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Bactericidal Activity of Single Dose of Clarithromycin plus Minocycline, with or without Ofloxacin, against *Mycobacterium leprae* in Patients

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Fifty patients with newly diagnosed lepromatous leprosy were allocated randomly to one of five groups and treated with either a month-long standard regimen of multidrug therapy (MDT) for multibacillary leprosy, a single dose of 600 mg of rifampin, a month-long regimen with the dapsone (DDS) and clofazimine (CLO) components of the standard MDT, or a single dose of 2,000 mg of clarithromycin (CLARI) plus 200 mg of minocycline (MINO), with or without the addition of 800 mg of ofloxacin (OFLO). At the end of 1 month, clinical improvement accompanied by significant decreases of morphological indexes in skin smears was observed in about half of the patients of each group. A significant bactericidal effect was demonstrated in the great majority of patients in all five groups by inoculating the footpads of mice with organisms recovered from biopsy samples obtained before and after treatment. Rifampin proved to be a bactericidal drug against *Mycobacterium leprae* more potent than any combination of the other drugs. A single dose of CLARI-MINO, with or without OFLO, displayed a degree of bactericidal activity similar to that of a regimen daily of doses of DDS-CLO for 1 month, suggesting that it may be possible to replace the DDS and CLO components of the MDT with a monthly dose of CLARI-MINO, with or without OFLO. However, gastrointestinal adverse events were quite frequent among patients treated with CLARI-MINO, with or without OFLO, and may be attributed to the higher dosage of CLARI or MINO or to the combination of CLARI-MINO plus OFLO. In future trials, therefore, we propose to reduce the dosages of the drugs to 1,000 mg of CLARI, 100 mg of MINO, and 400 mg of OFLO.

The standard regimen of multidrug therapy (MDT) recommended by the World Health Organization for paucibacillary leprosy lasts 6 months and consists of two drugs, dapsone (DDS), administered daily, and rifampin (RMP), administered monthly, and that for multibacillary (MB) leprosy lasts 24 months and consists of three drugs, DDS and clofazimine (CLO), administered daily, and RMP plus a supplemental higher dose of CLO, administered monthly (19, 20). The drugs given monthly are always administered under supervision. Since 1982, MDT has been intensively implemented in all areas where leprosy is endemic. By May 1996, 91% of registered leprosy patients in the world were being treated by MDT, nearly 8 million leprosy patients had already been cured by the treatment, and the global prevalence rate of leprosy was declining (18). Both MDT regimens have been well tolerated, and the relapse rates have been surprisingly low, of the order of 0.1% per annum (17).

Despite the success of the MDT, a newer generation of MTD regimens that are more effective or operationally less demanding is required (12). It would be extremely helpful if leprosy patients could be treated by fully supervised regimens based on a monthly administration of all of the drugs; this would significantly simplify the delivery of antileprosy chemotherapy by general health services and improve the rate of compliance of leprosy patients to the treatment. However, the components of a fully supervised, monthly administered regimen must fulfill the following requirements: (i) a single dose must display a certain degree of bactericidal activity against *Mycobacterium leprae* and (ii) the effective dosage must be well tolerated (21).

Previously, we and others have demonstrated that clarithromycin (CLARI) and minocycline (MINO) exert powerful bactericidal activities against *M. leprae* both in mice (10) and in lepromatous leprosy patients (2–6, 9) and that a single dose of CLARI plus MINO, with or without added ofloxacin (OFLO), exhibits certain bactericidal activity against *M. leprae* in both immunocompetent (normal) (11, 21) and nude mice (12). As a first step to develop a fully supervised, monthly administered MDT regimen, the objectives of the trial were to confirm the bactericidal effect of a single dose of CLARI-MINO, with or without OFLO, against *M. leprae* in lepromatous patients and to evaluate the risk of adverse events of the treatments, employing the standard MDT regimen (19) or its RMP or DDS-CLO component as the positive control.

MATERIALS AND METHODS

Patients. Between July 1992 and June 1994, 50 newly diagnosed lepromatous patients with high bacterial loads and active skin lesions were recruited into the trial by the Institut Marchoux, Bamako, Mali. Of the 50 patients, 37 were male and 13 were female, with a mean age of 31.3 ± 10.5 years (range, 15 to 60 years); 22 were classified as having polar lepromatous leprosy, and 28 were classified as having borderline lepromatous leprosy (14). During the first visit to the clinic, all patients denied having had previous antileprosy treatment and no DDS was detected in urine specimens. The patients were randomly allocated to one of the five groups, with 10 patients in each group; the groups were comparable with regard to patient pretreatment characteristics, including sex, age, classification of the disease, severity of skin lesions, mean bacterial index (BI) and morphological index (MI) in skin smears, and proportion of viable *M. leprae* in the bacterial population.

Chemotherapy. The patients of group I were treated with 1 month of the

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TABLE 1. Sample results from titrating the proportions of viable *M. leprae* organisms in mouse footpads

Patient[a]	Date of test[b]	No. of footpads showing multiplication[c] of *M. leprae*/no. footpads harvested at the following inoculum:				Proportion (%) of viable *M. leprae*[d]	Proportion (%) of viable organisms killed by treatment[e]
		5×10^3	5×10^2	5×10^1	5×10^0		
7	D0	10/10	5/10	2/10	1/10	0.28	
	D31	0/10	0/10	0/10	0/10	<0.006	>97.9
6	D0	10/10	10/10	6/10	4/10	4.35	
	D31	0/10	0/10	0/10	0/10	<0.006	>99.9
38	D0	10/10	10/10	10/10	8/10	27.47	
	D31	10/10	7/10	3/10	1/10	0.548	98.0
5	D0	9/10	9/10	4/10	3/10	1.38	
	D31	7/10	2/10	0/10	0/10	0.035	97.5
21	D0	10/10	7/10	4/10	0/10	0.55	
	D31	0/10	0/10	0/10	0/10	<0.006	>98.9

[a] Patients 7, 6, 38, 5, and 21 were treated, respectively, with regimens I, II, III, IV, and V. Patients in groups I to V ($n = 10$ for each group) were treated, respectively, with 1 month of the standard MDT regimen for MB leprosy; a single dose of 600 mg of RMP; 30 days of DDS and CLO in the standard MDT dosages for MB leprosy; a single dose of 2,000 mg of CLARI plus 200 mg of MINO; and a single dose of 2,000 mg of CLARI plus 200 mg of MINO plus 800 mg of OFLO.

[b] D0 and D31 refer, respectively, to before and after treatment.

[c] Multiplication is defined as $\geq 10^5$ AFB harvested per footpad.

[d] Derived from the equation 0.69/50% infectious dose (15).

[e] Comparisons of the proportions of viable *M. leprae* at the end of the trial and the numbers of organisms before treatment.

standard MDT regimen for MB leprosy, i.e., a single dose of 600 mg of RMP plus 300 mg of CLO on day 1 (D1), together with 100 mg of DDS and 50 mg of CLO daily for 30 days (19); those of group II were administered a single dose of 600 mg of RMP on D1; those of group III were treated with 30 days of DDS and CLO in the dosages of the standard MDT regimen for MB leprosy, i.e., 300 mg of CLO on D1, together with 100 mg of DDS and 50 mg of CLO daily for 30 days; those of group IV were administered a single dose of 2,000 mg of CLARI plus 200 mg of MINO on D1; and those of group V were treated with a single combined dose of 2,000 mg of CLARI and 200 mg of MINO plus 800 mg of OFLO. The same dosages of CLARI, MINO, and OFLO had been used for other clinical conditions, including leprosy (5, 13), but not in the combinations employed in our trial. For patients of groups II, IV, and V, placebos were given once daily from D2 to D30. The patients were hospitalized during the trial, and all of the drugs and placebos, including those administered daily, were given under strict supervision by medical personnel, so the surreptitious intake of RMP during the trial can be ruled out.

Examinations before and after the trial. The clinical, bacteriological, and other laboratory examinations undertaken have been described at length elsewhere (7, 9, 13). In brief, before starting treatment (D0), patients were subjected to a thorough physical examination, especially one for leprosy. Skin lesions were photographed; a lepromin test was performed; a chest X-ray examination was made; hepatic and renal function tests were carried out; skin smears were taken from six sites for measurement of BI and MI; and skin biopsies of two distinct, active lesions were performed for measurement of the proportion of viable *M. leprae* in mouse footpads after inoculation. Of the two biopsies, only the organisms from the lesion demonstrating the greater concentration of *M. leprae*, in terms of the $\log_{10}$ of the number of acid-fast bacilli (AFB) per milligram of tissue (7), or those from the lesion with the higher MI were selected for mouse inoculation. Except for the lepromin test and chest X ray, the examinations were repeated at the end of the trial, i.e., D31 after starting treatment. The skin smears were taken from the same six sites tested before treatment, and the skin biopsy sample for each patient was taken from the pretreatment site that had provided *M. leprae* for mouse inoculation. The clinical responses, in terms of amelioration of nasal obstruction, regression of infiltration, and flattening or disappearance of nodules, lepromas, or plaques, compared with the pretreatment manifestations, were scored as showing no change or improvement (7, 9, 13). The anti-*M. leprae* activities of the regimens were assessed by comparison of the MIs of the skin smears and the proportions of viable *M. leprae* recorded at the end of the trial with the pretreatment (D0) values. Adverse events of the treatments were assessed by the patients' complaints and the hepatic and renal function tests.

The proportion of viable organisms in the bacterial population was titrated by inoculating 10-fold serially diluted suspensions, prepared from a single skin biopsy sample from each patient, into the hind footpads of mice. In brief, each of the four dilutions of the suspensions with organisms recovered from the biopsies taken on D0 or D31 were inoculated into the footpads of 10 normal mice, with inocula of 5×10^3, 5×10^2, 5×10^1, or 5×10^0 organisms per footpad. The footpads were harvested 12 months after inoculation for counting of AFB by Shepard and McKae's method (16). In our laboratory, the final volume of the suspension prepared from each footpad was 2.0 ml. When 10 μl of the suspension was spread over the entire area of a circle (16) with diameter of 1.13 cm and examined with a microscope with a field diameter of 0.018 cm, detection of a single bacillus in the course of examining about 40 oil-immersion fields from two circles indicated the presence of 1.97×10^4 AFB per footpad. The organisms were considered to have multiplied (i.e., the inoculum included viable organisms) if $\geq 10^5$ AFB per footpad were harvested. A bactericidal effect of the treatment was defined as a significant decrease of the proportion of viable *M. leprae* in the treated group from its pretreatment value.

Statistical analysis. Except for the determinations of the proportions of viable *M. leprae*, results were analyzed and compared by the paired-sample Student *t* test and Fisher's exact probability calculation. Differences were considered significant at the 95% level of confidence. The proportions of viable organisms in the suspensions and the significance of their differences were calculated by the Spearman-Kärber method (15), employing the results of the harvests of *M. leprae* from the mouse footpads that had been inoculated with the serially 10-fold-diluted suspensions prepared from the single sample from each patient. In our trial, in which only normal mice were inoculated and the maximal inoculum was 5×10^3 AFB per footpad, a proportion of viable *M. leprae* as small as 0.006% could be measured. Typical results of such a measurement are shown in Table 1.

RESULTS

Clinical response. As shown in Table 2, clinical improvement was observed in about half of the patients of each group by D31 and the proportions of patients demonstrating clinical improvement did not differ significantly among the five treated groups.

Changes of BIs and MIs in skin smears. As is also shown in Table 2, by the end of the trial the mean BIs were virtually unchanged from the pretreatment values, except for the patients of group I, whose mean BI was marginally but significantly lower on D31 than on D0 ($P < 0.05$). On the other hand, the mean MIs decreased considerably among the patients of all five groups ($P < 0.01$), indicating that all the regimens displayed a certain degree of anti-*M. leprae* activity in lepromatous patients; as usual (12), no significant difference in the reductions of the MIs could be detected among the groups that had been treated with various effective regimens.

Bactericidal activities of the treatments against *M. leprae*. The pretreatment biopsy samples from 49 (98%) of the 50 patients harbored sufficient concentrations of viable *M. leprae*, and, therefore, these organisms could be detected by inoculation into the footpads of normal mice. However, the proportions of viable *M. leprae* varied widely among the pretreatment biopsy sample, ranging from a barely detectable level (0.006%) to more than 30%; the median values did not differ significantly among the groups, which were, respectively, 1.09, 0.26, 0.89, 1.38, and 1.96% for groups I, II, III, IV, and V.

As shown in Table 3, by D31 the proportions of viable

TABLE 2. Clinical responses and changes in BIs and MIs from patient skin smears

Group[a]	No. of patients showing indicated clinical response on D31		BI on[b]:		MI on[b]:	
	No change	Improvement	D0	D31	D0	D31[c]
I	2	8	4.61 ± 0.54	4.41 ± 0.67[c]	4.8 ± 1.8	1.4 ± 1.9
II	6	4	4.58 ± 0.55	4.43 ± 0.67	6.1 ± 2.2	1.0 ± 0.8
III	6	4	4.43 ± 0.62	4.51 ± 0.64	6.4 ± 3.0	3.5 ± 1.8
IV	4	6	4.35 ± 0.57	4.18 ± 0.70	7.3 ± 2.3	1.8 ± 1.1
V	3	7	4.82 ± 0.37	4.72 ± 0.33	5.1 ± 2.6	1.9 ± 1.4

[a] For the drug regimens of groups I to V, see Table 1, footnote *a*.
[b] Means ± standard deviations.
[c] Significantly smaller than the pretreatment (D0) value of the same group ($P < 0.01$).

organisms in patient biopsy samples had significantly decreased (≥90%) from the pretreatment values in 39 (79.6%) patients, remained unchanged in 4 patients, and slightly decreased in 6 patients. Because such a significant decrease of viable organisms was observed in the great majority of patients of all five groups, all five tested regimens displayed some degree of bactericidal activity.

It is important to point out that the bactericidal activities of the treatments of 11 patients (no. 5, 8, 9, 10, 13, 14, 20, 34, 38, 44, and 48) from groups III, IV, and V, or 47.8% of the 23 patients in the three groups showing significant bactericidal activities, were demonstrated only when the proportions of viable *M. leprae* were titrated; otherwise, bactericidal activity would be masked if only a single inoculum of 5×10^3 organisms per footpad was inoculated, because the proportion of footpads showing multiplication of *M. leprae* among footpads that had been inoculated with 5×10^3 organisms recovered from posttreatment biopsies did not differ significantly from that recovered from pretreatment biopsies (see patients 5 and 38 in Table 1). These findings indicate that the titration of the proportion of viable *M. leprae* in the bacterial population is a sensitive and precise method of quantifying the bactericidal effect of a treatment.

After treatment, the organisms from 28 (57.1%) of the 49 patients had lost their infectivity in the footpads of normal mice that had been inoculated with a maximum inoculum of 5×10^3 *M. leprae* per footpad, and two-thirds of the 28 patients had been treated with a single dose of RMP, either alone (group II) or in combination with DDS and CLO (group I). In fact, the organisms from all 19 patients of groups I and II had lost their infectivity after a single dose of treatment, whereas only 9 (30%) of the 30 patients that had been treated by regimens without RMP showed the same phenomenon ($P < 0.01$). Thus, RMP is still the most effective bactericidal drug against *M. leprae* and is more potent than any combination of the other drugs.

As is also shown in Table 3, the results of groups IV and V demonstrated that a single dose of CLARI-MINO or CLARI-MINO-OFLO displayed a certain degree of bactericidal effect against *M. leprae* in cases of human leprosy, which was similar to that of a month of daily treatment with DDS-CLO. However, the effects did not differ significantly between the groups treated with CLARI-MINO or with CLARI-MINO-OFLO.

The results of group III indicate that the bactericidal effect of 30 days of treatment with DDS-CLO administered daily is quite promising, since significant bactericidal activity was observed in 8 of the 10 patients and the organisms from 4 of them had lost their infectivity in the footpads of normal mice.

Leprosy reactions. During the 30-day trial, erythema nodosum leprosum developed in nine patients (four patients in group I, one patient in group III, and four patients in group V) and reversal reactions were noted in two patients (one patient each in groups II and V). In addition, acute neuritis occurred in two patients (one patient each in groups I and V). The reactions were rapidly controlled by the administration of prednisolone.

Adverse events of the treatments. Table 4 summarizes the major adverse events of the treatments. The most frequent events were those of the gastrointestinal system (nausea, vomiting, abdominal pain, or diarrhea) and were highly correlated to the regimens of treatment, occurring in 17 (85%) of the 20 patients in groups IV and V, i.e., those patients who were

TABLE 3. Testing of bactericidal activities among patients treated with various regimens

Group[a]	No. of patients with viable *M. leprae*[b] before treatment	No. of patients showing indicated bactericidal effect[c]			No. of patients whose *M. leprae* lost infectivity in normal mice[d]
		0%	1 to <90%	>90%	
I	9	0	0	9	9
II	10	0	3	7	10
III	10	2	0	8	4
IV	10	0	1	9	3
V	10	2	2	6	2
Total	49	4	6	39	28

[a] For the regimens of groups I to V, see Table 1, footnote *a*.
[b] Defined as *M. leprae* which had multiplied in the footpad of a normal mouse after the maximum inoculation of 5×10^3 organisms.
[c] Bactericidal activities were measured by comparing the proportions of viable organisms at the end of the trial with those before treatment. e.g., 0% indicates no decrease in the number of viable organisms from the pretreatment number.
[d] Refers to patients who harbored viable *M. leprae* in the pretreatment biopsy samples but who at the end of the trial showed no multiplication of *M. leprae* after their specimens (5×10^3 organisms per footpad) were inoculated into at least 10 footpads of normal mice.

TABLE 4. Major adverse events of treatments

Adverse event	% (*n*) of patients of indicated groups[a] showing adverse event	
	I, II, and III ($n = 30$)	IV and V ($n = 20$)
Nausea	6.7 (2)	30.0 (6)
Diarrhea	3.3 (1)	10.0 (2)
Abdominal pain	3.3 (1)	45.0 (9)
Vomiting	0 (0)	40.0 (8)
Dizziness	0 (0)	10.0 (2)

[a] For the regimens of groups I to V, see Table 1, footnote *a*.

treated with CLARI-MINO, with (group V) or without (group IV) OFLO, but occurring in only 2 (6.7%) of 30 patients in groups I, II, and III, i.e., those who were treated with regimens without CLARI, MINO, and OFLO; the frequencies of these events in the former groups were significantly greater than those of the latter groups ($P < 0.01$). Except for diarrhea, the frequency of each of the gastrointestinal events was also significantly greater in groups treated with CLARI-MINO, with or without OFLO ($P < 0.01$), than in groups not treated with CLARI-MINO. Although dizziness was reported only for patients treated with CLARI-MINO and may probably be attributed to the vestibular toxicity of MINO (1), because of its relatively low frequency and the small sample size per group, the difference in frequencies of dizziness among the groups did not attain statistical significance.

The great majority of these events were mild to moderate, occurred quite rapidly (between 15 min and 2 h after the administration of CLARI-MINO, with or without OFLO), and lasted for no more than a few hours before subsiding spontaneously. For those patients with vomiting, no drug debris was identified in the vomitus. Because the patients of groups IV and V received only a single dose during the trial, it is difficult to say whether the patients would have had to discontinue treatment because of the adverse events.

From the hepatic and renal function tests repeated at D31, the only abnormality with possible clinical significance was the elevation of the level of glutamic puruvic transaminase in the serum of patient 46, who had been treated with DDS-CLO.

DISCUSSION

The current clinical trial has clearly confirmed for lepromatous patients the following findings, which had been observed in earlier studies with nude mice (12). First, RMP remains by far the most effective bactericidal drug against *M. leprae*; its activity is greater than those of any combination of the new antileprosy drugs, i.e., CLARI, MINO, and OFLO; and it will continue to play a key role in the treatment of leprosy. Second, a single dose of CLARI-MINO, with or without OFLO, displayed a certain degree of bactericidal activity against *M. leprae*; a significant bactericidal effect (it killed ≥90% of viable *M. leprae* compared with the pretreatment value) was observed in three-fourths of the lepromatous patients. The bactericidal activities were quite similar between the groups treated with a single dose of CLARI-MINO and with CLARI-MINO-OFLO (Table 3), indicating that the addition of OFLO did not enhance the bactericidal activity of CLARI-MINO. However, the activity of a single dose of either drug combination did not differ significantly from that of DDS-CLO administered daily for 1 month, suggesting that it may be possible to replace the DDS and CLO components of the current MDT regimen with a monthly dose of CLARI-MINO, with or without OFLO. Finally, DDS-CLO administered daily for 1 month displayed significant bactericidal activity against *M. leprae* in the great majority of lepromatous patients, and the organisms from 4 of the 10 patients treated with this regimen had lost their infectivity in the footpads of normal mice, a degree of activity which was inconsistent with that observed in the experiment with nude mice (12) and which was much greater than had been expected (8).

With respect to the bactericidal activity displayed by a single dose of CLARI-MINO, with or without OFLO, although it has been claimed that no detectable bactericidal effect has been observed in leprosy patients after treatment with a single dose CLARI (2, 6) or MINO (3, 5) in clinical trials conducted by other investigators, these observations do not nullify our conclusion for the following reasons. First, only a single inoculum size, i.e., 5×10^3 AFB per footpad, was employed by the other investigators (2, 3, 5, 6) in measuring the viability of *M. leprae* after treatment and the bactericidal effect would have been masked if the proportions of viable *M. leprae* were not titrated, as was correctly pointed out by one of these investigators (5) and confirmed by our trial. Second, in one of these trials the proportions of footpads with viable *M. leprae*, in fact, decreased for six of eight patients after a single 200-mg dose of MINO (5).

Confirmation of the bactericidal activities in lepromatous patients of a single dose of the combination CLARI-MINO, with or without OFLO, and demonstration of the possibility of replacing daily, self-administered DDS-CLO components of the current MDT regimen with a monthly dose of CLARI-MINO, with or without OFLO, represent a major step toward the development of MDT drug combinations, such as RMP-CLARI-MINO or RMP-CLARI-MINO-OFLO, which consist only of drugs that are administered monthly and therefore may be fully supervised. Nevertheless, as shown in Table 4, the gastrointestinal adverse events were quite frequent among patients treated with a single dose of CLARI-MINO, with or without OFLO, indicating that the tolerance of the patients to the two combinations is poor. Because gastrointestinal adverse events had been both rare and mild in earlier clinical trials, in which patients were treated with 500 mg of CLARI plus 100 mg of MINO daily (9); or 400 mg of OFLO, 100 mg of DDS, and 50 mg of CLO daily together with 300 mg of CLO once every 28 days (13); or 800 mg of OFLO daily (13), the frequent gastrointestinal adverse events observed in the current trial may be attributed to the higher dosage of CLARI (2,000 mg) or MINO (200 mg) or the combination of CLARI-MINO plus OFLO; therefore, the dosages of the drugs should be reduced in the future clinical trials. The bactericidal activities against *M. leprae* did not differ significantly between mice treated with a single dose of 200 mg of CLARI per kg of body weight plus 50 mg of MINO per kg and with 100 mg of CLARI per kg plus 25 mg of MINO per kg (21), nor was there a difference between patients treated with 400 mg of OFLO daily and those treated with 800 mg of OFLO daily (13). Moreover, it was estimated that the area under the concentration-time curve of CLARI administered to mice in dosages of 100 or 200 mg/kg is equivalent, respectively, to that of 1,000- or 2,000-mg doses of CLARI in humans and that the area under the concentration-time curve of MINO administered to mice in dosages of 25 or 50 mg/kg is equivalent, respectively, to that of 100- or 200-mg doses of MINO in humans (21). Therefore, the dosages of the new drugs should be reduced to 1,000 mg of CLARI, 100 mg of MINO, and 400 mg of OFLO in future trials.

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