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# SHORT COURSE TWO MONTHS TREATMENT OF PAUCIBACILLARY LEPROSY WITH RIFAMPICIN PRELIMINARY RESULTS

by

S. R. PATTYN[1,4], BOURLAND, J.[2], WARNSDORFF, J.[3], CAP, A.[3] & SAERENS, E. J.[4]

[1]*Institute of Tropical Medicine, Nationalestraat 155, B-2000 Antwerpen, Belgium*
[2]*Damien Foundation, Bujumbura, Burundi*
[3]*All Africa Leprosy and Rehabilitation Training Centre (ALERT), Addis Ababa, Ethiopia*
[4]*University of Antwerp, Belgium*

*Summary* — The possiblity of treating paucibacillary leprosy by a short course rifampicin regimen was investigated in a pilot trial in Bujumbura and a controlled trial in Addis Ababa. Rifampicin was administered once weekly in a dose of 900 mg during 8 weeks.

Cinical improvement continued after the administration of RMP was stopped and no systemic adverse effects associated with the intermittent RMP administration were observed.

The follow-up period was one year. The clinical observations and examination of biopsies give the impression that this short course RMP treatment is not as good as standard dapsone therapy.

Three patients in the RMP group developed neuritis, this was not significantly different when compared with the dapsone group and the neuritis developed after the RMP treatment had been stopped. Continuing observation of the patients is neccessary.

KEYWORDS : Leprosy; Rifampicin; Burundi; Ethiopia

## Introduction

In a previous study on multibacillary leprosy (Pattyn *et al.*, 1975) it was found that there were no significant differences between the two rifampicin regimens used : 450 mg daily and 900 mg once weekly. Furthermore in the two regimens tested, the morphologic index reached base line values by the end of the second month of treatment.

Based on these results a therapeutic trial of paucibacillary leprosy involving the administration of 900 mg rifampicin once weekly for 8 weeks was carried out.

A pilot trial was undertaken in Burundi (J. B.) and a controlled trial in Addis Ababa (J. W. an A. C.).

## Material and Methods

### *Patient selection*

Previously untreated paucibacillary adult patients having no clinical signs of tuberculosis (a cough of more than 2 weeks duration) with indeterminate, TT or BT leprosy were selected at the out patient clinics. In Burundi only patients with minimal or no nerve involment and living within acceptable distance of the clinics were included in the trial.

*Pretreatment investigations*

The number and localisation of skin lesions were noted on especially devised charts. For one or 2 patches the diameter, erythema and nature of the edges was noted.

The classical superficial nerves most frequently involved in leprosy were recorded for hypertrophy, tenderness and spontaneous pain. Sensitivity of hands and feet were measured as were the different motor functions.

A biopsy of one patch was taken, fixed in formalin and examined in Antwerp. A scarification of an earlobe was taken and examined for acid fast bacilli (AFB).

*Chemotherapy regimens*

In Burundi selected patients were given 900 mg RMP once a week under supervision at the health centers. After the 8th dose the patients were given placebo dapsone tablets for self-administration.

In Addis Ababa patients were randomly allocated to one of two drug regimens :

A : Routine regimen consisting of dapsone 25 mg/day for 4 weeks followed by dapsone 50 mg/day. During the first two months patients came to the treatment clinic once a week to collect their tablets. Dapsone treatment was not supervized. Placebo rifampicin capsules were given.

B : Rifampicin 900 mg once a week during 8 weeks under supervision, followed by dapsone placebo tablets.

Follow up :

Clinical and neurological examination of patients was planned at 2 months and thereafter every 3 months during at least 3 years. In Burundi all clinical examinations were performed by the same person (J. B.) in Addis Ababa some examinations were performed by independent assessors. Biopsy specimens from the original lesion were taken after 2 months and thereafter every 6 months.

Patients developing reactions severe enough to have steroid therapy were withdrawn from the trial and put on standard dapsone therapy.

## Results

As stated above it was the original intention to have a follow up of the patients during 3 years. We are presenting the preliminary results of these trials at this moment since circumstances beyond our control will probably lead to a halt in the observations.

A. *Bujumbura*

The classification of the cases and length of follow-up is given in table 1. Clinically all patients except one showed moderate to considerable improvement. The Idt and TT cases showed the same number of patches but there

was repigmentation after 33 and 22 weeks respectively. Six of the 7 patients classified as BT improved and the mean number of skin patiches decreased from 30.1 to 17.3, although there were considerable individual variations in this respect. One of these patients had a normal pregnancy and delivery during the observation period, and a second became pregnant. The only patient who did not improve clinically was a young women 16 years old, whose lesions became more prominent, elevated, erythematous and showed some scaling during the observation. This was interpreted as a reversal reaction, which started to subside by the 59th week. By the 36th week this patient developed also mild neuritis of the right radial nerve, and both ulnar nerves (pain and tenderness), which did not require corticoid therapy, she was able to continue her normal activities and had her menarche 13 months after the start of the treatment. Three other patients developed mild neuritis : one patient at 7 months after the start of treatment developed hyperthrophy and tenderness in the tibial nerves, another had a mild ulnar neuritis at 8 weeks, in these patients and one other there was some hypoesthesia in the ulnar or tibial innervation regions. None of these required specific treatment.

TABLE 1

**Classification of cases in Burundi**

| Class | Number | Follow-up in weeks |
|---|---|---|
| LI | 1 | 57 |
| TT | 1 | 37, 37 |
| BT | 7 | 69, 64, 52, 59, 52, 37, 37 |

Comparison of the histologic slides learned the following : 3 cases with minimal lesions at the start did not show any notable difference between the first and the last biopsy. Four cases with extensive skin lesions at the start showed considerable improvement after 15 months.

## B. *Addis Ababa*

33 patients were taken into the trial (table 2). Six patients absconded for non medical reasons (2 in the DDS group and 4 in the RMP group) leaving for analysis respectively 9 and 13 patients. The number of skin lesions was very comparable in the LI and TT patients. Among the BT patients the RMP group shows a higher number of lesions, this is due however to one particular patient who had a very high number of lesions.

The follow-up varied between 26 and 64 weeks. Since it is difficult to tabulate the skin lesions their evolution is given as a narrative report.

### *The DDS group*

Idt lesions faded at 26 weeks, were vague to very vague at 36 weeks.

The TT patient had a centrally lealing lesion at the start, it did not show any appreciable change after 26 weeks. In BT patients most lesions were vague at 21 or 34 weeks. In 4 out of 6 cases for which the follow-up period is 50 weeks, lesions are very vague.

TABLE 2

**Analysis of cases in Addis Ababa**

| | | Group A (DDS) | Group B (RMP) |
|---|---|---|---|
| Taken in | | 10 | 17 |
| Absconded within 2 months | | 1 | 3 |
| Absconded after 2 months | | 1 (26 weeks) | 1 |
| Analysis | | 9 | 13 |
| Idt | | 2 (F1, M1) | 2 (M) |
| TT | | 1 (M) | 1 (F) |
| BT | | 6 (F4, M2) | 10 (F4, M6) |
| Number lesions | Idt | 2/9 | 2/7 |
| | TT | 1 | 2 |
| | BT | 2-24 mean 11.1 median 7 | 2-78 mean 16.7 median 4 |
| Duration | Idt | 35, 35 | 50, 50 |
| Follow-up | TT | 26 weeks | 51 |
| in weeks | BT | 58, 60, 48, 52, 36, 36 | 64, 64, 64, 64, 64, 52, 50, 39, 35, 35 |

F = female.
M = male.

*The RMP group*

Idt patches were fading or repigmented from the 23th week on. In the TT patient repigmentation of the lesions was noted after 1 year.

In the BT patients fading may start in some at 8 weeks, is always noticeable at 52 weeks : for 7 cases with a follow-up of 52 weeks, lesions are very vague sometimes with wrinkling, central healing or repigmentation. In one patient depigmentation increased at 52 weeks and was fading again on a later examination.

*Nerves*

The mean scores for the situation in the nerves is given in table 3. Only the BT group deserves any comment. At the start the patients were quite comparable : the mean scores for nerve hypertrophy being 2 versus 2.2 and for tenderness 0.4 versus 0.

At 8 weeks the RMP group on the whole shows a greater improvement than the DDS group with regard to the nerve hypertrophy although tenderness in the RMP group has increased from 0 to 0.7 its is however questionable if this difference is meaningful. By 21 weeks nerve improvement is equally good in both treatment groups and is maintained later on.

However three patients in the RMP group developed neuritis (after terminating chemotherapy) requiring corticoid therapy, and their scores are not included in the table. Their history is summarized in table 4. Patient no. 2 developed left auricular and facial paralysis at week 18, this is 10 weeks after the end of antileprosy treatment. She had no apparent nerve lesions at the start. Patient no. 6 developed a clawhand at week 8, this is at the last dose of RMP, nerves graded 3.1.0. at the start. Patient

TABLE 3

**Nerve involvement in Addis Ababa patients**

**DDS group**

| | Start | | | 8 weeks | | | 21 weeks | | | 36 weeks | | | 52 weeks | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | H | T | P | H | T | P | H | T | P | H | T | P | H | T | P |
| I | 2 | 0 | 0 | 1.5 | 0 | 0 | 1 | 0.5 | 0 | 2 | 0.5 | 0 | | | |
| TT | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | | | | |
| BT | 2 | 0.4 | 0 (6) * | 2 | 0.5 | 0 (6) | 0.25 | 0.2 | 0 (5) | 0 | 0.5 | 0 (4) | 0.5 | 0 | 0 (4) |

One BT patient had slight clawing of fingers from the start.

**RMP group**

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | 1/4 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| TT | 2 | 2 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 3 | 0 | 0 | 1 | 0 |
| BT | 2.2 | 0 | 0 (7) | 1.2 | 0.7 | 0 (7) | 0.4 | 0.4 | 0.2 (7) | 0 | 0.5 | 0 (7) | 1 | 0.2 | 0 (5) |

Three patients (2, 6, 21) developed neuritis requiring corticoid therapy.
H = hypertrophy; T = tenderness; P = painful nerves.
* Number of patients evaluated.

TABLE 4

**Data on the patients developing neuritis requiring corticoid therapy**

| No. | S | Age | Duration | Nerves at start H | T | P | Neuritis at | |
|---|---|---|---|---|---|---|---|---|
| 2 | F | 24 | 3 years | 0 | 0 | 0 | 18 weeks | Auricular, facial paralysis |
| 6 | M | 13 | 1 year | 3 | 1 | 0 | 9 weeks | Painful nerves/motor function loss 1. ulnar |
| 21 | M | 31 | 15 years | 8 | 1 | 0 | 12 weeks | Ulnar nerves tender/increase sensory loss |

These three patients had been treated with rifampicine 900 mg/week, from week 1 tot 8.

no. 21 had very important nerve involvement at the start (8.1.0.) which increased by the end of treatment and was accompanied by increased sensory loss. These 3 patients improved very well on corticoid therapy, only 1 of them (no. 6) has a remaining paresis in the area of the N. ulnaris. Comparison of the histological slides led to the following conclusions :

Of 8 cases with at least one year of follow-up, 3 had been treated with dapsone and 5 with RMP. In the biopsies of the dapsone treated patients there were hardly any abnormalities left. The biopsies of the RMP treated patients gave variable results : two were appreciated as unchanged two as diminished and one had only minimal lesions left. Of the 4 patients with the most extensive skin lesions at the start one was on RMP and 3 on dapsone. For these patients we have only biopsies at 30 or 34 weeks : the dapsone patients had their lesions much diminished, the RMP patients had clearly less improvement.

## Discussion

The clinical features of leprosy in the tuberculoid range of the spectrum are largely the result of a hypersensitivity reaction to *M. leprae*. Since rifampicin has a dramatic killing effect on *M. leprae*, as demonstrated in therapeutic trials in lepromatous leprosy (Shepard *et al.*, 1972), it should be expected that in paucibacillary leprosy healing of skin lesions continues after the arrest of a rifampicin treatment course sufficient to kill the etiologic agent. This expected course of events was observed in the present trials. The clinical lesions improved also after the RMP administration was stopped.

In Bujumbura only patients with minimal nerve involvment were included in the trial and only minor reversal reactions in nerves were observed. In AA 3 patients in the RMP group developed neuritis requiring corticoid therapy. In this small number of patients the difference in incidence of neuritis between the RMP and DDS group is not statistically significant.

The degree of nerve involvement at the start of treatment did not correlate neither with the chances for later occurrence of neuritis nor with the incubation time for its development. Since reversal reactions in paucibacillary leprosy are the result of an increased host defense mechanism these complications are perhaps to a certain extent unavoidable in a number of patients, and related to a delay in the detection and start of treatment.

These are preliminary data, a definite conclusion on the results of the short course 8 week intermittent rifampicin treatment of paucibacillary leprosy will only be possible when patients have been observed for a period sufficiently long to exclude relapses. At this point however the results of the clinical observations and the examination of biopsies at one year give the impression that the improvement after this short course rifampicin treatment is not as good as on standard dapsone therapy. Time only will bring the answer, and we do hope that circumstances will allow us to continue the observations. Furthermore many other short course drug regimens may be imagined which, if successful, could dramatically change the strategy of leprosy treatment.

From the present trial informations have been obtained which can be useful for future similar trials. The second biopsy taken at 2 months after the start of therapy is irrelevant and may be omitted. Patients in the short course regimen developing neuritis, should not be shifted to standard dapsone therapy with corticoids but should remain in their original group and be given corticoids when and if necessary.

Finally no systemic adverse effects associated with intermittent RMP administration have been observed in any of the groups. This may be due to the shortness of the intermittent RMP administraion or hese adverse effects may be less common in leprosy than in tuberculosis.

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**Kortdurende behandeling twee maanden rifampicine van paucibacillaire lepra. Voorlopige resultaten.**

*Samenvatting* — De mogelijkheid paucibacillaire lepra te behandelen met een kortdurende rifampicine toediening werd onderzocht in een piloot studie in Bujumbura en een gecontroleerde klinische proef in Addis Abeba. Rifampicine werd één maal per week toegediend, in een dosis van 900 mg, gedurende 8 weken.

Klinisch verbeterden de patiënten ook na het stoppen van de behandeling, en er werden geen nevenwerkingen waargenomen die zouden kunnen te wijten zijn aan een intermitterende toediening van RMP.

De follow-up periode bedroeg 1 jaar. Klinische observaties en onderzoek der huidbiopsieën geven de indruk dat op deze kortdurende RMP behandeling van paucibacillaire lepra niet evengoed is als de standaard dapsone behandeling.

Bij drie patiënten in de RMP groep trad een neuritis op. Deze incidentie was statistisch niet significant verschillend van die in de dapsone groep, daarenboven traden alle gevallen van neuritis ook op na het beëindigen van de behandeling. De patiënten worden verder gevolgd.

**Schéma de traitement de courte durée de la lèpre paucibacillaire par deux mois de rifampicine. Résultats préliminaires.**

*Résumé* — La possibilité de traiter la lèpre paucibacillaire par un traitement de courte durée à la rifampicine fut étudiée dans un essai pilote conduit à Bujumbura et un essai clinique contrôlé exécuté à Addis Ababa. La rifampicine fut administrée pendant 8 semaines à raison de doses hebdomadaires uniques de 900 mg.

L'amélioration clinique progressait après arrêt du traitement. Il n'y eut pas d'effets secondaires dûs à l'administration intermittente de rifampicine.

Le recul fut de un an. Les observations cliniques et l'examen des biopsies donnent l'mpression que le traitement présent à la RMP ne donne pas des résultats aussi bons que le traitement standard à la dapsone.

Trois malades dans le groupe RMP développèrent une névrite. Cette incidence n'est pas significativement différente de celle dans le groupe dapsone et les névrites se développèrent après arrêt du traitement. L'observation des malades continue.

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