A CLINICAL TRIAL OF ETHIONAMIDE AND PROTHIONAMIDE FOR TREATMENT OF LEPROMATOUS LEPROSY

TRANQUILINO T. FAJARDO, RICARDO S. GUINTO, ROLAND V. CELLONA, RODOLFO M. ABALOS, EDUARDO C. DELA CRUZ, AND ROBERT H. GELBER*

Leonard Wood Memorial Center for Leprosy Research, Cebu City, The Philippines

Abstract. In 1982–1984 we conducted a six-month clinical trial in 50 previously untreated lepromatous leprosy patients randomly assigned to directly observed monotherapy with one of two thioamides, ethionamide or prothionamide, each given six times a week at doses of either 250 mg or 500 mg. The findings of this study have only recently been analyzed, and the potential for the use of these thioamides in leprosy patients placed in perspective. However, because of the small number of patients included in this study, the results must be interpreted with some caution. Clinical improvement was noted in 74% of the patients treated with ethionamide and in 83% of those treated with prothionamide. Therapy was well tolerated and drug-related hepatotoxicity did not require discontinuation of therapy. The 500-mg dose of both ethionamide and prothionamide resulted in loss in Mycobacterium leprae viability more rapidly than did the 250-mg dose, and prothionamide at both dose levels was superior to the equivalent dose of ethionamide. Overall killing of M. leprae in this study was found to be similar to that obtained previously with dapsone and clofazimine, but less than was obtained with rifampin, minocycline, clarithromycin, pefloxacin, and ofloxacin.

INTRODUCTION

Concerns over primary and secondary dapsone-resistant leprosy in 1982 prompted the World Health Organization (WHO)1 to recommend multidrug regimens for the treatment of all forms of leprosy. These regimens include combinations of rifampin, dapsone, and clofazimine and have been widely implemented worldwide. Unfortunately, with this therapy, double-digit relapse rates have been obtained in those with multibacillary leprosy and particularly in those with high bacterial burdens in three disparate locales.2–4 Of the three antimicrobials included in the WHO regimens, only rifampin has been found to be bactericidal both for Mycobacterium leprae in the mouse model5–8 and in clinical trials,8–11 it being advocated by the WHO only once a month, primarily because of its expense. Clofazimine, although bactericidal in mice,7 is only bacteriostatic in humans,9 while dapsone is bacteriostatic in mice6,12 and in humans.9 Ethionamide and prothionamide were bactericidal in several studies in mice.5,7,12,13 In addition, 102 lepromatous leprosy patients were treated with ethionamide, 1 gram a day initially, and later due to gastrointestinal toxicity, 500 a day in adults and 250 mg a day in children, with most patients becoming bacteriologically skin smear negative after four years.14 In that study, unfortunately, the actual loss of M. leprae viability by the standard mouse inoculation was not conducted. Although both ethionamide and prothionamide have been used as single agents in a small number of leprosy patients5 monitored by mouse inoculation to assess the rate of loss of M. leprae viability, it has never been done in an organized study.

Nonetheless, prothionamide was used in combination with rifampin, isoniazid, and dapsone in leprosy patients in Malta15 and resulted in reliable cures, while being well tolerated. This experience in Malta provided the first suggestion that finite and not life-long therapy could result in a cure for all forms of leprosy. More than two decades ago with concerns for an increase in dapsone resistance,16 the WHO concluded that dapsone was no longer reliable and was trying to determine which other companion agent should be used with rifampin so as to preclude emergent rifampin resistance. For this purpose, either clofazimine or a thioamide, the only other agents known to be active against M. leprae at the time, were being considered. In 1982, clofazimine was selected primarily by the WHO1 over a thioamide for this purpose because of the established hepatotoxicity of daily thioamides when combined with daily rifampin17 and the limited experience with killing of M. leprae in humans by thioamides. However, the WHO1 allowed for the supplementation of clofazimine by ethionamide/prothionamide and substitution of clofazimine by thioamides in light-skinned individuals where the pigmentation changes induced by clofazimine were considered to be cosmetically unacceptable. Because of the aforementioned lack of experience with thioamides in treating leprosy and particularly their ability to kill the bacterium, in 1982 the WHO solicited and sponsored the present study to compare the safety and efficacy of ethionamide against prothionamide in multibacillary patients, with each being administered for six months at six weekly doses of 250 mg and 500 mg. In this study, clinical response, loss of M. leprae viability, side effects/toxicities, and lepra reactions were carefully monitored. These findings are only now being reported due to a serious delay in a thorough analysis of the results. In the intervening years, greater antimicrobial activity and lesser toxicity of other antimicrobial agents and regimens largely dampened the enthusiasm to pursue thioamides for treatment of leprosy. Furthermore, even prior to the completion of this present work the WHO recommended that clofazimine rather than a thioamide be a component of multidrug therapy (MDT), at least in part because of the established hepatotoxicity17 when daily rifampin and ethionamide were administered together. However, because of the large number of patients and mice required for monitoring this trial and since to date few agents are yet established to be effective for leprosy, this trial remains germane. This report was prompted by the findings that both thioamides resulted in moderate killing of M. leprae, the higher dosage of each agent was superior to the lower one, prothionamide resulted in a more rapid killing of bacilli at comparable dosage levels than ethionamide, and both thioamides were well tolerated and resulted in a generally salutary clinical response.

* Address correspondence to Robert H. Gelber, 220 Scenic Avenue, San Anselmo, CA 94960. E-mail: ikgelber@hotmail.com
MATERIALS AND METHODS

This study was conducted between 1982 and 1984, and all study patients were clinically and histopathologically polar lepromatous or borderline lepromatous without a history of leprosy therapy. The study was reviewed and approved by the Institutional Review Board of the Leonard Wood Memorial Center, which is registered with the National Institutes of Health. All trial patients provided informed written consent, were hospitalized for the six-month duration of treatment, and received directly observed therapy. A total of 50 previously untreated lepromatous patients were admitted into the study and randomly assigned by a table of random numbers to receive single doses six days a week for 24 weeks: group 1, ethionamide 250 mg; group 2, ethionamide 500 mg; group 3, prothionamide 250 mg; group 4, prothionamide 500 mg. The patients, clinical staff, and clinical assessment were entirely blinded as to which regimen was used.

In group I, 12 patients were admitted and completed 24 weeks of treatment. In group II, 13 patients were admitted, 11 completed 24 weeks of treatment, 1 patient left the study, and 1 patient was excluded because of surreptitious intake of dapsone. In Group III, 13 patients were admitted, 12 completed 24 weeks of treatment and 1 patient left the study. In group IV, 12 patients were admitted, 11 completed 24 weeks of treatment, and 1 patient left the study. None of those who left the study dropped out for reasons of drug intolerance, lepra reaction, or worsening of the disease.

Table 1 shows some of the salient features of the 46 patients who completed 24 weeks of therapy. During the course of the study, patients were seen six times a week, and clinical, dermatologic, and neurologic examinations were done. Blood chemistry and liver enzyme examinations were done every four weeks. At the conclusion of therapy, improvement was formally assessed. Definite improvement was considered to have occurred when marked subsidence of papulonodular lesions or fading and flattening of erythematous plaques were noted. Less dramatic improvement, such as softening and partial flattening of papulonodular lesions was graded as moderate improvement.

Throughout this study, patients were regularly and carefully monitored for the appearance of any side effects/drug toxicities and reactional states. It is noteworthy that during the treatment of lepromatous leprosy two kinds of inflammatory reactional states commonly complicated the death of bacilli: erythema nodosum leprosum (ENL) that was believed to be an immune complex disorder associated with elevated levels of tumor necrosis factor-α, and reversal reactions that are associated with an increasing cellular immune response and elevation in lesional and circulating cytokine levels. The ENL was considered mild when there were less than 10 tender papulonodules, moderate if there were 10–20 papulonodules with or without slight edema, joint pains, and severe if these were associated with either severe joint pains, edema, high fever and other constitutional signs and symptoms. Iritis, laryngitis, orchitis, and other involvement may also occur in severe ENL. Reversal reactions were considered mild if the manifestations were only confined to the original lesions, moderate if new lesions also appeared with or without nerve involvement, and severe when constitutional signs and symptoms were present with or without ulcers, blebs, or edema. In most instances, nerves were also involved. Slit skin smears for bacteriologic analysis and biopsy specimens for histologic analysis were obtained before the start of treatment and at the end of 24 weeks. There were six sites for bacterial smears per patient, both earlobes, and four others, preferably lesonal skin sites. Pretherapy and 24-week clinical phototransparencies were taken to assist clinical assessments.

The site large enough for sequential biopsies was selected on preliminary examination of the patient. From this site patients underwent serial skin biopsies prior to therapy and at 4, 8, 16, and 24 weeks after the initiation of therapy. Bacilli from these biopsies were injected into groups of mice in both hind footpads (5,000 M. leprae/footpad). One year after inoculation, two mice (four feet) were analyzed, and M. leprae therein were enumerated. If ≥106 bacilli were found viable M. leprae were considered to have been present in the corresponding biopsy. The number of patients found to harbor viable bacilli by the four treatment regimens and at various time intervals was compared statistically by the use of Fischer’s exact test.

After the completion of this trial, all thionamide-treated patients were then treated with dapsone (100 mg/day) and rifampin (600 mg/day) for one week and then transferred to the General Health Services where they received standard three-drug WHO MDT for two years.

RESULTS

The power of many of the observations was limited by the small number of patients enrolled in this study. Table 2 shows the clinical changes observed, by therapy group, for the 46 patients who completed 24 weeks of therapy. Clinical improvement was noted in 36 (78.2%) patients and no observ-
able clinical change in 10 (21.7%) patients. None of the pa-
tients showed deterioration of their illness or became clin-
ically worse. Definite clinical improvement was noted in onlyive patients, all receiving the 500-mg dose, three receiving ethionamide and two receiving prothionamide. No statisti-
cally significant differences in clinical response between the
two treatment regimens were noted. However, the group re-
ceiving 500 mg of prothionamide appeared to have the best
clinical response.

Table 3 shows the average bacteriologic index (BI) (a loga-
ithmic function of the number of acid-fast bacilli with a range
of 0 to 6) after 24 weeks of treatment. There was an overall
0.4 reduction in the average BI from a preliminary or pre-
therapy average of 4.5 to an average BI of 4.1 in all 46 patients
after 24 weeks of therapy, with no therapy regimen being
more effective.

Table 4 shows the occurrence and severity of lepra reac-
tions during the course of therapy by treatment group in the
46 patients who completed therapy. Lepra reactions occurred
at rates similar to that found with other effective antimicro-
bial regimens23 in 23 (50.0%) of the patients. They were mild
in 16 (34.8%) patients and moderate to severe in 7 (15.2%)
patients. Lepra reactions were observed in groups I and II in
13 (56.6%) patients. They were moderate to severe in 4
(17.3%) patients and mild in 9 (39.1%) patients. In groups III
and IV, lepra reactions occurred in 10 (43.4%) patients. They
were moderate to severe in 3 (13.0%) patients and mild in 7
(30.4%) patients. The occurrence of lepra reactions among
patients in groups I and II was slightly higher (56.5%) than in
groups III and IV (43.5%), but this difference was not statis-
tically significant. First attacks of lepra reactions occurred
during the first month in two patients as reversal reactions of
moderate severity; one patient in group II whose reactive
lesions subsequently subsided in a few weeks, and the other in
group IV who subsequently developed ENL during the 11th
week of treatment in addition to a reversal reaction and flare-
up and generalization of an underlying atopic dermatitis. In
the five subsequent months, ENL developed in 4, 3, 5, 6, and
3 patients, respectively, without any regimen showing signifi-
cant differences in the onset of these events. Erythema nodos-
um leprosum neuritis was observed in two patients, one in the
fourth month of therapy and one in the sixth month of
therapy. Reversal reactions developed in two other patients af-
after the first month of therapy, one in the fifth month of therapy
and one in the sixth month of therapy. All reaction lesions in the
trial patients were easily controlled with prednisone.

To monitor hepatic toxicity, monthly serum aspartate ami-
otransferase (AST) levels were determined. An AST level
greater than 35 units was considered elevated. Eighteen
(39.1%) of 46 patients had elevated AST levels. Elevated
AST levels were noted in four patients in group I, four pa-
tients in group II, four patients in group III, and six patients
in group IV. In 14 patients, the highest levels of AST ranged
from 35 to 88 units in any examination of the series of
monthly examinations. However, in four patients, AST levels
were greater than 100 units in at least one instance: one in
group 1, one in group 2, and 2 in group 3. Only one of these
four patients had signs and symptoms of hepatitis including
anorexia, nausea, and vomiting. During the eighth week of
treatment with 250 mg of prothionamide, this patient became
jaundiced and had a total/direct bilirubin level of 6.9/4.2 mg/
dL and a maximum AST level of 690 units. After discontinu-
tion of prothionamide therapy, signs and symptoms of hepa-
titis resolved and AST and bilirubin levels returned to normal
in two weeks. At that time, prothionamide therapy was rein-
stituted without recurrence of signs and symptoms of hepatitis
or elevations in AST levels throughout the six-month course
of prothionamide therapy. This patient and one of the other
four who had AST levels greater than 100 units had IgM
antibody to hepatitis B core antigen, and four were positive
for hepatitis B antigen.

Clinical drug intolerance in the form of salivation and nau-
sea associated with drug intake was reported by one patient in
group IV. This was relieved by premedication with meto-
clopramide. No abnormal liver function was noted at any
time in this patient. Another patient, also in group IV, had
headaches associated with drug intake within the first weeks
of treatment. She subsequently developed subacute atopic
eczema and a reversal reaction. Her AST levels were normal,
except for an AST level of 48 units during the 16th week.

The viability of M. leprae from serial skin biopsies obtained
in these studies is summarized in Table 5. Prior to the initia-
tion of therapy, M. leprae grew in mice tested with specimens
from the 46 trial patients completing therapy (Table 5). At
four weeks of therapy, no significant loss of M. leprae viability
was noted in the thioamide-treated patients (viable M. leprae
were found in 47 of 50 patients) or in any of the four treat-
ment regimens. By eight weeks of therapy, significant loss of

<table>
<thead>
<tr>
<th>Therapy group</th>
<th>No. of patients</th>
<th>Mean (SD) bacteriologic index (six sites)</th>
<th>Preliminary</th>
<th>24 Weeks</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>12</td>
<td>4.5 (0.3)</td>
<td>10</td>
<td>0.6(0)</td>
<td>11.1</td>
</tr>
<tr>
<td>II</td>
<td>11</td>
<td>4.6 (0.2)</td>
<td>4.0</td>
<td>0.5(0)</td>
<td>13.0</td>
</tr>
<tr>
<td>III</td>
<td>12</td>
<td>4.4 (0.5)</td>
<td>3.9</td>
<td>1.1(1.1)</td>
<td>11.3</td>
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<tr>
<td>IV</td>
<td>11</td>
<td>4.6 (0.2)</td>
<td>4.1</td>
<td>0.6(0)</td>
<td>10.8</td>
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<tr>
<td>Total</td>
<td>46</td>
<td>4.5 (0.3)</td>
<td>4.1</td>
<td>0.7(0)</td>
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<table>
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<tr>
<th>Therapy group</th>
<th>No. of patients</th>
<th>No. of patients with reaction</th>
<th>No. of patients without reaction</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>12</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>(58.3%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>11</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td>(54.5%)</td>
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</tr>
<tr>
<td>III</td>
<td>12</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>(41.7%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>11</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>(45.5%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>23</td>
<td>16</td>
<td>7</td>
<td>23</td>
<td>(50.0%)</td>
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</table>
viability was observed only in those patients treated with 500 mg of prothionamide daily ($P < 0.01$), wherein only 3 of 11 treated patients harbored viable *M. leprae*. At eight weeks the fraction of patients treated with 500 mg of prothionamide per day harboring viable *M. leprae* was significantly less than either those treated with 250 mg of ethionamide per day (10 of 12; $P = 0.01$) or 500 mg of ethionamide 12 of 13; $P = 0.002$). Although the fraction of patients treated with 250 mg of prothionamide 250 (9 of 13) was greater than that found for 500 mg of prothionamide, this result was not statistically significant ($P = 0.1$). By 16 weeks of therapy, highly significant killing ($P < 0.01$) of *M. leprae* was observed for all treatment regimens except 250 mg of ethionamide. At that time no viable *M. leprae* were found in patients treated with 500 mg of prothionamide. At 16 weeks of therapy the fraction of patients (9 of 12) treated with 250 mg of ethionamide who harbored viable bacilli was higher than in those treated with 500 mg of ethionamide (3 of 11; $P = 0.04$), 250 mg of prothionamide (2 of 11; $P = 0.01$), and 500 mg of prothionamide (0 of 11; $P < 0.001$). By 24 weeks significant killing of *M. leprae* was evident for all four treatment groups and for the first time in those treated with 250 mg of ethionamide, although 5 of 12 patients receiving this regimen still harbored some viable *M. leprae*. At 24 weeks, none of the patients treated with 250 mg of prothionamide or 500 mg of prothionamide harbored viable *M. leprae*. At 24 weeks the fraction of patients harboring viable *M. leprae* was significantly less ($P < 0.05$) for the two prothionamide treatment groups compared with those treated with 250 mg of ethionamide 250 mg, but not 500 mg of ethionamide.

When the total percentage of biopsies harboring viable *M. leprae* was compared for 8–24 weeks and 16–24 weeks, the two prothionamide treatment regimens resulted in a significantly reduced fraction ($P < 0.0001$) of biopsies with viable bacilli compared with the two ethionamide treatment regimens. Although biopsies obtained from the prothionamide-treated patients between 8 and 24 weeks had viable bacilli present in 14 of 69 instances, those treated with ethionamide had viable *M. leprae* in 41 of 71 instances. Similarly at 16–24 weeks, prothionamide resulted in the detection of viable bacilli in 2 of 45 biopsies, while ethionamide-treated patients harbored viable bacilli in 19 of 46 biopsies obtained over the same period. Between 8 and 24 weeks, significantly fewer viable *M. leprae* ($P < 0.0001$) were obtained in biopsies from those treated with 500 mg of prothionamide (3 of 33) than those treated with 500 mg of ethionamide (17 of 35). Over this same period 500 mg prothionamide also resulted in less viable *M. leprae* (3 of 33) than 250 mg of prothionamide (11 of 36) ($P = 0.04$). Five hundred milligrams of ethionamide was superior to 250 mg of ethionamide ($P = 0.02$); during the 16–24-week period, viable *M. leprae* being found in 5 of 22 and 14 of 24 biopsies, respectively, but this difference was not significantly different when eight-week data were included as well. The number of biopsies with viable *M. leprae* from patients treated with 500 mg of ethionamide either over 8–24 weeks (17 of 35) or 16–24 weeks (5 of 22) was not significantly different from that observed with 250 mg of prothionamide: 11 of 36 and 2 of 23, respectively.

### DISCUSSION

Although the number of patients per group in this study was small, being limited by the large number of mice required to monitor this trial (more than 4,000), published studies on the activity of other agents used to treat leprosy patients also include only 8–10 patients per group. Nonetheless, because of the small number of patients enrolled in the current study, the results should be interpreted with caution. However, certain findings do emerge. In this 24-week clinical trial of ethionamide and prothionamide monotherapy, each in a single six times a week dose of 250 mg or 500 mg for previously untreated lepromatous leprosy patients, clinical improvement was noted in 17 (74%) of 23 patients treated with ethionamide, which was not significantly different from that provided by prothionamide (19 [83%] of 23 patients). The decrease in the average BI was also not significantly different between those treated with ethionamide (12.1%) and those treated with prothionamide (11.1%). These rates were similar to those found previously with other agents active against *M. leprae*. Occurrence of lepra reactions was also not significantly different in those treated with ethionamide (13 [57%] of 23 patients) than in those treated with prothionamide (10 [44%] of 23 patients). Although hepatotoxicity can be a significant problem when daily ethionamide is used with daily rifampin for treatment of pulmonary tuberculosis, drug intolerance and symptomatic hepatotoxicity due to thioamide therapy were not observed in this study. This may be due to the monotherapy used herein and the relatively short duration of treatment used in this study.

In a previous studies in *M. leprae*-infected mice, ethionamide and prothionamide showed similar activity, with minimal effective doses in mouse diets of 0.01% and minimal inhibitory serum concentrations of 0.05 μg/mL. Although a minimal dietary concentration of ethionamide of 0.02% was observed in mice, higher concentrations (0.05–0.3%) were consistently more bacterioidal. In the treatment of tuberculosis, prothionamide has advantages over ethionamide because it is slightly superior in its activity against *M. tuberculosis* and is generally better tolerated.

In the current study, both ethionamide and prothionamide resulted in significant killing of *M. leprae*. Both 250 mg and 500 mg of prothionamide were superior to equivalent doses of ethionamide. For both ethionamide and prothionamide, a 500-mg dose resulted in greater killing of *M. leprae* then did 250 mg, and killing of *M. leprae* with 250 mg of prothionamide was indistinguishable from killing with 500 mg of ethionamide. However, the rate of loss of *M. leprae* viability obtained with these thioamides was similar to that obtained with dapsoné and clofazimine and considerably less than that obtained with the bactericidal agents rifampin (days to

<table>
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<tr>
<th>Table 5</th>
<th>Growth of <em>M. leprae</em>/total no. of patients</th>
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<tr>
<td></td>
<td>4 weeks</td>
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<tr>
<td>Group 1</td>
<td>Ethionamide, 250 mg/day</td>
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<td>Group 2</td>
<td>Ethionamide, 500 mg/day</td>
</tr>
<tr>
<td>Group 3</td>
<td>Prothionamide, 250 mg/day</td>
</tr>
<tr>
<td>Group 4</td>
<td>Prothionamide, 500 mg/day</td>
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In conclusion, ethionamide and prothionamide appeared to be well tolerated and without significant gastrointestinal or hepatic toxicity. The perceived drawbacks of thioamides in treatment of leprosy have been gastrointestinal intolerance, which we did not observe to an appreciable extent, and hepatic toxicity when combined daily with rifampicin. However, in our study, hepatotoxicity caused by ethionamide and prothionamide was minimal. Since the WHO is recommending rifampicin for treatment of leprosy only once a month, this toxicity in that setting may not be a significant problem. Both ethionamide and prothionamide in this present study showed demonstrable, although not superior, killing of \textit{M. lepraee}. Conversely, ethambutol, a bacteriostatic agent, is used for treatment of infection with \textit{M. tuberculosis} principally to guard against emergent isoniazid and rifampicin resistance. Similarly to these thioamides, prothionamide and ethionamide, in leprosy, though dapsone and clofazimine are only bacteriostatic in patients, they play a critical role in the WHO treatment regimens for leprosy by analogously preventing rifampicin resistance. Already prothionamide provided such a role in the successful treatment of leprosy and was well tolerated in a study in Malta. Thus, ethionamide and particularly prothionamide, which was found in this study to be more active against leprosy and is generally considered to be better tolerated, could have a place in the treatment of leprosy patients.

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Authors’ address: Tranquillo T, Fajardo, Ricardo S, Guinto, Roland V, Cellona, Rodolfo M, Abalos, and Eduardo C, Dela Cruz, Leonard Wood Memorial Center for Leprosy Research, Cebu City, Philippines, Telephone and Fax: 63-32-345-2751, E-mails: lwmcrr@cisv.net.ph, csc-epi@cisv.net.ph, and lwmcrr@cisv.net.ph. Robert H, Gelber, 220 Scenic Avenue, San Anselmo, CA 94960, Telephone: 415-154-8765, Fax: 415-454-8197, E-mail: ikgelber@hotmail.com.

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