Therapy of Leprosy with Rifampicin[1]

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Rifampicin or rifamycin AMP is the 3-(4-methyl-piperazinyl-iminomethyl) semi-synthetic derivative of rifamycin SV. Rifamycin SV itself is derived from rifamycin B, the fermentation product of *Streptomyces mediterranei.* In contrast to rifamycin SV and rifamide, another rifamycin derivative, which have to be administered parenterally, rifampicin is orally active.

The specific gram-positive antibacterial activity of rifampicin exceeds that of the whole group of penicillins, cephalosporins and broad spectrum antibiotics (tetracyclines, chloramphenicol, lincomycin, erythromycin and fusidic acid).

Rifampicin also displays a good effect against gram-negative bacteria and *Mycobacterium tuberculosis* (1).

The *in vivo* activity of rifampicin has been experimentally demonstrated in animals and in many clinical trials.

Experimental investigations on absorption, biological half-life, tissue distribution and excretion of rifampicin show that the drug reaches high mean blood levels after two hours and maintains bactericidal concentrations up to fifteen hours. The high concentrations encountered in inflammatory exudates (granuloma pouch), lacrimal gland, liver and other tissues reveal the high tissue affinity of rifampicin.

Findings collected in the human being show a good correlation with the experimental ones, especially when they refer to blood and tissue concentration, distribution and excretion, which is made principally through liver and kidney (4).

Rifamycines were first employed for the treatment of lepromatous leprosy by Opromola and Souza Lima in 1965 (5). Their results with the injectable form of the antibiotic and the fact that rifampicin is better absorbed and possesses bactericidal action, suggested to us in 1968 the possibility of trying it in the management of a few patients of leprosy at the Colonia Sommer, Buenos Aires.

MATERIALS AND METHODS

Since 1968 we have had the opportunity of treating 20 patients of both sexes, aged 18 to 82 years (mean: 43.6), with oral doses of rifampicin. They were afflicted with lepromatous leprosy in varying stages. Ten patients belonged to form L1, six to L2 and four to L3.

Aiming not only to determine if rifampicin was active against *Mycobacterium leprae* but trying also to set, tentatively at least, the most appropriate dosage, patients were treated by two dose regimes. Twelve patients received 150 mg daily and eight patients, 450 mg/day. Treatment with the drug was continous and without interruption. Four patients have been 17 months on the drug, another four 12 months, eight for 6 months and four for only 2 months.

The evaluation of the therapeutic results was based on the following parameters.

Clinical parameters. Clinical evolution was graded (2) as follows:

Stationary (*S*): patients not presenting any discernible modification of their clinical state,

Slight Betterment (*SB*): patients presenting slight flattening of lepromas and lessening of skin infiltration with paling of maculae,

Definite Betterment (*DB*): patients presenting greater reduction of infiltration lepromas flattening and partial skin-hair regrowth.

Marked Betterment (*MB*): markedly reduced infiltration, disappearance of lepromas, complete skin-hair regrowth, return of normal skin color.

Bacilloscopic parameters. Modifications

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in the number, morphologic and tinctorial characteristics of bacilli have been taken into consideration.

Sommer's scheme, as reported by Wilkinson *et al* ([9]), in association with Ridley's technic ([6]) is very useful, because it permits at a glance the appreciation of the bacilloscopic changes evidenced by a given patient, Figure 1. The Sommer's scheme is a graphic representation of the morphologic status of the bacilli and their number per microscopic field. The quality of bacilli per field is determined by Ridley's procedure and as charted (Figure 1) it is possible to appreciate at a glance the evolution of any leprosy patient. It is clear that any notation on the upper left reflects a severe state. When the trend of successive notations tend to the lower right quandrant the case is improving. The tinctorial characteristic of the bacilli can also be registered in the scheme adding a letter (T = typical; I = isolated; G = granular; IG = isolated granules).

Histopathology. Skin biopsies were obtained from all patients after the first year of treatment.

Laboratory determinations. At regular intervals R.B.C. and W.B.C.; E.S.R., B.U.N., blood sugar and urine analysis were performed.

RESULTS

Clinical results. The observed clinical results are tabulated according to the duration of therapy (Table 1), according to the dosage used (Table 2), in both instances relative to the severity of the initial presentation.

Bacilloscopic results. (Figure 1) Bacilloscopic negativity developed in 11 cases (55%), (Tables 3 and 4); of these patients, seven were L1, three were L2 and one was L3. Six were under treatment with 150 mg/day and the remaining five received 450 mg/day. In six patients (30%) who started treatment with mean bacillary val-

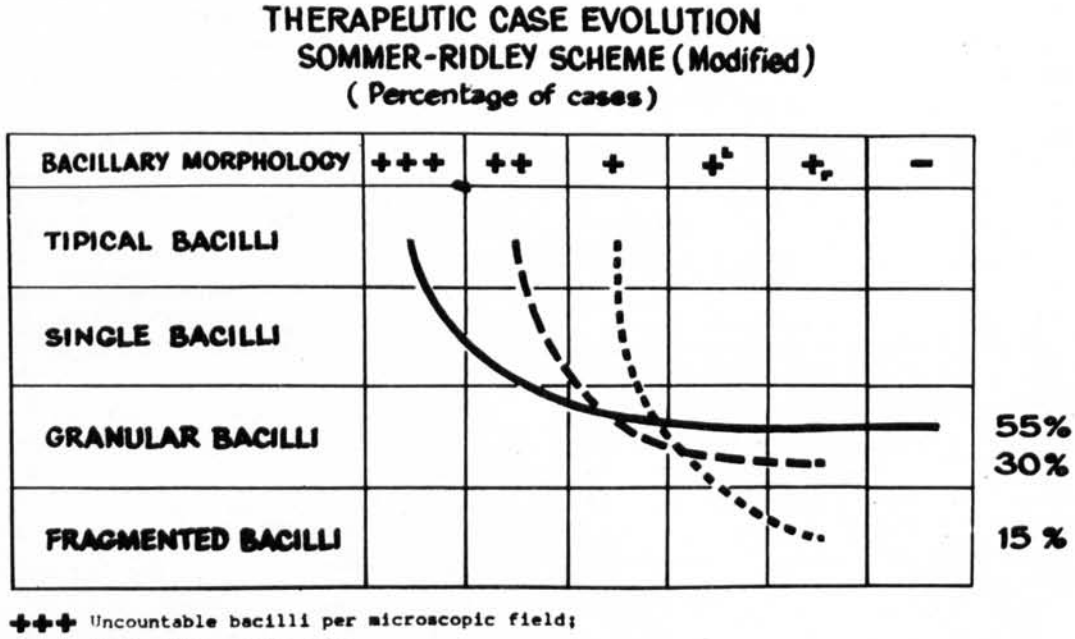

FIG. 1

TABLE 1. *Clinical results correlated with the duration of therapy.*

	2 months			6 months			12 months			17 months		
N	SB	DB	MB	SB	DB	MB	SB	DB	MB	SB	DB	MB
L1 10			3		1	2			2			2
L2 6					2	1			2			1
L3 4		1		1		1						1

SB=Slight betterment.
DB=Definite betterment.
MB=Marked betterment.

ues as high as uncountable typical bacilli and "globi" per field, a marked improvement with reduction of granulated bacilli to an average for the six cases of 2.6 bacilli per field, was seen. The remaining three cases (15%) presented also a marked betterment. The number of bacilli was reduced from an average of 10 to 30 per field to a mean, for the three cases, of 1.1 bacilli per field.

In the 20 patients studied the bacilloscopic investigations performed demonstrated, as signs of the efficacy of rifampicin, different degrees of morphologic and tictorial alterations of the bacilli. The effect on the bacilli appears very quickly and after only two weeks of treatment at a dose of 150 mg/day, it is possible to observe granularity of bacilli.

Histopathology. Histopathologic studies of skin biopsies were performed in all the patients completing one year of therapy.

In seven patients evident signs of involution of the lepromas were observed.

Degrees of involution are expressed in terms of reduction of infiltration, presence of fibrosis and disappearance of bacilli (Figure 1).

TABLE 2. *Clinical results correlated with drug dosage.*

	150 mg			450 mg		
N	SB	DB	MB	SB	DB	MB
L1 10			6		1	4
L2 6		2	2			2
L3 4	1	1				2

SB=Slight betterment.
DB=Definite betterment.
MB=Marked betterment.

From the group of patients on 150 mg/day, in the two cases treated for more than 12 months, signs of histopathologic involution were seen (L1 treated for 17 months and L2, 12 months).

Among the patients in the 450 mg/day, six were treated for 12 months or more. Of these, five presented clear histologic signs of involution (L1–12 months; L1–17 months; L2–12 months; L2–17 months and L3–17 months).

Leprotic lepromatous reaction. Two patients presented a lepromatous reaction during the therapy. One patient of the L1 type after 12 months of therapy on a dose of 150 mg/day developed a transient *erythema nodosum* without fever, which did not require withdrawal of the medication.

The second case, L2 type, developed a lepromatous reaction with severe fever after six months therapy with 150 mg/day. Because this patient did not respond to thalidomide, he was treated with ACTH and betamethasone; thus rifampicin therapy had to be interrupted.

Side effects. Rifampicin was well tolerated. Two patients had slight gastric disturbances which were easily controllable by changing the time of capsules ingestion ([6]).

Another patient presented slight signs of photo-sensitization.

Other medications. Four patients (3 of L2; 1 of L3) received together with rifampicin, 4-amino-N-10 methyl-pteroilglutamic acid. Two of these were on the 150 mg/day schedule and the other two on 450 mg/day. After six months in one case and more than

TABLE 3. *Time achievement of bacterial negativity.*

Bacilli negative in	2 months	1 case	(L1)
Bacilli negative in	6 months	3 cases	(L1,L1,L2)
Bacilli negative in	12 months	4 cases	(L1,L1,L1,L2)
Bacilli negative in	17 months	3 cases	(L1,L1,L3)

12 months in the remaining three, all became bacilli negative.

DISCUSSION

Rifampicin is the most rapid and active leprostatic agent available. The mechanism of action of the drug is species specific ([8]), consisting chiefly in its very strong binding capacity to bacterial RNA polimerase which is necessary for the transcription process. This circumstance assures on one hand the irreversibility of action of rifampicin (bactericidal action), and on the other hand that its effect cannot be interfered with by vitamins (folic acid) ([3]) or other medications.

Our results suggest that similar results can be achieved with either 150 mg/day or 450 mg/day, which is important with respect to the high price of the drug. The best bacteriologic results were obtained in those patients afflicted with less severe forms of the disease and in those treated for longer periods, chiefly exceeding six months. Morphologic and tictorial alterations of the bacilli seen a few days after beginning with rifampicin gave testimony of its speed of action.

TABLE 4. *Record of treatment results.*

Patient	Age Sex	Lepromatous type	Therapy (months)	Clinical[a]	Bacterial Index	Histopathology
150 MG/DAY						
1. P.M.	33 F	L1	2	MB	6.6 to neg.	
2. P.A.	70 M	L1	2	MB	4.2 to 1.1	
3. T.M.	31 F	L1	2	MB	2.8 to 1.1	
4. J.P.	24 M	L1	6	MB	1.7 to neg.	
5. R.A.	44 M	L1	6	MB	6.4 to neg.	
6. M.F.	18 M	L1	17	MB	4.4 to neg.	Slight involution
7. V.P.	30 M	L2	6	DB	6.6 to 1.8	
8. R.S.	40 M	L2	6	DB	6.7 to 1.1	
9. M.J.	42 M	L2	6	MB	4.6 to neg.	
10. J.C.	60 M	L2	12	MB	6.0 to neg.	Evident involution
11. M.S.	38 M	L3	2	MB	6.0 to 3.6	
12. R.S.	32 M	L3	6	SB	4.2 to 2.8	
450 MG/DAY						
13. R.G.	26 M	L1	6	DB	6.3 to 1.9	
14. A.R.	56 M	L1	12	MB	4.6 to neg.	
15. L.C.	51 M	L1	12	MB	3.6 to neg.	Evident involution
16. L.V.	32 M	L1	17	MB	6.2 to neg.	Slight involution
17. L.C.	43 M	L2	12	MB	4.0 to neg.	Slight involution
18. R.G.	41 M	L2	17	MB	6.0 to 1.8	Fibrosis
19. R.V.	82 M	L3	6	MB	6.0 to 3.8	
20. F.A.	80 M	L3	17	MB	6.3 to neg.	Marked involution

[a] SB = Slightly better.
DB = Definitely better.
MB = Much better.

It seems that lepromatous reaction and side effects will not constitute an obstacle to using rifampicin therapy, because of the low incidence of these effects.

SUMMARY

Twenty lepromatous leprosy patients were treated for two to seventeen months with rifampicin. Clinical improvement of three-fourths of the cases was achieved. Eleven patients became negative for acid-fast bacilli in a relatively short time. Bacilloscopic conversions depend only on the degree of severity of the disease and duration of therapy and not on dosage, being equal at 150 mg or 450 mg/day.

Side effects were scarce and only one severe lepromatous reaction was observed. Tolerability was very good considering the prolonged treatment periods.

RESUMEN

Veinte pacientes con lepra lepromatosa se trataron con rifampicina durante entre dos y diecisiete meses. Se obtuvo mejoría clínica en tres cuartas partes de los casos. Once de los pacientes se tornaron negativos para bacilos alcohol-ácido resistentes en un período relativamente corto. Las conversiones baciloscópicas dependen solamente del grado de severidad de la enfermendad y la duración de la terapia y no de la dosis, ya que fué igual con 150 mg o 450 mg por día.

RÉSUMÉ

Vingt malades atteints de lèpre lépromateuse ont été traités pendant deux à dix-sept mois par la rifampicine. Une amélioration clinique a été obtenue chez les trois-quarts des cas. Onze malades sont devenus négatifs pour les bacilles acido-résistants en un laps de temps relativement court. Le virage bactérioscopique ne dépend que du degré de gravité de la maladie et de la durée du traitement, et non de la posologie administrée, laquelle s'élevait à 150 ou à 450 mg par jour.

Les effets secondaires ont été rares. Une seule réaction lépromateuse grave a été observée. La tolérance a été excellente, si l'on considère la longue durée des traitements administrés.

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