Powerful Bactericidal Activity of Moxifloxacin in Human Leprosy^V

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In a clinical trial of moxifloxacin in eight multibacillary leprosy patients, moxifloxacin proved highly effective. In all trial patients, a single 400-mg dose of moxifloxacin resulted in significant killing ($P \leq 0.006$) of *Mycobacterium leprae*, ranging from 82% to 99%, with a mean of 91%. In all instances, no viable bacilli were detected with an additional 3 weeks of daily therapy, this observed rapid bactericidal activity being matched previously only by rifampin. On moxifloxacin therapy, skin lesions cleared exceedingly rapidly with definite improvement observed consistently after eight doses and progressive resolution continuing for the 56 days of the trial. Side effects, toxicities, and laboratory abnormalities were mild, not requiring discontinuation of therapy.

Fluoroquinolones have proven to be active against *Mycobacterium leprae* in rodents (10, 13, 18, 20, 31) and in clinical trials (9, 19, 26) in leprosy patients. The first studies of fluoroquinolones in *M. leprae*-infected mice found that ciprofloxacin was inactive while pefloxacin and ofloxacin were bactericidal (18, 20). We (13) tested several fluoroquinolones against *M. leprae* in mice, finding some, namely WIN5727, temafloxacin, and particularly sparfloxacin, to be superior to pefloxacin and ofloxacin. Furthermore, in the heavily infected, neonatally thymectomized Lewis rat, the combination of rifampin and ofloxacin was more regularly sterilizing than the combinations of both rifampin plus dapsone and rifampin plus clofazimine (10), rifampin, dapsone, and clofazimine being the three components of the widely implemented WHO-recommended regimens for treatment of multibacillary (MB) leprosy (36, 37). Clinical trials of pefloxacin and ofloxacin treatments in leprosy have demonstrated encouraging clinical responses and the clearance of viable *M. leprae* within 2 months (9, 19, 26), this rate of clearance being higher than those with dapsone and clofazimine (several months [32]), similar to those with minocycline (8, 12) and clarithromycin (3), but much lower than that with rifampin (29, 32, 34).

Moxifloxacin against *Mycobacterium tuberculosis* (6, 14, 23, 25) has been found to be more bactericidal in vitro than other quinolones and similar in bactericidal activity to rifampin. Also, moxifloxacin has been demonstrated in a murine model of tuberculosis to add to the sterilizing activities of isoniazid, rifampin, and pyrazinamide (27) and to provide significant bactericidal activity in the first few days of treatment of human tuberculosis, both as monotherapy (17, 24, 28) and as multidrug therapy (2, 15). As a result, trials with moxifloxacin treatment of active pulmonary tuberculosis are currently in progress, using it to both replace established agents and shorten the course of effective therapy of active pulmonary tuberculosis.

In a murine model of leprosy, moxifloxacin has been demonstrated to be more bactericidal than ofloxacin and, in that regard, as potent as rifampin (5). Because the 1-year WHO regimen (37)

for MB leprosy is still quite lengthy, some studies have found double-digit relapse rates even after 2 years of this regimen (11, 16, 22), and the emergence of rifampin-resistant *M. leprae* is of concern; the discovery of alternative bactericidal agents to treat leprosy remains a high priority. Thus, we embarked on this present clinical trial of moxifloxacin treatment for leprosy.

(Preliminary results of this study were presented at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 2006.)

MATERIALS AND METHODS

At the clinical branch of the Leonard Wood Memorial Leprosy Research Center, Cebu, Philippines, eight previously untreated MB leprosy patients without a history of leprosy treatment or lepra reactions and having a high bacteriologic index were recruited for this moxifloxacin trial. Fertile females and those under 18 years of age were excluded. The protocol for this study was approved by a local institutional review board (licensed by the National Institutes of Health), and written informed consent, including permission to publish photographs, was obtained from the volunteers. The participants were initially carefully and thoroughly examined, with emphasis on dermatologic and neurologic statuses, lesions were mapped, and clinical photographs were obtained. Prior to therapy, the study patients also underwent routine six-site skin smears, a skin biopsy from active lesions, a dermatopathologic evaluation by the method of Ridley and Jopling (30), determination of both *M. leprae* viability and dapsone and moxifloxacin sensitivities in mice, and laboratory evaluations, including a complete hematogram, measurements of serum glutamic pyruvic transaminase and blood urea nitrogen levels, and urinalysis.

All eight MB leprosy patients recruited to participate in the trial were males and ranged in ages from 22 to 49 years. The trial subjects had an average bacteriologic index of 3.8 to 5.1; seven were histologically found to be polar lepromatous, and one was borderline lepromatous. The patients were treated with a single initial dose of 400 mg moxifloxacin, no therapy for 7 days, and a daily observed 400-mg dose from day 8 to day 56. For the 2-month duration of the trial, the patients were hospitalized, were supervised in their intake of medication, were seen on a daily basis, underwent the previously described laboratory evaluations every 2 weeks, had serial clinical photographs taken, and were evaluated as to clinical progress, as well as any adverse side effects/toxicities.

Serial skin biopsies for *M. leprae* viability were performed prior to therapy and on days 7, 14, 28, and 56 after the initiation of therapy, and *M. leprae* bacilli were therein inoculated in groups of hind footpads of mice in the amounts of 50 (not on days 28 and 56), 500 (not on day 56), and 5,000 *M. leprae* bacilli/footpad. Also, from the biopsy samples obtained prior to therapy, *M. leprae* sensitivities to dapsone and moxifloxacin were assessed. For these determinations of drug sensitivity, groups of mice infected with 5,000 *M. leprae* bacilli per footpad were either untreated or treated continuously with three levels of dietary dapsone (0.0001%, 0.001%, and 0.01%) or 50 mg/kg moxifloxacin five times weekly by gavage. From these mice, 6 months after footpad infection, four hind feet from two mice were harvested and pooled and the numbers of *M. leprae* bacilli were therein enumerated microscopically. In these and all other instances, growth of $\geq 10^5$ *M. leprae* bacilli was considered evidence that the initial inoculum was viable or, in the case of drug sensitivity

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TABLE 1. *M. leprae* viability

Patient no.	Day	<i>M. leprae</i> viability in four-feet harvests after ^a :		No. of footpads growing <i>M. leprae</i> /no. of footpads inoculated with indicated no. of <i>M. leprae</i> bacilli			Viable <i>M. leprae</i> (%)	Organisms killed by treatment (%)	<i>P</i> value (vs day 0)
		8 mo	12 mo	5,000	500	50			
1	0			17/19	9/10	2/8	2.419		
	7	—	—	0/10	2/10	0/7	0.035	99	<0.001
	14	—	—	0/10	0/9	0/9	0.022	99	<0.001
	28	—	—	0/10	0/6		0.022	99	<0.001
	56	—	—	0/9			0.022	99	<0.001
2	0	+	+	17/8	1/4	0/7	0.341		
	7	—	N/A	0/8	0/7	0/7	0.022	≥94	<0.001
	14	—	—	1/10	1/10	0/10	0.035	90	<0.001
	28	—	—	0/10	0/10		0.022	≥94	<0.001
	56	—	—	0/10			0.022	≥94	<0.001
3	0	+	+	16/16	1/7	3/10	0.605		
	7	—	+	2/10	0/9	0/10	0.035	94	<0.001
	14	—	—	0/10	0/10	0/11	0.022	≥96	<0.001
	28	—	—	0/8	0/8		0.022	≥96	<0.001
	56	—	—	0/10			0.022	≥96	<0.001
4	0	+	+	12/12	6/8	7/7	12.278		
	7	+	+	8/8	7/8	1/8	2.182	82	0.002
	14	—	—	4/10	0/10	0/10	0.055	>99	<0.001
	28	—	—	0/10	0/10		0.022	>99	<0.001
	56	—	—	0/10			0.022	>99	<0.001
5	0	+	+	15/15	5/7	4/7	4.212		
	7	+	+	7/7	4/10	0/10	0.548	87	0.005
	14	—	—	0/8	0/10	0/10	0.022	99	<0.001
	28	—	—	0/10	0/9		0.022	99	<0.001
	56	—	—	0/10			0.022	99	<0.001
6	0	+	+	22/23	9/11	3/10	2.591		
	7	—	+	12/14	4/12	2/16	0.451	83	0.006
	14	—	—	0/13	0/13	0/11	0.022	99	<0.001
	28	—	—	0/10	0/10		0.022	99	<0.001
	56	—	—	0/10			0.022	99	<0.001
7	0	+	+	36/36	23/23	16/19	15.165		
	7	+	+	13/18	3/17	1/20	0.194	99	<0.001
	14	—	—	3/24	0/21	0/21	0.029	>99	<0.001
	28	—	—	0/10	0/10		0.022	>99	<0.001
	56	—	—	0/10			0.022	>99	<0.001
8	0	+	+	34/34	18/18	16/21	12.612		
	7	—	+	19/26	17/21	3/21	1.743	86	<0.001
	14	—	+	11/21	1/15	0/18	0.085	99	<0.001
	28	—	—	0/10	0/10		0.022	>99	<0.001
	56	—	—	0/10			0.022	>99	<0.001

^a +, viable bacilli observed; —, viable bacilli not observed; N/A, not applicable.

assessment, drug resistant. For purposes of assessing *M. leprae* viability from each biopsy sample, the number of *M. leprae* bacilli obtained from the hind feet of two mice (four feet) infected with 5,000 *M. leprae* bacilli per footpad was enumerated both 8 and 12 months after footpad infection. Furthermore, in order to quantitate *M. leprae* killing and determine whether significant killing had occurred, 10 or more individual footpads from each inoculum size were harvested, preferably 1 year after infection or, at times, at mouse death 6 or more months after footpad infection. From these results, the percentage of viable *M. leprae* was obtained, the percentage of bactericide was calculated, and the probability that killing occurred and the probability that differences in *M. leprae* viabilities were recognized were assessed by the method of Spearman and Karber (33). On days 28 and 56, when certain footpads inoculated with smaller amounts of *M. leprae* were not evaluated, these calculations assumed that if footpads inoculated with larger amounts of *M. leprae* showed no *M. leprae* growth in all footpads, those inoculated with smaller amounts would as well.

At the completion of this trial, all subjects were treated with multidrug therapy as currently recommended by the WHO (37).

RESULTS

In all eight patients, prior to therapy (day 0), viable *M. leprae* was consistently observed in four-feet harvests from mice infected

with 5,000 *M. leprae* bacilli both 8 and 12 months after footpad infection and in the large majority of single-foot harvests. In all eight patients, their *M. leprae* samples obtained prior to the moxifloxacin trial were fully susceptible to both dapson and moxifloxacin, because multiplication of *M. leprae* was inhibited in mice treated with each of the three levels of dietary dapson and 50 mg/kg moxifloxacin five times weekly by gavage (data not shown).

The results for *M. leprae* viability and killing obtained using sequential biopsy samples from the eight trial patients obtained for both four-feet harvests and single-foot harvests are presented in Table 1. Single-dose therapy (day 7) resulted in significant *M. leprae* killing ($P \leq 0.006$) in all patients, ranging from 82% to 99%, (mean, 91%). After an additional week of daily moxifloxacin (day 14), significant killing ($P < 0.001$) was even more impressive, ranging from 90% in one patient to 99% in six patients (mean, 97%). Between day 7 and day 14, significant *M. leprae* killing ($P < 0.0001$) was observed in patients 4 to 8, ranging from 84% to 97% (mean, 93%), but not in patients 1 to 3. Utilizing the

FIG. 1. Clinical photographs.

results for both four-foot harvests and single-foot harvests in these eight patients after a single dose of moxifloxacin (day 7), some viable bacilli were detected in seven of eight patients (not patient 2), and after an additional week of daily moxifloxacin (day 14), in four patients (patient 2, 4, 7, and 8) but not in the other four (patient 1, 3, 5 and 6). In all eight patients, no viable *M. leprae* was detected at days 28 and 56.

The levels of viable *M. leprae* bacilli detected from four pooled footpads and from any individual footpad were quite similar, individual footpads being marginally more sensitive only at the day 14 harvests in three of eight patients. As harvesting mouse footpads at 12 months as opposed to 8 months allows a greater period of time for

M. leprae multiplication to be observed, it is not surprising that harvesting at 12 months proved more sensitive in detecting viable *M. leprae* than harvesting at 8 months; from the day 7 biopsy samples, three patients (patients 3, 6, and 8) demonstrated viable *M. leprae* at 12 months but not at 8 months. Also, no biopsy sample was found to harbor viable *M. leprae* in the 8-month harvest but not in the 12-month harvest.

Improvement in skin lesions occurred remarkably rapidly. In Fig. 1, we present sequential clinical photographs of three representative trial patients. Though subtle improvements in skin lesions were noted in some patients on day 7 after a single dose of moxifloxacin, in all eight patients, definite improve-

ment was observed with an additional week of daily moxifloxacin (day 14). All eight patients, by that time, had loss of erythema in skin lesions, and in four patients, fading of macules, nodules and/or plaques was observed. In all eight patients, continued improvements in skin lesions were observed throughout the 56-day trial period.

During the trial period, evanescent dizziness was noted in three patients, and diarrhea or epigastric pain was each noted in one patient. These symptoms did not lead to moxifloxacin treatment discontinuation. Patient 1 developed mild erythema nodosum leprosum on day 21, which lasted 3 days and did not require corticosteroids. Reversal reactions were not observed during moxifloxacin therapy in any of the trial patients. Of the seven patients who did not develop lepra reactions during moxifloxacin administration, four had erythema nodosum leprosum and two had reversal reactions after the completion of moxifloxacin therapy and while on standard WHO multidrug therapy.

Laboratory abnormalities found during this trial were confined to elevations of serum glutamic pyruvic transaminase to 2 to 3 times the normal level in three patients on day(s) 28 and/or 56 without symptoms of hepatitis, one of these patients experiencing a fall in hematocrit from 39% to 27% on day 56 of unknown etiology. All laboratory abnormalities found during the course of the trial normalized after discontinuation of moxifloxacin therapy.

DISCUSSION

In this clinical trial of moxifloxacin treatment of MB leprosy, we found moxifloxacin to be rapidly bactericidal for *M. leprae* (bactericidal activity matched previously only by rifampin), to clear skin lesions regularly and uniformly quickly (perhaps a function of moxifloxacin's anti-inflammatory and immunomodulating effects) (4, 35), and to be devoid of serious side effects or toxicities. Thus, if our findings are confirmed by others in clinical trials, this presents an opportunity for moxifloxacin to be included as a component of a new generation of multidrug therapy.

The key to the short-course chemotherapy of tuberculosis has been regimens including two or more bactericidal agents (1, 7, 21). In the 1-year WHO (37) regimen for MB leprosy, only rifampin (29, 32, 34), not dapsone (32) or clofazimine (32), is bactericidal for *M. leprae* in patients. Though pefloxacin/ofloxacin (9, 19, 26), minocycline (8, 12), and clarithromycin (3) clear viable *M. leprae* bacilli in MB patients more rapidly than dapsone or clofazimine (32), in the Philippines, they do not result in significant killing following a single dose, and each requires a few months to reliably clear all viable *M. leprae* bacilli (3, 8, 9). On the other hand, in this present study, moxifloxacin was demonstrated to consistently result in killing of *M. leprae* in a single dose and to clear viable bacilli within days or weeks, similar to the rate previously demonstrated only by rifampin (29, 32, 34). Thus, as demonstrated herein, moxifloxacin may provide the key and be the only drug other than rifampin which is consistently bactericidal for *M. leprae* in clinical trials—providing, for leprosy, an important second bactericidal agent with prospects analogous to those demonstrated previously by rifampin for tuberculosis, a more reliably efficacious and shorter course of treatment.

If the results of this current study can be confirmed by others, a regimen including daily observed rifampin and moxifloxacin treatments, perhaps with an additional agent such as minocycline, of one or a few months, presents sufficient promise for MB leprosy to suggest that such a clinical trial would be warranted. Ideally, this regimen would be compared in a randomized double-blind trial with the 1-year WHO multidrug therapy, wherein relapse rates after the completion of therapy would be the only valid measure of treatment efficacy. Because in our experience (11) relapse in MB leprosy begins to occur only 6 years after the completion of therapy and generally 10 years thereafter and we (11) and others (16, 22) have found relapse rates to be much higher in patients with a high bacterial burden, in order to maximize the potential of the proposed study, at least 100 patients who are polar lepromatous or borderline lepromatous would need to be recruited in each arm and undergo annual follow-up for at least 15 years. If such a rifampin-moxifloxacin regimen proves effective against MB leprosy, a short-course regimen including rifampin and moxifloxacin might provide the long-sought single effective regimen for all forms of leprosy.

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