A Comparative Clinical Trial in Multibacillary Leprosy with Long-Term Relapse Rates of Four Different Multidrug Regimens

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Abstract. As a participant in a multicenter trial, we evaluated the relapse rate in 189 multibacillary (MB) leprosy patients treated with four different regimens and followed-up for as many as 12 years after the initiation of treatment. Treatment regimens included 1 year of WHO MDT (a regimen including dapsone, clofazimine, and rifampin), 2 years of WHO MDT, 1 month of daily rifampin and daily ofloxacin, and 1 year of WHO MDT plus an initial 1 month of daily rifampin and daily ofloxacin. Relapse rates after 9 and 12 years from the initiation of therapy in the three regimens that included WHO MDT were 0–3%, whereas relapses occurred in those treated with the 1-month regimen alone at a significantly greater rate (P < 0.05): 11% at 9 years and 25% at 12 years. Relapses occurred late, beginning at 5 years after the initiation of therapy, and were confined to those patients histopathologically borderline lepromatous and polar lepromatous having a high bacterial burden. Prospects for an alternative effective short-course therapy of leprosy are presented.

INTRODUCTION

In 1943,1 the sulfones provided the first effective antimicrobial therapy for leprosy, heretofore frequently a progressive, unrelenting, and deforming disease because of the unique tropism of the causative bacteria, Mycobacterium leprae, for the peripheral nervous system. On the sulfone of choice, dapsone, lepromatous skin lesions slowly resolved, and, in general, peripheral neuropathy ceased its progression. However, in the 1950s,2 it was recognized that dapsone resistance became a clinical concern in some patients, and despite prolonged, often lifelong, and continued daily dapsone administration, new lesions appeared. Later dapsone resistance3 was confirmed in the mouse model, first described by Shepard in 1960.4 Although the incidence of drug resistance is much higher in tuberculosis after monotherapy, even with bactericidal agents, and although dapsone is bacteriostatic in leprosy patients, surprisingly secondary dapsone resistance only affected ~2.5% of leprosy patients treated with dapsone monotherapy.5 Furthermore, the most severe lepromatous form of leprosy is by far more baciliferous, higher than any other human disease, and unlike in tuberculosis, is associated with a permanent pathogen-specific anergy.6 Later, in some locales, primary dapsone resistance seemed to be developing in high frequencies,7,8 whereas not in others.9,10 In any event, in 1982, the WHO11 advocated multidrug therapy for all forms of leprosy with combinations of dapsone, clofazimine, and, most importantly, rifampin, which was the only one bactericidal for M. leprae in a clinical trial it among the three.12–14 The WHO regimens were designed, not only to prevent drug resistant relapse, but to allow a finite period of treatment, first 2 years,11 and now 1 year,15 for the most severe multibacillary (MB) leprosy patients who had been treated previously with dapsone alone lifelong. More recently antimicrobials of three classes—fluoroquinolones (poxiloxin and ofloxacin),16–19 tetracyclines (minocycline),20,21 and macrolides (clarithromycin)22,23—were found far more active against M. leprae in both mice and patients than dapsone and clofazimine. Against this background in both mice and in humans, the WHO organized a multidrug trial of four regimens to treat MB leprosy—1 year of MDT (dapsone, clofazimine, and monthly rifampin), 2 years of MDT, 1 month of daily rifampin and ofloxacin, and 1 year of MDT combined initially with the 1-month daily regimen. Follow-up in most centers ceased after a few years. Such a short follow-up has not proved generally useful, because we24 found previously that MB leprosy relapse after 2 years of MDT only begins 6 years after the completion of therapy and often much later. Herein we present data on relapse frequencies in patients treated with those four regimens in the Philippines for a minimum of 9 years and at times as many as 12 years after the initiation of therapy.

MATERIALS AND METHODS

In 1991, the WHO organized a multicenter initially double-blinded clinical trial of four regimens to treat MB leprosy. At the Leonard Wood Memorial Clinical Branch in Cebu, Philippines, 189 patients were recruited to participate in this trial. This included 147 men and 42 women ranging in age from 15 to 60 years, with a mean of 28 years. Patients were required to have a bacteriologic index (BI), a logarithmic measure of the number of AFB in the dermis ≥ 2+ at one or more of six skin smear sites. In Cebu, skin biopsies for skin classification by the method of Ridley and Jopling25 were obtained in all of but two patients. By these means, leprosy presents a spectral disease ranging in severity as follows: tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB), borderline lepromatous (BL), and lepromatous leprosy (LL). It is noteworthy that the vast majority of patients recruited in Cebu were found to be LL or BL. The demographics and leprosy characteristics in patients treated with each of the four trial regimens are summarized in Table 1.

Patients were excluded if they could not be expected to be observed daily for the first month of the trial, had previously received rifampin or a fluoroquinolone, had a previous lepra reaction requiring prolonged steroid therapy, were <15 years old or >65 years of age, were known to be allergic to any trial drugs, were pregnant or breast feeding, had tuberculosis, severe lung disease, or bronchial asthma requiring theophylline, and had cancer, diabetes, severe hypertension, renal, hepatic cardiac disease, epilepsy, or any other medical condition that adversely affect compliance with treatment or follow-up. Before therapy, to exclude some of these conditions, urine for sugar, albumin, and urobinogen was obtained.

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The protocol for this study was approved by the Steering Committee of The Therapy of Leprosy of the WHO (THELEP), a local institutional review board and an ethical committee of the Health Services of the Philippine government. Patients were enrolled in the study only after obtaining written informed consent; in the case of those < 18 years old, written informed consent was by a parent. Patients were assigned to one of four regimens through a system of pre-coded treatment packs, incorporating identical-looking placebo preparations as appropriate.

The four regimens used are presented in Table 2 and were 1) 1 year of WHO MDT consisting of daily dapsone 100 mg and daily clofazimine 50 mg (unsupervised) and monthly supervised rifampin 600 mg and clofazimine 300 mg (supervised), 2) 1 year of WHO MDT as just described plus an initial month of supervised daily rifampin 600 mg and daily ofloxacin 400 mg, 3) 1 month of daily rifampin 600 mg and daily ofloxacin 400 mg (supervised), and 4) 2 years of the WHO MDT regimen. After the completion of 1 year of the trial, the study was unblinded, but only for Regimen 4, which was continued for another year.

Patients were generally assessed annually by clinical examination and skin smears (six sites). Either the appearance of new skin lesions or an increase of BI at any skin smear site was cause to suspect relapse. Relapse was concluded to have occurred only by independent confirmation by a local leprosy expert, not regularly involved in the conduct or the follow-up of the trial, generally supported by a confirmatory skin biopsy and mouse pad inoculation confirming *M. leprae* viability. MB relapses found in this present study were first detected in the fifth year, many somewhat later, and on average more than one half the duration of follow-up; therefore, this report rather than expressing relapse occurrences in patient-years, which hence could be misleading, these are presented for each individual occurrence and as the observed relapse frequency, found both 9 and 12 years after the initiation of treatment. The frequency of relapse detection was compared using the Fisher exact test.

Additionally, *M. leprae* viability and drug sensitivity obtained from relapse cases were generally assessed in the mouse model. For this purpose, groups of mice were infected in both hind footpads with 5,000 *M. leprae* and fed continuously a diet containing no drug, dapsone 0.01 %, dapsone 0.001 %, and clofazimine 0.001 %, whereas other mice received rifampin 10–20 mg/kg/5 times weekly by gastric gavage. Six months after footpad infection, *M. leprae* was enumerated from those footpads. We considered that, if the number of *M. leprae* exceeded 100,000, viable bacilli were present in the inoculum and, in drug-treated mice, resistance was obtained.

This report largely confines itself to an evaluation of relapses in Cebu in MB patients followed up annually for as many 12 years, whereas other aspects of the trial results and those on relapses in other centers will be the subject of a separate forthcoming report.

### Results

Table 3 presents findings of the patients treated with each of the four trial regimens at Day 28 and annually up to 12 years on the number of individuals examined, relapsed, not examined, and lost to follow-up because of either death or migration.
It is noteworthy that the rate of annual follow-up was high and similar for the four trial regimens during the first 9 years after the initiation of therapy. In this study, follow-up was obtained for 1,728 patient-years for the full complement of patients (an average 82% of trial patients seen on annual follow-up)—493 patient-years (82% annually) for Regimen 1, 498 patient-years (85% annually) for Regimen 2, 558 patient-years (85% annually) for Regimen 3, and 179 patient-years (71% annually) for Regimen 4. After 9 years, follow-up became inconsistent. After 9 years of follow-up, relapses were found in 1 of 57 patients (2%) on Regimen 1, 1 of 55 patients (2%) on Regimen 2, 7 of 64 patients (11%) on Regimen 3, and 0 of 20 patients (0%) on Regimen 4. Another relapse occurred in a patient on Regimen 2 who absconded after the first month of treatment and reappeared in the seventh year after the initiation of therapy with a relapse; this patient was not considered in this overall analysis. Analogous relapse rates for those followed up for the full 12 years were 1 of 36 (3%) on Regimen 1, 1 of 36 (3%) on Regimen 2, 10 of 40 (25%) on Regimen 3, and 0 of 9 (0%) on Regimen 4. It is noteworthy that the 12 relapses occurred in 10 patients on Regimen 3, 1 on Regimen 1, 1 on Regimen 2, and 0 on Regimen 4. The relapse rate on Regimen 3 at both 9 (11%) and 12 (25%) years was greater \( (P < 0.05) \) than the three other regimens, and no significant differences were found in relapse rates in patients treated on Regimens 1, 2, and 4.

The first two relapses noted on Regimen 3 occurred in the fifth year of follow-up, and four others occurred in the sixth year after the initiation of therapy. The one relapse in patients on Regimen 1 occurred in the sixth year of follow-up, and the two on Regimen 2 occurred in the seventh and ninth years. Patients treated on Regimen 3 were the only ones where relapses were noted > 9 years after the initiation of treatment, one relapse occurring 11 years and two occurring 12 years thereafter.

The initial clinical, histologic, and bacteriologic characteristics of the 13 relapse cases found before therapy, during therapy, and on relapse are presented in Table 4. It is noteworthy that all relapses occurred in patients who were initially BL or LL and had an initial BI of 2.6 or greater. Eight of the 12 relapses occurred in patients with an initial BI of \( \geq 4+ \). Relapse histology was LL in 7, BL in 4, and BB in 1. In all relapse patients, the BI at the time of diagnosis fell at 2 years of treatment.
of the 13 relapses, the average BI was \( \leq 1+ \) the year before relapse detection. In all instances, relapse was associated with a rising average BI: one instance, \(< 1+\); six instances, between \(1+\) and \(< 2+\); five instances, \(> 2+\).

We were able to obtain \(M. leprae\) from 9 of the 12 patients who completed their treatment regimen, as well as 1 patient on Regimen 2 who ultimately relapsed but only received 1 month of therapy. \(M. leprae\) from all 10 patients grew in untreated mice, confirming that all of our observed relapses harbored viable \(M. leprae\). Only one of the subjects was dapsone resistant—to 0.001% dapsone in diet but not 0.01%, a level that is far exceeded in patients receiving the normal dose of 100 mg dapsone daily, and hence, of no clinical significance. Another patient was resistant to clofazimine, whereas all others were sensitive to this agent. Only the patient who discontinued Regimen 2 prematurely was found to be rifampin resistant.

**DISCUSSION**

The relapse rate obtained by the 1-month regimen of daily rifampin and ofloxacin was found significantly higher than was observed on the three regimens that included at least 1 year of the MB regimen recommended by the WHO. Regimens to treat pulmonary tuberculosis, which results in a relapse frequency >5%, have generally been considered unacceptable. By that criteria, the relapse rate (0–3%) on the three regimens including WHO MDT should be considered adequate, whereas those following the 1-month regimen are unacceptable (11% after 9 years and 25% after 12 years). Furthermore, although we believe the relapses detected in the study most likely result from the re-growth of persisting \(M. leprae\), they may also be a consequence of re-infection.

It is noteworthy that the relapses found in this study were generally sensitive to dapsone, rifampin, and clofazimine, and none were multidrug resistant. The mechanism and genetic loci of \(M. leprae\) resistance for dapsone and rifampin have been identified, and their rates were found in this study in relapsed patients similar to those found elsewhere. On the other hand, the mechanism for clofazimine resistance has as yet not been defined, its frequency in relapse patients was not generally studied, and other than the one case detected in this study, only one other has been documented in the literature.

A concern with the efficacy of the regimens that included WHO MDT is that, despite the prolonged follow-up of 9 and at times 12 years, this follow-up may still be too short. Although in three studies such a duration of follow-up after multidrug therapy of MB leprosy proved sufficient to detect a high relapse rate, in one other study, more than one half of the relapses detected occurred later. In any event, it is important to prolong the follow-up of this study to certify the true risk for relapse.

It is noteworthy that in a regimen akin to our 1-month one, Pattyn and Grillone found that, after an intensive 6-week regimen for MB leprosy, which included daily rifampin, clofazimine, and ofloxacin and weekly minocycline, 18 of 136 patients (13%) relapsed at 10 years of follow-up. Despite the failures in that study and our 1-month regimen, in both trials, the majority of the patients were apparently cured. These studies thus offer the hope that a more bactericidal short-course regimen might yet be found and prove more reliably curative.

In a separate unpublished study from our experience in Cebu in paucibacillary (PB) leprosy patients treated with Regimen 3 (daily rifampin 600 mg and daily ofloxacin 400 mg for 1 month), who were skin smear negative before initiation of therapy, we found a single relapse in 66 patients (2%) after fully 12 years of annual follow-up. Certainly such a regimen is acceptable and probably preferred to the 6-month regimen currently recommended by the WHO—daily dapsone and monthly rifampin. Importantly, PB leprosy is the major form of the disease found in India and Africa, therein affecting 90% of leprosy patients.

The success of WHO MDT in PB leprosy and the majority of MB patients makes it clear that successful finite regimens for all forms of leprosy are possible. However, 6 months of treatment for PB leprosy and 1 year for MB leprosy are still operationally difficult and far too long. Certainly, although 6-month regimens for pulmonary tuberculosis had proven successful, even this duration is considered too long, and shorter ones are being pursued. It is noteworthy that Consigny and others found that moxifloxacin was profoundly bactericidal for \(M. leprae\) in mice and far superior to ofloxacin. Furthermore, in a pilot clinical trial of moxifloxacin in Cebu in MB leprosy patients, all lepromatous or borderline lepromatous, not only did lepromatous lesions clear extraordinary rapidly, but their \(M. leprae\) was killed far faster, only equaled previously by rifampin, than had been found previously for other fluoroquinolones, and, in fact, all other previously evaluated antimicrobials in leprosy, including other components of WHO MDT dapsone and clofazimine, as well as minocycline and clarithromycin. The short course therapy of tuberculosis has required two or more bactericidal agents. Thus moxifloxacin appears the first antimicrobial, other than rifampin, that is truly bactericidal in leprosy patients. From our current experience of the success of 1 month of daily therapy with ofloxacin and rifampin regularly in PB leprosy, herein in the majority of patients with MB leprosy, as well as the experience of Pattyn with an intensive 6-week regimen for MB leprosy, a regimen that substitutes ofloxacin with moxifloxacin when combined with rifampin presents a far more promising short-course regimen for leprosy with the prospect of proving superior and of shorter duration than WHO MDT. For PB leprosy, our experience showed already that a duration of 1 month should be sufficient. Future studies in MB leprosy with short-course chemotherapy with a regimen containing moxifloxacin and rifampin are certainly in order. If successful, this might allow for a single effective regimen for all forms of leprosy.

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**REFERENCES**