INTERNATIONAL JOURNAL OF LEPROSY

Volume 49, Number 4
Printed in the U.S.A.

A Controlled Trial to Compare the Therapeutic Effects of Dapsone in Combination with Daily or Once-Monthly Rifampin in Patients with Lepromatous Leprosy[1]

Diltor Vladimir Araujo Opromolla, Claudio Joaquim Sampaio Tonello, A. Colin McDougall, and S. J. Yawalkar[2]

The first results with rifampin SV in the treatment of leprosy were reported by Opromolla ([12]) in 1963 at the Eighth International Leprosy Congress, Rio de Janeiro, while the pioneer publications ([9, 16]) on the orally active rifamycin, rifampin, in leprosy appeared 7 years later. Although rifampin is the most potent bactericidal drug used in leprosy for more than 10 years, wide differences of opinion exist among leprologists with respect to the dosage, dose-intervals, and duration of treatment ([7, 10, 11, 13, 18]). Mainly in view of the enormous problems posed by the widespread emergence of dapsone-resistant strains of leprosy bacilli, the present generally accepted trend is to use two or preferably three antileprosy drugs for an initial intensive treatment of multibacillary, namely lepromatous (LLs and LLp) and borderline-lepromatous (BL), forms of leprosy ([2,3,6,14,15,17,19]). Untreated lepromatous patients may harbor as many as 10^{11} leprosy bacilli, of which about 10% are likely to be viable ([1]). Rifampin, being a highly potent bactericidal drug, markedly reduces the number of viable bacilli, but it neither curtails the duration of treatment nor eliminates the persistent, viable, drug-sensitive leprosy bacilli in multi-bacillary forms of leprosy.

This paper incorporates the results from the Brazilian center in a Ciba-Geigy sponsored multicenter trial carried out in Brazil, India, and Senegal to delineate the clinical, bacteriological, and histological effects of adding Rimactane® (rifampin) 450 mg daily or 1200 mg once monthly in a single oral dose to dapsone 50 mg daily in patients with lepromatous leprosy. The results from the trial center at Dakar in Senegal, already reported by Languillon, *et al.* ([8]), are the first to show the efficacy and practicability of a once-monthly 1200 mg single oral dose rifampin schedule as a component of combination regimes for the initial treatment of patients with lepromatous leprosy.

PATIENTS AND METHODS

Patients. Thirty-six patients with lepromatous (LLs and LLp) leprosy were admitted to this open, between-patient, controlled trial. Excluding one dropout due to incomplete follow-up, the evaluable trial population comprised 35 patients, 27 males, and 8 females, ranging in age from 12 to 68 years (Table 1). The two treatment groups were homogeneous with respect to number, age, and average pre-treatment bacteriological index (BI) of the skin smears. A larger number of females (6 vs 2) and patients with subpolar lepromatous leprosy (12 vs 6) received treatment with Regimen A.

Methods. The diagnosis was confirmed by a nose-blow smear and skin biopsy. The patients were allocated by a randomized code to one of the following treatment regimens:

a) 450 mg Rimactane® (Ciba-Geigy rifampin) daily + 50 mg dapsone daily;
b) 1200 mg Rimactane® in a single oral

[1] Received for publication on 9 March 1981; accepted for publication on 30 June 1981.

[2] Prof. D. V. A. Opromolla, M.D., Director Medical Service; C. J. S. Tonello, M.D., Physician, Hospital Lauro Souza Lima, Bauru (SP), Brazil; A. C. McDougall, M.D., F.R.C.P., Research Physician, Department of Dermatology, The Slade Hospital, Headington, Oxford, U.K.; S. J. Yawalkar, M.D., D.V.D., F.R.S.T.M. & H., Medical Research, Ciba-Geigy, Basle, Switzerland.

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

Regimen	No. of patients	Age range in years	Sex		Average BI (skin) at start
			Male	Female	
A	17 (12[a])	12–68	11	6	3.6
B	18 (6[a])	14–64	16	2	3.5

[a] Patients with subpolar leprosy (LLs).

dose given in the presence of the physician once monthly + 50 mg dapsone daily.

The duration of the trial treatment was 6 months. Clinical examination and laboratory investigations (skin and nose blow smears, skin biopsies, routine blood and urine examinations) were carried out as reported in Languillon's paper ([8]). Clinical, bacteriological, and histopathological assessments were made by independent assessors unaware of the treatment the patients were receiving. Skin biopsies for histopathology and Logarithmic Bacterial Index of Biopsies (LIB) were sent to Oxford.

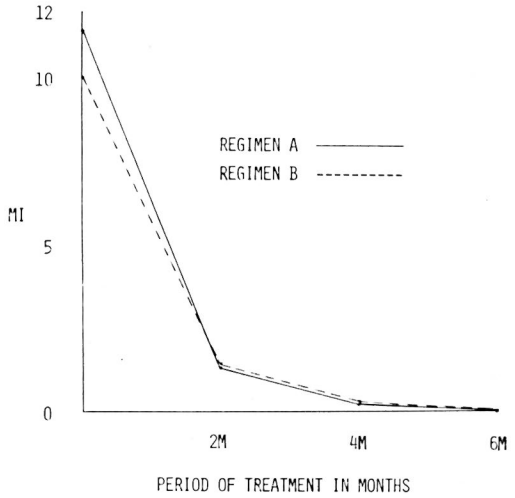
RESULTS

Clinical. Moderate to marked clinical improvement was observed in 88% and 83% of the patients treated with Regimens A and B respectively (Table 2).

Bacteriological assessments.

Skin Smears:

Morphologic Index (MI). The average pre-treatment MI of the skin smears was 11.4% in patients on Regimen A and 10% in patients on Regimen B (The Figure). The rate of fall of MI averages was practically identical with both regimens. Except in two patients, the MI averages of the skin smears reached the base-line value (0–1%) within 4 months' treatment. After 4 months' treatment, the mean MI in one patient on Regimen A was 1.16% and in one patient on Regimen B it was 1.2%.



THE FIGURE. Fall of average MI of skin smears.

Bacteriologic Index (BI). The average decreases in the BI (Ridley's scale) of the skin smears were 0.7 and 0.6 in patients treated with Regimens A and B respectively (Table 3).

Nose Blow Smears:

Morphologic Index (MI). In 13 patients on Regimen A the initial (Day 0) examination proved negative for uniformly stained, solid leprosy bacilli. In the remaining four patients the average pre-treatment MI of the nose-blow smears was 4.7%, and it reached zero after 2 months' treatment.

Uniformly stained, solid bacilli were detected in the initial examination of the nose-blow smears in 9 out of 18 patients treated

TABLE 2. *Degree of clinical improvement.*

Regimen	No. of patients	Marked	Moderate	Slight	Nil
A	17 (7[a])	3	12	2	—
B	18 (10[a])	6	9	2	1

[a] Number of clinically severe cases.

TABLE 3. *Average decrease in BI of skin smears after 6 months' treatment.*

Regimen	No. of patients	Average BI of skin smears		Average decrease in BI
		Start	6 months	
A	17	3.6	2.9	0.7
B	18	3.5	2.9	0.6

TABLE 4. *Average decrease in BI of nose-blow smears.*

Regimen	No. of patients	Average BI of nose-blow smears		Average decrease in BI
		Start	6 months	
A	7	1.9	0	1.9
B	11	2.18	0.45	1.73

with Regimen B. The average pre-treatment MI of these patients was 6.6%, and it reached zero within 2 months in seven patients and within 4 months in two patients.

Bacteriologic Index (BI). The Bacteriologic Index of the nose-blow smears could be determined on Day 0 in seven patients on Regimen A and in 11 patients on Regimen B. The average decreases in the BI (Ridley's scale) were 1.9 and 1.73 after 6 months' treatment with Regimens A and B respectively (Table 4).

Histopathologic evaluations. On examination of skin biopsies, the clinical diagnosis of lepromatous leprosy was confirmed in all patients admitted to this trial. Following 6 months' treatment with Regimens A and B, the average decreases in the LIB were 0.25 and 0.38 respectively (Table 5).

Morphologic Index of skin biopsies. In both treatment groups the average pre-treatment percentage of the uniformly stained, solid bacilli in the skin biopsies was 29% (5–64%). After 6 months it reached the base-line value (0–1%) in all patients treated with Regimen B and in 15 out of a total of 17 patients treated with Regimen A. In two patients on Regimen A, the post-treatment MI average was 2%.

Adverse effects. Mild to moderate erythema nodosum leprosum (ENL), not necessitating discontinuation of the trial treatment, was reported during the second month in one patient on Regimen A and in two patients on Regimen B. Other possible adverse effects, such as "flu" syndrome, anuria, oligura, hemolytic anemia, thrombocytopenia, and anaphylactic shock were not observed in this trial.

DISCUSSION

In this trial center, moderate to marked clinical improvement was observed in 88% and 83% of the patients treated with Regimens A and B respectively. In general, marked clinical improvement was less frequently reported in the Brazilian than in the African ([8]) and Indian ([5]) patients admitted to the Ciba-Geigy sponsored multicenter trial carried out according to the same trial plan. Marked clinical improvement was reported with Regimen A in 18%, 53%, and 67% of the patients treated at the Brazilian, Indian ([5]), and African ([8]) trial centers respectively, while with Regimen B the same degree of clinical improvement was observed in 33%, 46%, and 73% of the Brazilian, Indian ([5]), and African ([8]) patients admitted to this multicenter trial respectively.

In this trial center, Regimens A and B resulted in average falls of 0.7 and 0.6 in the BI of skin smears and 1.9 and 1.73 in the BI of nose-blow smears respectively. In Languillon's trial center ([8]), Regimens A and B resulted in average falls of 1.8 and 1.6 in the BI of skin smears, and 3 and 2.7

TABLE 5. *Average decrease in Logarithmic Bacterial Index (LIB) of skin biopsies.*

Regimen	No. of patients	Average LIB		Average decrease in LIB
		Start	6 months	
A	17 (12[a])	5.30	5.05	0.25 (4.7%)
B	18 (6[a])	5.42	5.04	0.38 (7.0%)

[a] Number of patients with subpolar lepromatous leprosy (LLs).

in the BI of the nose-blow smears respectively. These data revealed that the nose-blow smears were more sensitive indicators of the bacteriologic evolution than the skin smears. The average decreases in the BI of the skin smears reported in the Indian center ([5]) were 1.5 and 1.7 in patients treated with Regimens A and B respectively. These findings show that with the identical treatment bacteriologic regression was slower in the Brazilian patients than in the African and Indian patients with lepromatous leprosy.

Following 6 months' treatment with Regimens A and B the average decreases in the LIB were 4.7% and 7% respectively. These decreases were of the order of those quoted by Languillon, *et al.* ([8]), namely 7.6% and 7.9% for Regimens A and B respectively. The average decreases in the LIB in the Indian center ([5]) were 6.7% with Regimen A and 10.2% with Regimen B.

Both treatment regimens were tolerated well, and discontinuation of the trial treatment was not reported in any of the 35 patients treated at this trial center. Mild or moderately severe ENL reactions were observed in one patient on Regimen A and in two patients on Regimen B. Other adverse effects reported ([4]) with intermittent rifampin therapy in patients with tuberculosis, such as "flu" syndrome, anuria, oliguria, thrombocytopenia, and anaphylactic shock were observed neither at this trial center nor at the African ([8]) and Indian ([5]) trial centers of this multicenter trial.

Despite the more than 10 times difference in the total rifampin dosage between the regimens, the results in a total of 93 patients with lepromatous leprosy from this trial center and from the Indian and African trial centers revealed that the therapeutic effects of adding rifampin 450 mg daily or 1200 mg once monthly in a single dose to a standard dapsone regime for 6 months were practically identical. Considering the good therapeutic efficacy and tolerability, the lower cost of treatment, and the possibility of administration under supervision, once monthly 1200 mg rifampin given in a single oral dose for up to 6 months, along with a standard dapsone regimen, should be recommended for large-scale, initial, and intensive treatment of patients with lepromatous (LLs and LLp) and borderline lepromatous (BL) leprosy.

SUMMARY

In this controlled trial in 35 patients with lepromatous leprosy the therapeutic effects of adding rifampin 450 mg daily (Regimen A) or 1200 mg once a month (Regimen B) to a standard dapsone regimen of 50 mg daily were practically identical. Moderate to marked clinical improvement was observed in 88% and 83% of the patients treated with Regimens A and B respectively. The average rates of decrease in the MI of the skin smears and nose-blow smears were similar. The average decreases in the BI of the skin smears were 0.7 and 0.6 in patients on the Regimen A and B respectively. Following 6 months' treatment with Regimens A and B the average decreases in the Logarithmic Bacterial Indexes of Biopsies were 4.7% and 7% respectively. The once-monthly rifampin schedule was well tolerated and did not lead to "flu" syndrome, anuria, oliguria, hemolytic anemia, thrombocytopenia, or anaphylactic shock. This trial revealed the satisfactory efficacy, good tolerability, and practicability of a supervised once-monthly 1200 mg single oral dose rifampin schedule as a component of combination regimes for the initial treatment of patients with lepromatous (LLs and LLp) leprosy.

RESUMEN

En este ensayo controlado con 35 pacientes con lepra lepromatosa, los efectos terapéuticos resultantes de adicionar 450 mg diarios de rifampina (régimen A) ó 1200 mg una vez por mes (régimen B) al tratamiento convencional de 50 mg diarios de dapsona, fueron practicamente idénticos.

El 88% (régimen A) y el 83% (régimen B) de los pacientes mostraron moderada o marcada mejoría clínica. En ambos casos, los IM en los extendidos de linfa cutanea y de exudado nasal, disminuyeron con la misma velocidad promedio. La disminución promedio en el IB de los extendidos de linfa cutanea fue de 0.7 con el régimen A y de 0.6 con el régimen B. Después de 6 meses de tratamiento, la disminución promedio en el índice bacteriológico logarítmico de las biopsias fue de 4.7 para el régimen A y del 7% para el régimen B. La administración una vez al mes de rifampina fue bien tolerada y no condujo al síndrome de "influenza," anuria, oliguria, anemia hemolítica, trombocitopenia, o choque anafiláctico. Este ensayo

reveló la satisfactoria eficacia, la ausencia de reacciones indeseables y la practicabilidad del régimen supervisado con una sóla dósis oral de 1200 mg de rifampina en combinación con dapsona para el tratamiento inicial de pacientes con lepra lepromatosa (LLs y LLp).

RÉSUMÉ

Au cours d'un essai contrôlé mené chez 35 malades atteints de lèpre lépromateuse, on a observé que les effets thérapeutiques obtenus à la suite de l'addition d'une dose de 450 mg par jour de rifampicine (posologie A) ou de 1200 mg de ce médicament une fois par mois (posologie B), en supplément à une posologie standard de dapsone de 50 mg par jour, étaient identiques. On a noté une amélioration clinique modérée ou marquée chez 88 pour cent et 83 pour cent des malades traités respectivement par la posologie A et par la posologie B. Les taux moyens de diminution de l'Indice Morphologique dans les frottis cutanés et dans les produits de mucus nasal étaient semblables. Les diminutions moyennes notées dans l'Index Bactériologique des frottis cutanés étaient respectivement de 0,7 et de 0,6% chez des malades traités par les posologies A ou B. Après 6 mois de traitement par l'une ou l'autre de ces posologies, les diminutions moyennes de l'Indice Bactérien Logarithmique des biopsies étaient respectivement de 4,7% et de 7%. Le traitement comprenant l'administration de rifampicine, une fois par mois, était bien tolérée, et n'a pas entraîné de syndrome grippal, d'anurie, d'oligurie, d'anémie hémolytique, de thrombocytopénie, ou de choc anaphylactique. Cet essai a montré qu'une posologie faisant appel à l'administration supervisée d'une dose mensuelle clinique de 1200 mg de rifampicine, comme élément d'une posologie combinée pour le traitement initial des malades atteints de lèpre lépromateuse (LLs et LLp), était satisfaisante sur le plan de l'efficacité, bien tolérée, et pratique.

REFERENCES

1. Committee on Experimental Chemotherapy. Experimental chemotherapy of leprosy. Bull. WHO **53** (1976) 425–433.
2. Ellard, G. A. Editorial on combined treatment for lepromatous leprosy. Lepr. Rev. **51** (1980) 199–205.
3. Girdhar, B. K. and Desikan, K. V. "Pulsed" rifampicin therapy in leprosy (abstract). Int. J. Lepr. **48** (1980) 223.
4. Girling, D. J. and Hitze, L. Adverse reactions to rifampicin. Bull. WHO **57** (1979) 45–49.
5. Ghosh, S., McDougall, A. C., Hajra, S. K. and Yawalkar, S. J. Controlled comparison of therapeutic effects of DDS in combination with daily or once-monthly rifampicin in patients with lepromatous leprosy. Data on file, Medical Dept., Ciba-Giegy, Basle.
6. Heathrow Meeting Report, ILEP. Lepra **1** (1977) 12.
7. Languillon, J. La Rifampicine et Ethambutol dans la maladie de Hansen. Acta Leprol. **46** (1972) 123–131.
8. Languillon, J., Yawalkar, S. J. and McDougall, A. C. Therapeutic effects of adding Rimactane® (rifampicin) 450 mg daily or 1200 mg once monthly in a single dose to dapsone 50 mg daily in patients with lepromatous leprosy. Int. J. Lepr. **47** (1979) 37–43.
9. Leiker, D. L. and Kamp, H. First results of treatment of leprosy with Rifadin. Lepr. Rev. **41** (1970) 25–30.
10. Levy, L., Shepard, C. C. and Fasal, P. Death of *M. leprae* following treatment of leprosy patients with 1500 mg rifampicin in a single dose. Int. J. Lepr. **41** (1973) 490.
11. Namba, M. and Hazama, S. Effect of rifampicin on leprosy: comparative study with several doses and intervals of administration. Int. J. Lepr. **44** (1976) 198.
12. Opromolla, D. V. A. First results of the use of rifampicin SV in the treatment of lepromatous leprosy (abstract). Int. J. Lepr. **31** (1963) 552.
13. Pattyn, S. R., Rollier, M. J., Rollier, R., Saerens, E. J. and Dockx, P. A controlled clinical trial of continuous and intermittent rifampicin therapy during initial three months period in lepromatous leprosy. Lepr. Rev. **46** (1975) 129–139.
14. Pearson, J. M. H., Haile, G. S., Barnetson, R. St. C. and Rees, R. J. W. Dapsone-resistant leprosy in Ethiopia. Lepr. Rev. **50** (1979) 183–199.
15. Rees, R. J. W. Combined therapy in principle and practice for the control of dapsone resistance. Lepr. Rev. **49** (1978) 97–100.
16. Rees, R. J. W., Pearson, J. M. H. and Waters, M. F. R. Experimental and clinical studies on rifampicin in treatment of leprosy. Br. Med. J. **1** (1970) 89–92.
17. Rees, R. J. W., Waters, M. F. R., Pearson, J. M. H., Helmy, H. S. and Laing, A. B. G. Long-term treatment of dapsone-resistant leprosy with rifampicin. Int. J. Lepr. **44** (1976) 159–169.
18. Waters, M. F. R., Rees, R. J. W., Pearson, J. M. H., Laing, A. B. G., Helmy, H. S. and Gelber, R. H. Rifampicin for lepromatous leprosy: nine years' experience. Br. Med. J. **1** (1978) 133–136.
19. WHO Expert Committee on Leprosy. Fifth Report. WHO Technical Report Series, No. 607. Geneva: World Health Organization, 1977.