Therapeutic Effects of Adding Rimactane[R] (Rifampicin) 450 Milligrams Daily or 1200 Milligrams Once Monthly in a Single Dose to Dapsone 50 Milligrams Daily in Patients with Lepromatous Leprosy [1,2]

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The first results with rifampicin SV in the treatment of leprosy were reported in 1963 at the Eighth International Leprosy Congress, Rio De Janeiro ([12]), while the pioneer publications on the orally active rifamycin, rifampicin in leprosy appeared seven years later ([8, 15]). Although rifampicin has been used in leprosy for about ten years, wide differences of opinion exist among leprologists with respect to the dosages, dose-intervals and duration of treatment. The dosages used to date have varied from 150 mg daily ([11, 22]) to 900 mg daily ([7]). Other daily dose schedules used are: 300 mg ([7, 10]); 450 mg ([13]); and 600 mg ([7, 15, 19]). With regard to dose intervals, rifampicin has so far been administered thrice weekly ([11]), twice weekly ([11]), once weekly ([13, 16, 21]), and 600 mg daily on two consecutive days every four weeks ([20]). Rifampicin lends itself much better to intermittent treatment than other antileprosy drugs. This probably results from its very rapid killing effect on *M. leprae*. The duration of treatment with rifampicin varied considerably, namely from one single dose of 1500 mg ([9]) to seven years ([16]).

Although rifampicin is the most potent bactericidal antileprosy drug available today, it is now known that it alone cannot significantly shorten the duration of treatment in lepromatous leprosy. Therefore, dapsone continues to be the standard treatment for the majority of leprosy patients, comprising predominantly nonlepromatous cases. However, initial intensive combined treatment with at least two or preferably three bactericidal drugs has now been aptly advocated for the treatment of multibacillary, namely lepromatous (LL and LI)[4] and borderline-lepromatous (BL) cases of leprosy, in order to attempt to: a) reduce infectivity and lead to the faster arrest of transmission; b) prevent the emergence of drug resistance; c) eradicate the persistence of viable, drug-sensitive *M. leprae* more efficiently; and d) curtail the length of treatment.

Monotherapy with rifampicin is to be avoided as the first case of rifampicin resistant leprosy treated with rifampicin 600 mg daily, confirmed by the mouse foot pad test, has already been reported ([6]). On the basis of mouse foot pad tests, Pattyn and Saerens ([14]) suggested that 1200 mg rifampicin administered once every two or four weeks could be used as an introductory treatment of lepromatous leprosy. The main objective of this trial was to delineate the clinical, bacteriologic and histopathologic effects of adding Rimactane[R] (rifampicin) 450 mg daily or 1200 mg once monthly in a single dose to dapsone 50 mg daily in patients with lepromatous leprosy.

MATERIALS AND METHODS

Patients. The clinical material comprised 30 lepromatous leprosy patients: 23 males and 7 females ranging in age from 12 to 65 years. The diagnosis was confirmed by **nose-**

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[4] LL = polar lepromatous leprosy; LI = subpolar lepromatous leprosy.

blow smear and skin biopsy. The patients were otherwise healthy and did not give histories of previous treatment. Patients with a Morphologic Index (MI) of less than ten and a Bacteriologic Index (BI) of less than four (Ridley's scale) in the skin smears were excluded from this trial. Pregnant females, patients with anemia, thrombocytopenia, tuberculosis, alcoholism, renal or liver disease, or having a recent history of treatment for tuberculosis were not included in this trial.

Trial design and treatment regimens. This was a controlled, between-patient trial with single-blind assessments in hospitalized as well as ambulant cases of lepromatous (LL and LI) leprosy. The patients were allocated by a randomized code to one of the following treatment regimens: a) 450 mg Rimactane[R] (Ciba-Geigy rifampicin) daily + 50 mg dapsone daily ([4]); b) 1200 mg Rimactane[R] in a single dose given in the presence of the physician once monthly + 50 mg dapsone daily ([4]). The duration of the trial treatment was six months. In patients developing lepra reactions the trial treatment was continued until they needed additional medication for controlling the reaction.

Treatment groups. The two treatment groups were homogeneous with respect to age, sex and severity of the disease. Each treatment group comprised 15 patients having lepromatous leprosy. Three and two cases of subpolar lepromatous leprosy (LI) received treatment with Regimens A and B respectively (Table 1).

Clinical examination. Thorough clinical examinations were carried out at the beginning of the trial (Day 0) and at the end of the second, fourth and sixth months. The clinical assessments were performed by a physician who was unaware of the treatment regimen. Depending on the degree of regression of the lesions, clinical improvement was classified into the following four grades:

TABLE 1. *Distribution of cases with regard to age, sex and subtype of leprosy.*

Regimen	No. of patients LL and LI	Age in years Range	Mean	Sex Male	Female	Average BI (skin) at start
A	15 (3)[a]	12–55	33.9	12	3	4.8
B	15 (2)[a]	20–65	32.5	11	4	4.9

[a] Subpolar lepromatous leprosy (LI).

TABLE 2. *Delineation of laboratory investigations.*

Investigations	Performed on
Skin smears were taken by the slit and scrape method from both ear lobes and four other selected sites for BI and MI. After averaging the scores of all these six smears taken from a patient at the same time, the mean BI and MI values thus obtained were recorded.	Day 0 and at the end of 2, 4 and 6 months (from the same sites 3 mm to 5 mm apart).
Nose-blow smears were prepared from the discharge obtained by the first nose blow in the morning on paper or cellophane for BI and MI. Duplicate smears were sent to Dr. McDougall, Oxford.	Day 0 and at the end of 1 week and 1, 2, 4, and 6 months.
Skin biopsies for histopathology and LIB[a] were sent to Dr. McDougall, Oxford.	Day 0 and at the end of 6 months (from the same site 5 mm to 8 mm apart).
CBC, platelets, ESR (Westergren) and routine urine examination.	Day 0 and at the end of 2, 4, and 6 months.

[a] Logarithmic Bacterial Index of biopsies.

1 = nil —no change
2 = slight —slight diminution in the size of lesions
3 = moderate —moderate (< 50%) regression of the lesions
4 = marked —marked regression of the lesions characterized by considerable (> 50%) diminution in the size of the lesions and disappearance of some of them.

Laboratory investigations. Table 2 delineates the laboratory investigations carried out in this trial. Bacteriologic and histopathologic assessments were made by independent assessors unaware of the treatment the patients were receiving.

RESULTS

Clinical. Marked clinical improvement was observed in 10 and 11 patients on Regimens A and B respectively (Table 3).

Bacteriologic assessments. *Morphologic Index (MI).* Both regimens produced a rapid reduction in the MI of the skin (Fig. 1) as well as of the nose-blow smears (Fig. 2). The MI averages either reached zero or came nearly to zero, namely less than five, within two months' treatment. The rate of fall of MI averages was practically identical with both regimens. The MI of the skin and nose-blow smears, checked after four and six months, were found to be zero.

Bacteriologic Index (BI). Tables 4 and 5 show that the average decreases in the BI (Ridley's scale) of the skin smears as well as of the nose-blow smears were closely similar after six months' treatment with Regimens A and B. With both regimens the BI of the nose-blow smears showed a relatively greater decrease than that of the skin smears.

Histopathologic evaluations. On examination of skin biopsies, the clinical diagnosis of lepromatous leprosy was confirmed in all 30 patients admitted to this trial. The data from

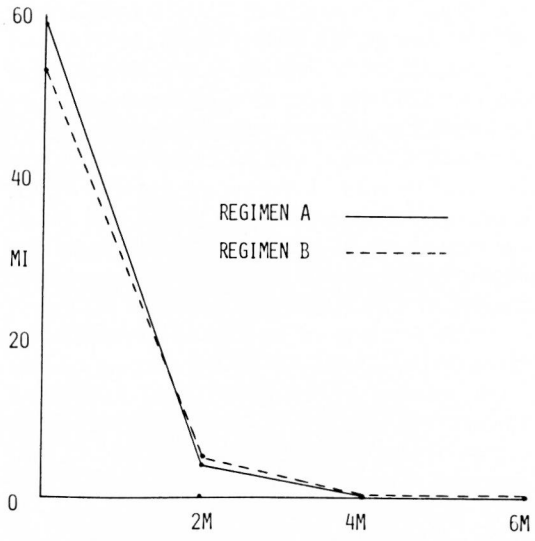

FIG. 1. Fall of MI averages of skin smears.

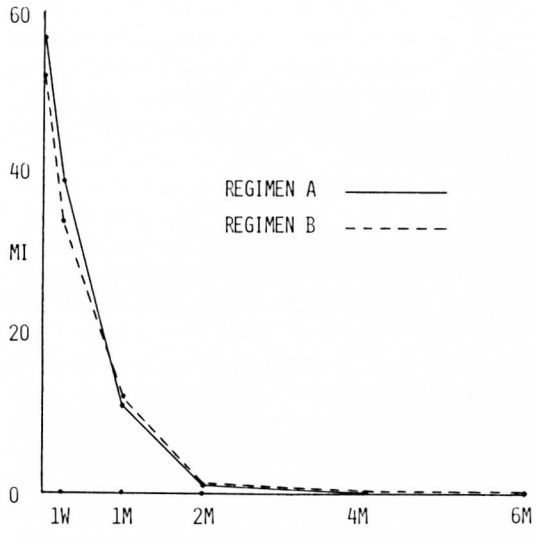

FIG. 2. Fall of MI averages of nose-blow smears.

TABLE 3. *Degree of clinical improvement.*

Regimen	No. of patients	Marked	Moderate	Poor
A	15 (5)[a]	10	3	2[b]
B	15 (4)[a]	11	4	0

[a] Clinically severe cases.
[b] Treatment discontinued due to adverse reactions.

TABLE 4. *Average decrease in BI of skin smears after six months' treatment.*

Regimen	No. of patients	Average BI of skin smears Start	6 months	Average decrease in BI
A	13[a]	4.8	3	1.8
B	15	4.9	3.3	1.6

[a] Treatment was discontinued prematurely in two patients, Table 7.

TABLE 5. *Average decrease in BI of nose-blow smears.*

Regimen	No. of patients	Average BI of nose-blow smears Start	6 months	Average decrease in BI
A	13[a]	4.6	1.6	3
B	15	4.5	1.8	2.7

[a] Treatment was discontinued prematurely in two patients, Table 7.

pre- and post-treatment skin bopsies from 16 patients revealed that following treatment with Regimens A and B the average decreases in the LIB values were practically identical (Table 6). Assessments for the LIB could not be carried out in all patients as some specimens were either not of full skin thickness or were lost in transit.

Adverse effects. Adverse reactions were observed in 4 of a total of 30 patients treated. Due to *erythema nodosum leprosum* (ENL) and hemolytic anemia in two patients on Regimen A, the treatment had to be discontinued after the seventh and eighth weeks, respectively (Table 7). ENL and attacks of neuritis were brought under control and interruption of the trial treatment avoided in two patients on Regimen B. In one patient treated with Regimen B hemolytic anemia was detected at the end of six months' treatment. Toxic effects, such as anuria and thrombocytopenia were not observed.

DISCUSSION

Pattyn *et al* [13] reported that a once-weekly dose of 900 mg rifampicin was as effective as a daily dose of 450 mg rifampicin during the first three months of introductory treatment of patients having lepromatous leprosy, but until now no data have been available on once-monthly treatment with this highly potent drug. To our knowledge, this is the first controlled clinical trial employing a regimen comprising a once-monthly single-dose rifampicin schedule. Contrary to expectations and despite the large, i.e., more than ten times, difference in total dosage, this trial revealed that the therapeutic effects of adding Rimactane 450 mg daily or 1200 mg once monthly in a single dose to a standard dapsone regime were practically identical. Clinical and histopathologic improvements and bacteriologic regression, indicated by the decreases in the BI and MI of the skin and nose-blow smears, were quite satisfactory and closely similar after six months' treatment with Regimens A and B.

There was a good correlation between the rates of fall of the MI of the skin and nose-blow smears (Figs. 1, 2). The nose-blow smears were, however, more sensitive indicators of the bacteriologic evolution. In general, the rates of fall of the MI were slower than those quoted by Rees *et al* [15], who in their early clinical trial observed that with 600 mg rifampicin daily the MI reached a base line of 0-1 faster, i.e., after only four weeks, than with 50 mg twice weekly dapsone treatment where this result was achieved in 20 weeks. In this connection it is known that the bacilli lose the ability to multiply some weeks before they lose microscopically detectable amounts of protoplasm [18].

After treatment with other drugs the reported average annual fall in the BI was about 1+ [8], while in this trial Regimens A and B resulted in average falls of 1.8 and 1.6 in the BI of skin smears, respectively, in only six months.

TABLE 6. *Average decrease in Logarithmic Bacterial Index (LIB) of biopsies.*

Regimen	No. of patients	Average LIB		Average decrease in LIB	
		Start	6 months		
A	8 (3)[a]	4.85	4.48	0.37	(7.6%)
B	8 (2)[a]	4.55	4.19	0.36	(7.9%)

[a] Subpolar lepromatous leprosy (LI).

TABLE 7. *Adverse effects observed during trial treatment.*

Regimen	Patient No.	Adverse effects	Trial treatment
A	320[a]	Severe ENL and hemolytic anemia	Discontinued after 8th week
	328	Hemolytic anemia and icterus	Discontinued after 7th week
B	304	ENL and severe neuritis during 4th month	Continued
	325	Attacks of severe neuritis during the entire treatment period	Continued

[a] Had G6PD deficiency.

Following six months' treatment with Regimens A and B the average decreases in the LIB were practically identical, namely 7.6% and 7.9% respectively and were in order of those quoted by Ridley ([17]), i.e. 5.5% and 14% for polar and subpolar lepromatous leprosy, respectively, in patients treated with dapsone. The findings of this trial correspond to those of Holmes *et al* ([5]) who, on studying the effect of rifampicin, clofazimine and B1912 on the viability of *M. leprae* in established mouse foot pad infection, reported that once-monthly administration of drugs produced effects similar to those of continuous administration. Furthermore, based on the mouse foot pad studies in previously untreated patients, rifampicin in a single dose of 1200 mg proved as effective as a single dose of 1500 mg or a daily dose of 600 mg in terms of the rate at which *M. leprae* were killed ([10]).

On the basis of experience with intermittent rifampicin therapy in tuberculosis ([3]), it was presumed that once-monthly rifampicin administration might lead to more renal adverse effects but none were observed in this trial. Treatment with Regimen A containing daily rifampicin was discontinued in two patients, in one due to severe ENL and hemolytic anemia, and in the other because of hemolytic anemia and icterus. As hemolytic anemia is fairly rare with rifampicin ([1]), the relatively high incidence in this trial (Table 7) could be due to parasitic infections, dapsone and/or G6PD deficiency.

In general, and contrary to expectations, Regimen B with the once-monthly rifampicin schedule was better tolerated. Thrombocytopenic purpura, anuria and uremia did not occur and there was no evidence to suggest that the incidence of lepra reactions was increased by the addition of once-monthly rifampicin to dapsone. From a practical standpoint, once-monthly 1200 mg rifampicin administration offers the following advantages over the 450 mg daily rifampicin schedule:

1. Although the total dosage is less by more than ten times, the therapeutic efficacy is practically identical. On the basis of nose-blow assessments, once-monthly administration is likely to have practically the same effect in arresting the transmission of the disease.

2. To date the high cost is the main obstacle to the large scale use of rifampicin in leprosy. The once-monthly schedule would signify a substantial cost reduction in the treatment of

leprosy and will thus be economically more acceptable in many countries.

3. The once-monthly single rifampicin dose can be administered easily under paramedical or medical supervision; it ensures regular treatment and follow-up, thus avoiding misuses of this expensive drug.

4. Concomitant administration of 600 mg rifampicin daily significantly ($p < 0.001$) reduces the plasma half-life of dapsone ([2]). As the total dose is significantly less, the once-monthly rifampicin schedule would probably have a practically negligible overall effect on the rate of dapsone clearance.

SUMMARY

The clinical, bacteriologic and histopathologic effects of adding Rimactane 450 mg daily or 1200 mg once-monthly to a standard dapsone regimen were practically identical in 30 lepromatous leprosy patients. Rimactane 1200 mg once-monthly in a single dose for six months could, on the basis of this trial, be therapeutically and economically an ideal and easily supervisable component of combination regimens for large scale, initial and intensive treatment of multibacillary (LL, LI and BL) types of leprosy.

This trial has to a great extent solved the problems of rifampicin therapy in leprosy with regard to dosage, dose intervals and duration of the treatment, which have baffled leprologists for so many years. This has been the first controlled clinical trial to demonstrate the practicability and utility of a once-monthly single dose rifampicin schedule in the initial treatment of multibacillary forms of leprosy.

It is suggested that a combination regimen comprising dapsone 50-100 mg daily (1.5-2 mg/kg body weight), Lamprene [R] 100 mg on alternate days, and rifampicin 1200 mg once-monthly in a single dose for six months using long-term follow-up merits further investigation. This triple-drug regimen might prove optimally effective, reasonably safe and fairly economical for the initial treatment of patients with LL, LI and BL leprosy. Furthermore, this combination regimen could result in faster arrest of transmission, and may prevent the emergence of drug resistance.

RESUMEN

Los efectos clínicos, bacteriológicos e histopatológicos resultantes de la adición de Rimactano, 450 mg diarios o 1200 mg una vez al mes, al tratamiento estándard con dapsona, fueron practicamente idénticos en 30 pacientes con lepra lepromatosa. En base a los resultados de este ensayo, el Rimactano a 1200 mg mensuales durante 6 meses podría ser, tanto desde el punto de vista terapéutico como del económico, un componente ideal de una quimioterápia combinada de aplicación en gran escala en el tratamiento inicial y en el tratamiento intensivo de los tipos multibacilares de lepra (LL, LI, BL).

Este ensayo ha resuelto en gran parte los problemas del tratamiento con rifampicina en lepra en relación a dósis, intervalo de las dósis y duración del tratamiento, los cuales han preocupado a los leprólogos durante muchos años. Este ha sido el primer estudio controlado para demostrar la practicabilidad y la utilidad de aplicar una sóla dósis mensual de rifampicina en el tratamiento de las formas multibacilares de la lepra.

Se sugiere que merece mayor investigación la utilización de un tratamiento combinado compuesto por 50-100 mg diarios de dapsona (1.5-2 mg/kg de peso corporal), 100 mg de Lampreno [R] en días alternados y 1200 mg de rifampicina en una sóla dósis mensual durante 6 meses, con evaluaciones a tiempos prolongados. Este esquema con tres drogas podría resultar óptimamente efectivo, razonablemente seguro y considerablemente económico, en el tratamiento inicial de los pacientes con lepra LL, LI y BL. Además, este tratamiento combinado podría dar como resultado una interrupción más rápida de la transmisión y podría evitar la aparición de resistencia a drogas.

RÉSUMÉ

On a constaté que les effets cliniques, bactériologiques et histopathologiques de l'addition de Rimactane à la dose de 450 mg par jour ou de 1200 mg une fois par mois, à un traitement standard à la dapsone, étaient pratiquement identiques ches 30 malades atteints de lèpre lépromateuse. Ainsi qu'il ressort de cet essai, le Rimactane administré en une fois à la dose de 1200 mg une fois par mois et pour 6 mois, pourrait être idéal du point de vue thérapeutique et économique; de plus il pourrait constituer une addition facile à surveiller pour des régimes combinés, à mener sur une large échelle, pour le traitement initial et intensif des types de lèpre multibacillaires (LL, LI et BL).

Cet essai a, pour une grande part, résolu le problème de la thérapeutique par la rifampicine dans la lèpre, en ce qui concerne le dosage, l'intervalle d'administration, et la durée du traitement, questions qui ont rendu les léprologues perplexes pour tant d'années. Ceci a constitué le premier essai clinique contrôlé visant à démontrer le caractère pratique et l'utilité d'une dose clinique mensuelle de rifampicine pour le traitement initial des formes multibacillaires de lèpre. On suggère qu'un régime combiné com-

prenant de la dapsone à la dose de 50-100 mg par jour (1½-2 mg/kg de poids corporel), du Lamprène[R] à la dose de 100 mg tous les deux jours, et de rifampicine à la dose de 1200 mg une fois par mois en dose unique pour 6 mois, mérite davantage d'être étudié. Ce régime triple pourrait se révéler optimal sur le plan de l'efficacité, raisonnablement sans danger, et économiquement avantageux pour le traitement initial des malades atteints de lèpre LL, LI et BL. De plus, ce traitement combiné pourrait entraîner une interruption plus précoce de la transmission, et pourrait prévenir l'apparition de résistance médicamenteuse.

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