PARALLEL ASSESSMENT OF 24 MONTHLY DOSES OF RIFAMPIN, OFLOXACIN, AND MINOCYCLINE VERSUS TWO YEARS OF WORLD HEALTH ORGANIZATION MULTI-DRUG THERAPY FOR MULTI-BACILLARY LEPROSY

LAARNI G. VILLAHERMOSA, TRANQUILINO T. FAJARDO JR., RODOLFO M. ABALOS, ROLAND V. CELLONA, MARIA V. BALAGON, EDUARDO C. DELA CRUZ, ESTERLINA V. TAN, GERALD P. WALSH, AND DOUGLAS S. WALSH

Leonard Wood Memorial Center for Leprosy Research, Cebu, The Philippines; Dermatology Service, Department of Medicine, Dwight D. Eisenhower Army Medical Center, Fort Gordon, Georgia

Abstract. Monthly doses of rifampin, ofloxacin, and minocycline (ROM) are expected to be effective treatment for multi-bacillary leprosy. Patients with MB leprosy received ROM (n = 10) or World Health Organization multi-drug therapy (MDT) (n = 11). Treatment with ROM was given as 24 consecutive monthly observed doses of rifampin (600 mg), ofloxacin (400 mg), and minocycline (100 mg). Treatment with MDT was given as 24 consecutive monthly observed doses of rifampin (600 mg) and clofazimine (300 mg), and unobserved daily dapsone (100 mg) and clofazimine (50 mg). Twenty patients completed the 24-month regimens with >99% compliance. Treatments with ROM and MDT were safe, tolerable, and caused similar improvements in lesions, bacterial indices, and histology. All MDT recipients developed clofazimine-induced pigmentation. Six ROM and nine MDT recipients assessed at five or more years after completion of treatment had no evidence of relapse. Twenty-four months of treatment with ROM is a safe, well-tolerated, and convenient regimen that may provide an alternate therapy to MDT for MB leprosy. Larger trials with sufficient follow-up would better define the role of ROM.

INTRODUCTION

In 1982, the World Health Organization recommended rifampin, dapsone and clofazimine as a two-year multi-drug therapy (MDT) for multi-bacillary (MB) leprosy.1,2 By 1998, with growing evidence that less than 24 months of therapy were effective, the recommended duration was reduced to one year.3,4 To date, more than 10 million leprosy patients treated with one- or two-year regimens of MDT have been removed from prevalence records, but incidence rates have remained steady.2,5,6

Despite the success of MDT, there is still a need for developing effective alternative regimens for MB leprosy that are operationally less demanding for patients and providers.2 In addition to supervised monthly rifampin and clofazimine doses, MDT requires daily self-administration of dapsone and clofazimine, which is rife with compliance and drug resistance issues.2 Moreover, dapsone is associated with infrequent but sometimes serious toxicities, especially in those with glucose-6-phosphate dehydrogenase deficiency, and clofazimine-induced skin pigmentation, a stigma in many communities, may be the leading cause for MDT refusal or default.7–9

Ofloxacin and minocycline have potent bactericidal activity against Mycobacterium leprae, and when combined with rifampin as ROM provide effective single dose therapy for paucibacillary (PB) leprosy.2,10,11 For MB leprosy, 24 monthly doses (pulsed) of supervised ROM are advocated for patients refusing or unable to take MDT.12,13 To date, however, there is only one formal report of ROM in treating MB leprosy, whereby 118 MB patients received 24 monthly doses of ROM over a 24–36-month period with good clinical response during dosing, but without long-term follow up.7,14 Nonetheless, according to mouse footpad and limited human bactericidal studies, and the kinetics of M. leprae drug resistance rates, a sufficient number of monthly ROM doses should be highly effective for MB leprosy.7,10,15

We conducted a parallel assessment of 24 supervised monthly doses of ROM versus two-year MDT in 21 MB leprosy patents. ROM and MDT were safe and tolerable, and provided similar clinical, bacteriologic, and histologic improvements. A majority of ROM and MDT recipients were assessed at five or more years, with all showing sustained clinical and bacteriologic improvements and no relapses.

PATIENTS AND METHODS

Study site and enrollment. This study was reviewed and approved by the Leonard Wood Memorial (LWM) Institutional Review Board and was conducted at the LWM Clinical Research Branch located at the Eversley Childs Sanitarium (Cebu, The Philippines). Enrollment was conducted in 1995 and 1996, with the last treatment in 1998. After treatment, self-directed follow-up occurred through year five, followed by active follow-up in years six through eight, the estimated peak relapse incubation period for rifampin-containing MB leprosy regimens.16

Consenting male and female patients 16–60 years old were eligible for enrollment if they were diagnosed with MB leprosy and underwent a physical examination that included routine hematology and biochemical tests. Exclusion criteria included concomitant systemic disease other than leprosy or ingestion of any anti-leprosy drug in the past three months. Women were excluded if they denied menstruation within the past 30 days. Routine slit skin smears from six standard sites (earlobes, posterior aspects of upper arms, lower back) were conducted to determine M. leprae load, whereby 100 oil-immersion fields (1,000×) were microscopically examined by an experienced technician and reported as a bacterial index (BI) on a 0 to 6+ scale.17,18 MB leprosy was defined as any patient with at least one of six smear sites having a BI ≥ 1+, along with a histologic diagnosis of borderline or lepromatous leprosy.19

Interventions and outcome measurements. Volunteers were sequentially assigned in 1:1 fashion to receive ROM or MDT. ROM was monthly doses of rifampin (600 mg), ofloxacin (400 mg), and minocycline (100 mg) administered under supervision for 24 consecutive months. MDT (World Health Organization) was supervised monthly doses of rifampin (600 mg), ofloxacin (400 mg), and minocycline (100 mg) administered under supervision for 24 consecutive months. MDT (World Health Organization) was supervised monthly doses of rifampin (600 mg), ofloxacin (400 mg), and minocycline (100 mg) administered under supervision for 24 consecutive months. MDT (World Health Organization) was supervised monthly doses of rifampin (600 mg), ofloxacin (400 mg), and minocycline (100 mg) administered under supervision for 24 consecutive months.
mg) and clofazimine (300 mg) for 24 months, and unsupervised daily dose of dapsone (100 mg) and clofazimine (50 mg/day) for 24 months. Ofloxacin (200-mg tablets; Bimedix, Inc., Cebu City, The Philippines) and minocycline (100-mg capsules; Wyeth, Inc., Cebu City, The Philippines) and rifampin (600-mg tablets) were obtained commercially. MDT drugs were provided by The World Health Organization in open-label blister packs. Study medications were stored at room temperature.

Clinical examinations were conducted and slit skin smears from six sites as described earlier to enumerate acid-fast bacilli were prepared at 3, 6, 12, and 24 months. Lesion resolution was graded numerically in comparison with enrollment as none (0), some (1+), or marked (2+), and in comparison with the most recent assessment as worse, no change, or improved. Lesional biopsies, obtained in proximity of a smear site with the highest number of bacilli to the greatest extent possible, were done at 3, 6, 12, or 24 months as tolerated. Biopsies were reported as logarithmic index of bacilli in biopsies (LIB), a conventional histologic grading method for leprosy incorporating bacillary load and tissue reaction (bacillary index x granuloma fraction), and expressed as % improvement over baseline.20 Volunteers were asked open-ended questions regarding adverse events. Patients with lepra reactions, to include reversal reaction (RR), characterized by swelling and erythema of existing leprosy lesions, and erythema nodosum leprosum (ENL), comprised of crops of tender papulonodules, fever, and malaise, were promptly treated with tapering doses of oral prednisolone.

Follow-up for clinical and bacteriologic response was for two years during treatment, with additional, self-directed (passive) post-treatment follow-up through five years, and active follow-up in years six through eight. Treatment failure and relapse were defined as a worsening of existing lesions or the appearance of new lesions, with an increase in BI of at least 2+ at any of the six routine sampling sites.

**Data collection and analysis.** Data were recorded on standardized case report forms, entered into a computerized database (Excel 2000®, Microsoft, Redmond, WA), and cross-checked for agreement. Graphical and statistical analyses were done by SigmaPlot 8 (SPSS, Inc., Chicago, IL) and SigmaStat version 2.03 (SPSS, Inc.), respectively. Outcomes included safety and tolerability, lesion morphology, histology (LIB), BI, and post-treatment follow-up.

**RESULTS**

**Subjects.** Volunteer demographics are shown in Table 1. All patients lived in the Cebu City area. Of 21 enrollees, 10 ROM and 10 MDT recipients completed 24 months of treatment. One MDT patient defaulted at 21 months because of employment relocation, but attended self-directed follow up 14 months after the last observed MDT dose. Compliance for ROM and observed MDT doses, based on scheduled versus actual doses, was > 99% for both arms.

**Clinical and bacteriologic responses.** ROM and MDT were safe and well tolerated, with no serious adverse events. All MDT recipients developed clofazimine-induced pigmentation. Lesion resolution was steady during treatment, with all patients achieving marked improvement by 24 months (Figure 1). Histologic improvement paralleled clinical responses (Figure 2). Steady improvement in BI occurred throughout the study for both treatment groups (Figures 3 and 4). There were no treatment failures, but at the end of treatment, only a single patient (ROM group) attained a BI of 0.

Six ROM and 10 MDT patients attended a total of 23 self-directed or active post-treatment follow-up visits (Figures 3 and 4, respectively). At self-directed visits, there were no specific complaints, and all patients had sustained improvement in clinical features without evidence of relapse. For active follow-up during years six through eight, six ROM and nine MDT recipients were assessed, all with no relapse.

There were five RR and two ENL in each treatment group during the dosing period, with most RR occurring within the first six months, and most ENL occurring after six months. All RR were graded as mild, with cutaneous involvement and malaise but no neurologic signs. Similarly, all ENL were graded as mild, with skin lesions, low-grade fevers, and malaise, but no neurologic signs. All reactions responded well to tapering oral prednisolone (15–30 mg/day starting doses) administered on an out-patient basis, with no loss of function or deformity. There were no missed ROM or MDT treatments due to reactions. One MDT patient, with left ulnar nerve enlargement and tenderness at 14 months, responded well to tapering oral prednisolone (30 mg starting dose). Two mild

![Figure 1](image.png) Lesion improvement during treatment. Maximum scores were 20 for rifampin, ofloxacin, and minocycline (ROM) and 22 for multi-drug therapy (MDT).

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>ROM</th>
<th>MDT</th>
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<tr>
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<td>Male:female ratio</td>
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<td>Mean enrollment BI (range)</td>
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<td>Histology on enrollment</td>
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* ROM = rifampin, ofloxacin, and minocycline; MDT = multi-drug therapy; BI = bacillary index; BL = borderline lepromatous; LL = lepromatous.
RR in the fourth post-treatment year (1 ROM and 1 MDT) improved with tapering oral prednisolone.

**DISCUSSION**

Despite the success of World Health Organization MDT for treatment of MB leprosy, new regimens that are at least as effective as MDT and more appealing to patients are still needed.\(^2,15\) To that end, ROM given as 24 supervised monthly doses is advocated as an alternate regimen for MB leprosy in certain situations, but clinical reports describing this regimen are scarce.\(^2,10,12,13\) Indeed, beyond studies describing the acute bactericidal effects of single doses of ROM in MB patients, one case report describes a woman with MB leprosy receiving 22 monthly doses of ROM,\(^7\) and one field study describes good clinical responses in 118 MB patients receiving 24 monthly ROM doses within a 24–36-month period, but with unclear follow-up.\(^14\) Anecdotally, an MB patient at our clinic who had relapsed twice after a two-year treatment with MDT completed 12 doses of monthly ROM in 1995 and has remained relapse free (Cellona R, unpublished data).

Here, we conducted a parallel comparison between ROM and two-year MDT to first establish that 24 consecutive monthly doses of ROM is comparable to MDT. We found ROM to be as safe and effective as MDT during dosing, causing no skin pigmentation, and conferring similar clinical, bacteriologic, and histologic improvements, without increased rates of lepra reactions. Post-treatment follow-up was limited by being self-directed for the first five years, but active follow-up during years six through eight in a majority of ROM and MDT patients depicted similar long-term safety and efficacy. Previously, patients receiving an intense six-week regimen of daily rifampin and ofloxacin and weekly minocycline showed a notable increase in relapses during years 8 through 11 of follow-up, underscoring the importance of adequate follow-up to better define optimal regimens and efficacy of ROM.\(^21\)

Regimens such as ROM are especially useful for patients concerned about clofazimine-induced skin pigmentation, compliance issues (daily unsupervised dosing of dapsone and clofazimine for one year or longer), or sensitivity to an MDT component.\(^8\) Indeed, clofazimine may also cause gastrointestinal upset, and dapsone has a notable side effect profile with infrequent but potentially serious toxicities, especially in leprosy patients.\(^8,9,22–24\) Treatment defaults, up to 40% for MDT in some regions, might be reduced by using ROM in selected patients.\(^25–27\) In The Philippines, ROM costs four times more than MDT for similar duration regimens, prohibiting mass administration. Nonetheless, our ROM cohort, comprised of patients acquainted with the stigma and inconvenience of conventional leprosy treatment, displayed satisfaction because of the lack of skin pigmentation and the ease of monthly dosing. Ostensibly, patients treated with ROM may remain anonymous to the community, and even their families.

Ofloxacin and minocycline are potent anti-\textit{M. leprae} medications that in combination with rifampin are rapidly integrated into leprosy treatment regimens, especially as a single-dose therapy for PB leprosy.\(^2\) For MB leprosy, supervised monthly ROM represents an ideal, effective alternate regimen to MDT with reduced operational burdens and risks of
side effects, and potentially shorter treatment durations. Indeed, experimental data depicting ofloxacin and minocycline as significantly more potent than dapsone and clofazimine against M. leprae, coupled with an understanding of M. leprae burdens in MB disease and drug resistance frequencies, support the notion that a similar number of monthly doses of ROM as MDT (observed) will provide comparable long term efficacy. Indeed, chemotherapy studies in neonatally thymectomized rats infected with M. leprae show that minocycline plus rifampin, but not rifampin alone, eliminate all viable M. leprae, suggesting minocycline may be a critical component to any rifampin-based regimen. Because clofazimine has anti-inflammatory properties, there has been concern that there may be increased or more severe ENL in reactions with regimens such as ROM that do not contain clofazimine. However larger cohorts will be required to better assess this.7,14,30

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Authors’ addresses: Laarni G. Villahermosa, Tranquilino T. Fajardo, Jr., Rodolfo M. Abalos, Roland V. Cellona, Maria V. Balagon, Eduardó C. Dela Cruz, and Esterlina V. Tan, Leonard Wood Memorial Hospital, Fort Ord, CA 93951. Reprint requests: Douglas S. Walsh, Dermatology Service, Eisenhower Army Medical Center, Fort Gordon, GA 30905.

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