4 | 3.7 | 3.1 | 2.2 | 1.5 | |
| | Neg.[a] | — | — | — | — | — | — | 3 | |
| | Nasal mucosa BI | 3.8 | 3.2 | 2.2 | 1.8 | 0.7 | 0 | 0 | |
| | Neg.[a] | — | — | 1 | 4 | 6 | 14 | 14 | |

[a] Number of patients with BI = 0.

TABLE 4. *Number of months patients were treated for ENL.*

| No. months | Group A | | Group B | |
|---|---|---|---|---|
| | During treatment | After treatment | During treatment | After treatment |
| 0 | 8 | 1 | 5 | 4 |
| 1 | 4 | 4 | 5 | 4 |
| 2 | 2 | 2 | 2 | 4 |
| 3 | 1 | 1 | | |
| 4 | | 1 | 1 | 2 |
| 6 | | 2 | 1 | |
| 7 | | 2 | | |
| 13 | | 1 | | |
| 21 | | 1 | | |
| Mean no. months of ENL | 0.7 | 5 | 1.3 | 1.4 |

TABLE 5. *Number of patients from whom skin homogenates were inoculated into mouse foot pads after treatment.*

| Group | Months after short treatment | | | |
|---|---|---|---|---|
| | 31 | 36 | 40 | 45 |
| A | — | — | 15 | 3 |
| B | 1 | 14 | 4 | — |

## DISCUSSION

Although formal randomization was not applied in the present trial, the results are useful because the patients were allocated to the two regimens in the order of their arrival at the institute. Although there were more women in group B at intake ($p = 0.05$, Fisher's exact test), there was no significant difference in the sex ratio of those analyzed ($p = 0.10$). In all other respects the two groups were comparable. There was no difference in the clinical and bacteriological evolution of the two groups.

Since the importance of primary DDS resistance in the area was not appreciated at the time (even secondary DDS resistance was only documented in West Africa in 1978[6]), pretreatment mouse foot pad inoculations were not performed.

Since we did not have immunodepressed rodents at our disposal to detect persisting or surviving *M. leprae,* at intervals after treatment skin homogenates were inoculated into normal mice, a method which sometimes detects *M. leprae* ([11]). No persisting *M. leprae* were found, although the use of more sensitive animals or blind passages one year after inoculation might have revealed their presence ([4]). However, the aim of the mouse foot pad inoculations was also to detect larger numbers of surviving organisms which could have remained undetected by the classical bacteriologic examinations.

Histopathologic examinations of a number of biopsies in the late phases of the study showed aggregations of macrophages containing granular acid-fast materials; some were even empty. Granular acid-fast bacilli could also be found at times in the arrector pili muscles or in arterial walls.

As in previous studies with intermittent rifampin ([12, 16]), there were no toxic effects from the twice weekly 600 mg RMP administration for six months, although admittedly the number of patients is small. Complications due to intermittent RMP administration are related to the interval, the dose, and the duration ([6]). Twice weekly 600 mg gave no complications among a total of 29 patients. The exact 95% confidence limits for a binomial distribution with these results are 0–12% ([2]). Thus the upper 95% confidence limit is 12%. In contrast with many other trials, no liver toxicity from the RMP + PRO combination was observed, at least not as acute hepatitis, since chemical liver function tests were not performed. The absence of hepatitis in the present trial may be the result of a) RMP being given from the start twice weekly instead of daily, or b) the fact that all patients except one were new patients, never treated previously [in one series in Africa (unpublished data) the daily combination RMP + PRO produced considerably more hepatitis in patients with longstanding previous DDS therapy], or c) a chance observation due to the small number of patients having taken the RMP + PRO combination.

The continuing decrease of the BI in skin and nasal mucosa after treatment has been stopped is the best illustration of the possibility of treating multibacillary leprosy for a finite period of time, if rifampin is included in the regimen. Once efficacious chemotherapy has killed all or almost all bacilli, the source for new ones being dried

up, the human body slowly eliminates the cadavers and the BI continues to decrease.

Although persisting bacilli have been shown to be present in most multibacillary patients even during rifampin therapy ([14, 17]), it is by no means certain that all of them give rise to relapses off treatment.

The question of the duration of follow-up has been discussed recently by one of us ([1]). In paucibacillary leprosy, 50% of the relapses occur within three years after the end of therapy. The mechanisms for relapse in multibacillary leprosy being identical, namely, regrowth of bacilli still viable at the end of treatment by multiplying with an unaltered generation time and in a host with reduced defense capability, there is no reason why in multibacillary leprosy also 50% of relapses should not occur within three years after stopping antibacterial treatment. In the present study, the patients were followed for 5 and 4½ years.

The results of Regimens A and B have 95% upper confidence limits ([2]) of 20% and 23%, respectively. However, when the results of the two regimens are added, the 95% upper confidence limit for six months twice weekly 600 mg rifampin in combination with prothionamide and DDS or DDS alone, followed by six months' DDS, is 12%.

The study could not demonstrate any advantage of prothionamide added to RMP + DDS for any of the parameters measured. Nevertheless, with the present evidence of widespread and increasing secondary and primary dapsone resistance, which was unknown in West Africa at the time the trial was started, it would be very dangerous to apply the two-drug Regimen A on a larger scale, particularly in patients previously treated with dapsone as monotherapy, since this would increase considerably the risk of RMP being administered essentially as monotherapy (if the bacilli were already resistant to DDS), leading to the disaster of the selection of RMP-resistant *M. leprae.* Therefore, if it is reasonable to test the value of six months' RMP therapy of multibacillary leprosy in a larger number of patients, it should be done in association not only with DDS but also with one or preferably two other drugs: clofazimine and ethionamide or prothionamide, the latter in a dosage and/or combination that avoids liver toxicity.

Since DDS is mainly bacteriostatic and slowly bactericidal ([7, 8, 13, 15]), we do not believe that the second semester of daily dapsone adds much to the value of the regimens tested. It has been clearly shown in studies on the chemotherapy of tuberculosis that during an effective continuation phase (after an initial multiple-drug phase) bactericidal rather than bacteriostatic drug(s) should be used ([5]). In fact, the role of bacteriostatic drugs is rather the prevention of the selection of mutants resistant to the powerful bactericidal drugs ([7, 18]).

It is, therefore, worthwhile to apply six months' regimens of combined chemotherapy, including rifampin, to a greater number of patients to see whether the confidence limits of our results can be narrowed, and to provide longer follow-up periods to verify our hypothesis that 50% of the relapses would occur during the three years following the end of treatment.

The difference between lifelong treatment (by DDS monotherapy) and relatively short-course chemotherapy may seem incredible to many a leprologist; it is all the difference between a powerful bactericidal drug and a mainly bacteriostatic one. However, the main task should always be kept in mind: the protection of RMP from the selection of RMP-resistant mutants.

## SUMMARY

Two therapeutic regimens of one-year duration were administered to two groups of 20 previously untreated mutibacillary leprosy patients. Regimen A was rifampin 600 mg twice weekly, prothionamide 500 mg, and dapsone (DDS) 100 mg daily for six months, followed by 100 mg DDS daily for another six months. Regimen B was identical to Regimen A but without prothionamide. Follow-up was for 4½ and 5 years in 15 and 14 patients, respectively. Clinical improvement was rapid, and the bacterial index (BI) of the patients diminished by one unit per year after stopping treatment. Five patients were skin-smear negative at 54 months. The BI in the nasal mucosa became negative after 48 months. There were many attacks of erythema nodosum leprosum between month 3 of treatment until 13 and 21 months.

Up to now no relapses have been observed. These results have confidence limits

of 20% and 23%, respectively. However, when the results of the two regimens are added, the confidence limit for six months' twice weekly rifampin together with DDS and followed by six months of DDS and 4½ years follow-up is 12%.


## RESUMEN

Se administraron 2 esquemas de tratamiento de un año de duración a dos grupos de 20 pacientes con lepra multibacilar sin tratamiento previo. El esquema de tratamiento A consistió en rifampina 600 mg 2 veces por semana, protionamida 500 mg, y dapsona (DDS) 100 mg diarios durante 6 meses, continuando con 100 mg de DDS diarios por otros 6 meses. El esquema B fue idéntico al A pero sin protionamida. El seguimiento de los casos se hizo durante 4.5 años (15 pacientes) y 5 años (14 pacientes). El mejoramiento clínico fue rápido y el índice bacteriológico (IB) disminuyó en una unidad por año después de suspender el tratamiento. Las preparaciones de linfa cutánea fueron bacteriológicamente negativas en 5 pacientes aún después de 54 meses. El IB en la mucosa nasal llegó a ser negativo después de 48 meses. Hubieron muchos ataques de eritema nodoso leproso entre los 3 y 21 meses de tratamiento.

Hasta ahora no se han observado recaídas. Estos resultados están dentro de los límites de confianza del 20 y 23% respectivamente. Sin embargo, cuando los resultados de los 2 esquemas de tratamiento se suman, el límite de confianza para el tratamiento por 6 meses con rifampina 2 veces por semana junto con DDS, seguido por 6 meses de DDS, es del 12% en un seguimiento de 4 años y medio.

## RÉSUMÉ

On a administré deux schémas thérapeutiques d'une durée d'une année à deux groupes de 20 malades atteints de lèpre multibacillaire et qui n'avaient pas été traités auparavant. Le schéma A consistait en: rifampicine 600 mg deux fois par semaine, prothionamide 500 mg, et dapsone (DDS) 100 mg par jour pendant six mois, suivi de 100 mg de DDS quotidiennement pendant six autres mois. Le régime B était identique au régime A, à la différence qu'il ne contenait pas de prothionamide. Le suivi de cette étude s'est étendu sur 4½ ans chez 15 malades et 5 ans chez 14 autres. L'amélioration clinique a été rapide, et l'index bactérien (BI) a diminué d'une unité par an parès l'arrêt du traitement. Cinq malades présentaient des frottis cutanés négatifs après 54 mois. L'index bactérien dans le mucus nasal est devenu négatif après 48 mois. On n'a pas relevé d'épisodes d'érythème nouex lépreux entre le troisième mois de traitement et avant le treizième ou le vingt et unième mois.

A ce jour aucune rechute ne fut observée. Ces résultats ont un intervalle de confiance de 20 et 23% respectivement. Mais lorsque les résultats des deux régimes sont additionés, l'intervalle de confiance pour guérison après six mois de rifampicine à raison de 2 doses par semaine associé à la DDS et suivi de 6 mois de DDS est de 12% après 4½ de suivi.


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