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High Relapse Rate among Lepromatous Leprosy Patients Treated with Rifampin plus Ofloxacin Daily for 4 Weeks

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Fifty-one lepromatous leprosy patients, all of whom had relapsed after previous dapsone (DDS) monotherapy, were treated between 1990 and 1991 with 600 mg of rifampin (RMP) plus 400 mg of ofloxacin (OFLO) daily for 4 weeks, and the great majority of the patients were followed up at least once a year after completion of the treatment. After only 173 patient-years of follow-up, 5 relapses had been detected; the overall relapse rate was 10.0% (confidence limits, 1.7 and 18.3%), or 2.9 relapses (confidence limits, 0.4 and 5.4) per 100 patient-years. The unacceptably high relapse rate indicated that 4 weeks of treatment with daily RMP-OFLO was unable to reduce the number of viable *Mycobacterium leprae* organisms to a negligible level. In addition, the *M. leprae* from one of the relapses were proved to have multiple resistance to DDS, RMP, and OFLO. To avoid further relapses, the follow-up was terminated and the great majority of the patients were retreated with the standard 2-year multidrug therapy from 1994. No further relapse has been diagnosed since the beginning of retreatment.

Since the recommendation of multidrug therapy (MDT) by a World Health Organization study group in 1982 (21, 22), more than 8 million leprosy patients around the world have completed their treatment with the MDT regimens (20). Despite the success of the MDT regimens, a newer generation of regimens that are more effective or operationally less demanding is required (12). One of the needs (12) is to shorten significantly the duration of treatment for multibacillary (MB) leprosy.

Because ofloxacin (OFLO) displayed very promising bactericidal activity against *Mycobacterium leprae* in a murine model (4), and because 4 weeks of treatment with 400 mg of OFLO daily produced remarkable clinical improvement and killed at least 99.99% (4 orders of magnitude) of *M. leprae* bacilli in lepromatous leprosy patients (5, 13), it was thought that, in combination with rifampin (RMP), by far the most bactericidal drug against *M. leprae* (12), OFLO might provide the potential to increase the effectiveness and to shorten the duration of antileprosy chemotherapy, and that it was likely that all RMP-resistant mutants in an untreated lepromatous leprosy patient, estimated to be no more than 10^4, could be eliminated within 4 weeks of treatment with an OFLO-containing regimen (5, 13).

Between June 1990 and June 1991, 51 patients with lepromatous leprosy were admitted to the Institut Marchoux. All of them had relapsed after dapsone (DDS) monotherapy. Based on the available information with respect to DDS-resistant leprosy in Mali (8), many of the relapses had probably been caused by the emergence of DDS-resistant *M. leprae*. Because these patients were living in the rural areas of Mali where MDT was not yet available, and they were unable to visit the nearest health centers regularly in order to receive the monthly supervised MDT treatment for 24 months, the patients were hospitalized in the Institut Marchoux and treated with a combination of RMP plus OFLO daily for 4 weeks; the long-term efficacy of this treatment was assessed by the relapse rate of MB leprosy.

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MATERIALS AND METHODS

Patients. There were 51 patients, 39 males and 12 females, with a mean age of 42 ± 11 (range, 20 to 60) years by the time of admission; 38 were classified as polar lepromatous (LL) and 13 were borderline lepromatous (BL) by the Ridley-Jopling classification (16). All had relapsed after a mean duration of 11 ± 8 (range, 1 to 35) years of DDS monotherapy; according to the records, none of them had been treated previously with RMP. Informed consent to the treatment with RMP plus OFLO daily for 4 weeks was obtained from the patients.

Before the trial, all of the patients showed multiple active skin lesions of LL or BL leprosy, such as diffuse infiltration, erythemas, plaques, nodules, or lepromas. The great majority of the patients had high bacterial loads, with a mean bacterial index (BI) of 4.31 ± 0.87 (range, 1.30 to 5.16; 38 cases with a BI of ≥4.0 and 13 cases with a BI of <4.0), and the mean LOGAFB, i.e., the number ($\log_{10}$) of *M. leprae* bacilli per mg of tissue (5), was (3.5 ± 5.1) × 10^6 (range, 4.9 × 10^3 to 2.1 × 10^7). Solid-staining bacilli were detected in the skin smears from 46 (90.2%) of the 51 patients, with a mean morphological index (MI) of 3.2 ± 4.9% (range, 0 to 32.0%). The viability of *M. leprae* organisms had been tested by mouse footpad inoculation (see below) with organisms recovered from the skin biopsy samples of 50 patients (all except patient 10), and multiplication of *M. leprae* (hence the demonstration of viable *M. leprae*) had been observed in the mouse footpads that had been inoculated with the organisms recovered from the biopsy samples of 46 (92%) patients; *M. leprae* organisms from 30 patients had multiplied in ≥2/3 of harvested mouse footpads, indicating that, before the trial, the great majority of patients harbored proportions of viable *M. leprae* organisms that could easily be detected by inoculation into footpads of immunocompetent (normal) mice. Susceptibility to DDS and RMP (9) was tested with 10 strains of *M. leprae* isolated from the biopsy samples taken before treatment with RMP-OFLO, and susceptibility to OFLO (19) for 3 of the 10 strains was also tested; 7 of the 10 strains were found to be resistant to DDS, but all were susceptible to RMP or OFLO.

Chemotherapy. Patients were hospitalized until completion of the treatment, which consisted of 600 mg of RMP plus 400 mg of OFLO daily for 4 weeks. Both drugs were administered under supervision by medical personnel, and the 4-week treatment was completed for all 51 patients.

Follow-up. After completion of the treatment, the patients were asked to return to the Institut Marchoux at least once a year. Whenever a patient came to the clinic, a thorough physical examination was carried out, with special emphasis on the evolution of preexisting leprosy lesions and the detection of suspected new lesions. Skin smears were taken from the same sites (normally six) originally examined if no such examination had been repeated within the past 12 months, and from any suspected new lesion(s).

Relapse was suspected if the BI at any site was found to have increased by at least 2+ (2 $\log_{10}$) over the previous value or if a new skin lesion was observed with a BI greater than that in any preexisting lesion (7, 15). Further examinations included repeating the physical examination, retesting the skin smears, and taking a biopsy sample from the suspected lesion in order to test the viability and

TABLE 1. Clinical response and changes in BI and MI from the skin smears

Date[a]	*n*	No. (%) of patients with clinical improvement score[b]			Mean BI	Mean MI
		0	1+	2+		
D0	51				4.31 ± 0.87	3.2 ± 4.9
D28	51	8 (15.7)	33 (64.7)	10 (19.6)	4.08 ± 1.04	0.5 ± 0.7
Y1	49[c]	4 (8.2)	24 (49.0)	21 (42.8)	3.47 ± 1.19	0.01 ± 0.06

[a] D0, pretreatment; D28, at the end of 4 weeks of treatment with daily RMP-OFLO; Y1, 1 year after stopping RMP-OFLO.
[b] 0, no change compared with D0; 1+, slight but definite amelioration; 2+, significant improvement.
[c] Including patient 40, who relapsed with new lesions at 12 months after stopping treatment.

the susceptibility of the organisms to RMP, OFLO, and DDS by mouse footpad inoculation. Relapse was diagnosed if two of the following three criteria were met (7, 15): (i) the occurrence of a definite new skin lesion, (ii) confirmation of an increase of the BI at any site by at least 2+ over the previous value, and (iii) demonstration of viable *M. leprae* by mouse footpad inoculation.

Testing for viability and drug susceptibility of *M. leprae*. A bacterial suspension was prepared from skin biopsy samples, and 5×10^3 acid-fast bacilli (AFB) were inoculated into each of the hind footpads of normal mice according to Shepard's method (17). Inoculated mice were randomly allocated to an untreated control group with at least 10 mice and five treatment groups with 8 to 10 mice each; the treatments began 1 week after inoculation and continued until the organisms were harvested. Among the treated mice, three groups were treated, respectively, with a mouse diet containing 0.0001, 0.001, or 0.01% DDS (9), and one group each was treated by esophageal cannulation (gavage) with either 10 mg of RMP/kg of body weight once weekly (3) or 150 mg of OFLO/kg 5 times weekly (4). Six to eight months after inoculation, footpads from untreated control mice were harvested for AFB counting (17), and the harvests were repeated at regular intervals until the average number of organisms per footpad reached 5×10^5; at that time, harvests of *M. leprae* were performed immediately from the footpads of all of the treated groups. The presence of viable organisms in a biopsy sample was indicated by multiplication of *M. leprae* (defined as $\geq 10^5$ AFB per footpad harvested 12 months after inoculation) identified in at least one of 10 harvested footpads from untreated control mice; otherwise the specimen was considered to have contained a proportion of viable organisms insufficient to be detected by inoculation into footpads of normal mice. For the drug susceptibility test, the isolate was defined as drug susceptible if multiplication of *M. leprae* was observed only in untreated mice and not in any treated mouse; the isolate was defined as drug resistant if multiplication of *M. leprae* was observed in at least one treated mouse; the result was considered inconclusive if multiplication of *M. leprae* was observed in only a few of the untreated control mice and in none of the treated mice (9).

Statistical analysis. Results were analyzed by the Student *t* test and Fisher's exact probability calculation. Differences were considered significant at the 95% level of confidence. In calculating the overall relapse rate and the relapse rate per 100 patient-years, the number of relapsed patients was used as the numerator, while the number of patients eligible for analysis of relapse or the total duration of follow-up, in patient-years, respectively, was used as the denominator.

RESULTS

Clinical response and changes of BIs and MIs in skin smears. As shown in Table 1, clinical improvement was observed in almost 85% of patients at the end of 4 weeks of treatment, but the improvement that was scored as 2+ was seen in fewer than one-fourth of the improved patients. One year after treatment was stopped, more than 90% of the patients demonstrated improvement and the percentage of patients showing 2+ improvement had increased significantly over that at the end of treatment ($P < 0.05$).

As is also shown in Table 1, the mean BI at the end of 4 weeks of treatment did not differ significantly from the pretreatment value; however, the proportion of patients with MIs of >0 had decreased significantly from 46 of 51 (90.2%) before treatment to 28 of 51 (54.1%) ($P < 0.01$) at the end of 4 weeks of treatment, and the mean MI had also decreased during the same period ($P < 0.01$).

Adverse reactions to the treatment. During the 4 weeks of treatment with RMP-OFLO, 11 patients had the following complaints: nausea, 3 cases; diarrhea, 10 cases; abdominal pain, 1 case; and dizziness, 1 case. All the events were mild and transitory, were not accompanied by significant findings on physical examination, and subsided spontaneously despite continuation of the treatment. Therefore, it is difficult to attribute these complaints to the treatment.

Leprosy reactions during the treatment. Ten patients developed erythema nodosum leprosum during treatment with RMP-OFLO: two at the 2nd week and four each at the 3rd and 4th weeks of treatment. The erythema nodosum leprosum reactions were rapidly controlled with prednisolone. No reversal reaction was observed during the trial.

Results of follow-up after completion of RMP-OFLO. Of the 51 patients, only patient 26 never returned for a follow-up examination; he died 1 year after completion of his RMP-OFLO treatment. Thus, 50 patients are eligible for analysis of the relapse rate. Five additional patients (no. 8, 30, 32, 39, and 40) died at various intervals during the initial 4 years of follow-up. Forty-nine patients (98%) were examined before the end of the 1st year of follow-up, with one relapse (patient 40); 41 (87.2%) of the 47 patients who survived without evidence of relapse at the end of the 1st year were examined before the end of the 2nd year of follow-up, with two additional relapses (patients 5 and 11); 37 (84.1%) of the 44 patients who survived without evidence of relapse at the end of the 2nd year were examined before the end of the 3rd year of follow-up, with another relapse (patient 41); and 34 (91.9%) of the 37 patients who survived without evidence of relapse at the end of the 3rd year were examined before the end of the 4th year of follow-up, with an additional relapse (patient 34). Therefore, a majority of patients were regularly examined during follow-up. The duration of follow-up after RMP-OFLO treatment was calculated by the intervals between the date of completion of the treatment and (i) the date of last visit without relapse for those not yet retreated with MDT (see below), (ii) the date of beginning of retreatment with MDT for those without evidence of relapse, and (iii) the date of diagnosis of relapse. The mean duration of follow-up for the 50 patients was 41 ± 12 (range, 11 to 66) months after RMP-OFLO, and the total duration of follow-up was 2,052 patient-months, or 171 patient-years.

As shown in Table 1, both the BI and the MI continued to decline after treatment was stopped. At approximately 1 year after the completion of treatment, the mean BI and MI were significantly smaller than at the end of treatment ($P < 0.05$ and $P < 0.01$, respectively), and only 3 (6.1%) of 49 patients had MIs of >0.

However, 5 relapses were detected between 12 and 40 months after RMP-OFLO was stopped, yielding an overall relapse rate of 10.0% (confidence limits, 1.7 and 18.3%), or 2.9 relapses (confidence limits, 0.4 and 5.4) per 100 patient-years. In addition, the *M. leprae* from patient 40, one of those who relapsed, was proved to have multiple resistance to DDS, RMP, and OFLO by mouse footpad inoculation and molecular analysis (1). To avoid further relapse in this particular group of patients, we decided to stop the follow-up and to retreat them

with the standard 2-year MDT regimen for MB leprosy, which became available in most parts of Mali in 1994–1995. By the end of 1996, 42 (89.4%) of 47 surviving patients had been retreated with MDT. While the 5 patients who relapsed were retreated as soon as the diagnosis of relapse was confirmed (3 in 1992 and 1 each in 1993 and 1994), 30 of 37 nonrelapsing patients were retreated in 1994, 5 were retreated in 1995, and 2 were retreated in 1996. No further relapses have been detected since the beginning of retreatment with MDT. Nonetheless, the duration of follow-up after completion of MDT has been short, as most of these patients have just completed the 2-year course of MDT.

Characteristics of the patients who relapsed. As shown in Table 2, the diagnoses of the five relapses were based on the following evidence: (i) the appearance of new lesions of lepromatous leprosy, i.e., nodules or plaques, (ii) a significant increase in BI over the previous values, and (iii) the demonstration of viable *M. leprae* by mouse footpad inoculation. The mean incubation period for the five relapses was 24.6 ± 10.5 months (range, 12 to 40 months) after completion of RMP-OFLO.

Based on the average BI at the beginning of treatment with RMP-OFLO, the 50 cases can be divided into two groups: BI $\geq$ 4.0 (37 cases) and BI $<$ 4.0 (13 cases). There were four relapses among the former group and one relapse among the latter group ($P > 0.05$). Therefore, no clear correlation between relapse and the bacterial load of the patient before treatment was detected.

The results of drug susceptibility testing of the organisms recovered from the relapsed lesions are also presented in Table 2. The results of the isolate from patient 11 were inconclusive (9) because multiplication of *M. leprae* was observed only in 1 of 10 untreated mice; three isolates (from patients 5, 34, and 41) were susceptible to both RMP and OFLO; and one isolate (from patient 40) was resistant to DDS, RMP, and OFLO by mouse footpad inoculation, and this result was also confirmed by molecular analysis (1).

DISCUSSION

RMP displays very rapid and powerful bactericidal activity against *M. leprae* in patients with MB leprosy. Virtually immediately after treatment with a regimen that contains RMP is begun, the great majority of the viable *M. leprae* organisms are killed. The proportion of surviving organisms is so small that viable organisms cannot be detected by inoculation of normal mice with 5×10^3 to 10^4 organisms per footpad (14) and are detected in only a minority of instances by inoculation of thymectomized, irradiated, and bone marrow-reconstituted (T900R) mice with 10^5 *M. leprae* bacilli per footpad (2). Although OFLO is less bactericidal than RMP (12), 4 weeks of treatment with 400 mg of OFLO daily killed at least 99.99% of viable *M. leprae* organisms in MB leprosy patients (5, 13). Therefore, as expected, after 4 weeks of treatment with daily RMP-OFLO, the great majority of the patients in the present trial showed various degrees of clinical improvement, together with a significant decline of the MI in the skin smears. Clinical and bacteriological examinations carried out 1 year after completion of treatment revealed that the improvements continued, indicating that the 4-week treatment with RMP-OFLO had a profound impact. None of the bacilli recovered from the skin biopsy samples taken from three nonrelapsing patients (no. 29, 38, and 51) at 2 to 3 years after RMP-OFLO multiplied in the footpads of normal mice, suggesting that, after treatment with RMP-OFLO, the proportion of viable *M. leprae*

TABLE 2. Summary of the five cases of lepromatous leprosy relapse after 4 weeks of treatment with daily RMP plus OFLO

Case no.	Yr of birth	Sex	Classification	Duration of previous DDS monotherapy (yr)	Average BI[a] by:			New lesion(s)				*M. leprae* from relapsed lesion		
					Beginning of R-O	End of R-O	Last visit before relapse	Diagnosis of relapse	Incubation period (mo)[b]	Clinical feature	MI (%)	BI	Viability[c]	Susceptibility[d] to: RMP	Susceptibility[d] to: OFLO	Susceptibility[d] to: DDS
34	1942	M	LL	3	5.00	5.00	4.60	5.00	40	Nodules	2.5	5+	10/10	S (0/10)	S (0/10)	ND
40	1935	M	LL	1	4.80	4.80	3.30	5.00	12	Nodules	7.0	5+	7/12	R (3/8)	R (3/10)	R to 0.01% (4/6)
41	1950	M	LL	9	5.00	5.00	4.60	5.00	29	Nodules	34.0	5+	5/5	S (0/5)	S (0/5)	S to 0.0001% (0/5)
05	1935	M	LL	1	4.50	3.80	2.50	4.66	21	Nodules	20.0	5+	8/8	S (0/6)	S (0/6)	ND
11	1942	M	BL	5	3.10	1.00	1.00	3.66	21	Plaques	0.5	4+	1/10		Inconclusive	

[a] Calculated from the results of all (normally six) sites. R-O, RMP plus OFLO.

[b] Interval between stopping treatment with daily RMP plus OFLO and the diagnosis of relapse.

[c] Viability of *M. leprae* was determined by inoculation with 5,000 bacilli per footpad of immunocompetent mice. Results were expressed as the number of mice showing multiplication of *M. leprae*/number of mice from which footpads were harvested in untreated control group.

[d] S, susceptible; R, resistant; inconclusive, multiplication of *M. leprae* was observed in very few untreated control mice; ND, not done. Results in parentheses are the number of mice showing multiplication of *M. leprae*/number of mice from which footpads were harvested in the treated group.

bacilli had decreased to a level undetectable by inoculation of normal mice.

However, the numbers of *M. leprae* bacilli that can be recovered from a skin biopsy sample from a leprosy patient and can be inoculated into a mouse footpad are relatively small. Even by inoculation of nude mice with 10^6 to 10^7 organisms per footpad, one can measure only the initial 99.999% killing of *M. leprae* (5, 10–13), whereas an active lepromatous patient may begin treatment with a total of 10^{10} to 10^{11} viable organisms. Thus, the failure to demonstrate multiplication of *M. leprae* even in nude mice at the end of treatment may not be taken as evidence that all viable *M. leprae* bacilli within the hosts have been killed. In other words, the therapeutic effect of RMP-containing combined regimens cannot be evaluated adequately by classic clinical trials. The only way to evaluate the long-term efficacy of various RMP-containing combined regimens is to measure the relapse rate after treatment. We had reported earlier that, among lepromatous patients, the relapse rate after short-course treatment with several RMP-containing regimens was unacceptably high, more than 1 per 100 patient-years, although the initial responses of the patients to the treatments were very favorable (6, 15).

In the present trial, after only 173 patient-years of follow-up, five relapses were detected. The overall relapse rate was 10.0% (confidence limits, 1.7 and 18.3%), or 2.9 relapses (confidence limits, 0.4 and 5.4) per 100 patient-years, indicating that 4 weeks of treatment with daily RMP-OFLO was unable to reduce the numbers of viable *M. leprae* bacilli in the hosts to such a level that the risk of relapse after stopping treatment would be negligible. In addition, the *M. leprae* bacilli from one of the patients who relapsed were demonstrated to be multiply resistant to DDS, RMP, and OFLO (1). To avoid further relapses in this particular group of patients, the follow-up was terminated and the great majority of patients were retreated with the standard MDT (21, 22). No further relapses have been detected since the beginning of retreatment.

The incubation period of relapse, i.e., the intervals between the end of treatment and the occurrence of relapse, in the present trial was 24.6 ± 10.5 months (with the shortest interval being only 12 months), which was significantly shorter ($P < 0.01$) than the 62.7 ± 18.7 months observed among patients who relapsed after treatment with standard MDT (7). There are at least two possible explanations for the difference in incubation periods of relapse between the two trials. The first explanation is that the regimen of RMP-OFLO given daily for 4 weeks was less bactericidal than the 2-year standard MDT regimen. The second explanation, which is related to the pretreatment characteristics of the patients rather than to the efficacy of the regimen, is that before treatment, the mean BI of the patients in the present trial was 4.31 ± 0.87, a value significantly greater ($P < 0.05$) than the 3.80 ± 1.09 in the trial with the standard MDT regimen (7); because the bacterial load was greater in the patients of the present trial, it is likely that at the end of treatment, the number of persisting *M. leprae* bacilli (18) was also greater, resulting in a greater risk and earlier onset of relapse. Whatever the explanation, our earlier conclusion (6, 7) that the incubation period of relapse after treatment with any RMP-containing regimen was long, at least 5 ± 2 years, should be revised.

With respect to the multidrug-resistant *M. leprae* isolated from one of the relapsing patients, the resistance to DDS obviously resulted from previous DDS monotherapy. It is unlikely that resistance to both RMP and OFLO developed simultaneously during the 4 weeks of treatment with daily RMP plus OFLO, because the treatment was fully supervised and the frequency of double-resistance mutations in *rpo*β and *gyrA* is around 10^{-14} (10^{-7} for each mutation), whereas the total number of viable *M. leprae* bacilli harbored by a patient with lepromatous leprosy is no more than 10^{11}. We believe that this strain of *M. leprae* had successively acquired resistance to DDS and RMP (3) before the RMP-OFLO treatment and that the patient was treated, in effect, with OFLO monotherapy, leading to the selection of OFLO-resistant mutants. Although the patient's history did not indicate that he had received RMP before the trial, self-administration of antibiotics is not uncommon in some parts of the world, even in rural areas of developing countries. Therefore, this case suggests that MB leprosy patients relapsing after previous treatment should not be treated with combinations of RMP plus only a single new antibiotic.

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