Rapid killing of *M. leprae* by moxifloxacin in two patients with lepromatous leprosy

FE ELEANOR F. PARDILLO, JASMIN BURGOS, TRANQUILINO T. FAJARDO, EDUARDO DELA CRUX, RODOLFO M. ABALOS, ROSE MARIA D. PAREDES, CORA EVELYN S. ANDAYA & ROBERT H. GELBER
Leonard Wood Memorial Center for Leprosy Research, Cebu, Philippines

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Summary

Introduction  Previously we reported a 2-month clinical trial of moxifloxacin therapy in eight patients with MB leprosy (7 LL and 1 BL), finding both rapid killing of *M. leprae* and clinical improvement, without serious side effects or toxicities. Here we report the outcomes in two patients treated with moxifloxacin.

Design  Two previously untreated LL patients were treated with a single 400 mg dose of moxifloxacin, no therapy for 7 days and then daily 400 mg moxifloxacin for 48 days. Clinical response, viability of *M. leprae* in the skin, and side effects/toxicities were carefully monitored.

Results  In both patients a single dose of moxifloxacin resulted in significant killing of *M. leprae* (\( P < 0.001 \% \)). In both patients no viable *M. leprae* were found after 15 doses of moxifloxacin. Improvement in skin lesions occurred again remarkably rapidly and no untoward effects were noted.

Conclusion  Loss of viable *M. leprae* was quite rapid, similar to that found previously only for rifampicin, patients improved rapidly, and moxifloxacin was well tolerated.

Introduction

Recently we\(^1\) reported a clinical trial of moxifloxacin in eight lepromatous leprosy patients. In that clinical study we found that a single standard moxifloxacin dose of 400 mg resulted in consistently significant killing of *M. leprae*, averaging 91\%, and an additional 3 weeks of daily therapy in all trial patients resulted consistently in complete loss of viable *M. leprae* from the skin. Previously it had been demonstrated in lepromatous leprosy that antimicrobials of three classes, pefloxacin/ofloxacin,\(^2\)\(^-\)\(^4\) minocycline\(^5\)\(^,\)\(^6\) and clarithromycin\(^7\) clear viable *M. leprae* from the dermis more rapidly than dapsone and clofazimine.\(^8\) However, when
tested as single dose in patients with leprosy in The Philippines, none of the aforementioned newer agents produced significant killing of *M. leprae*, and each required administration for a few months to regularly clear all detectable viable *M. leprae* from the skin.4,6,7

Furthermore, moxifloxacin treated MB leprosy patients (7 LL and 1 BL) improved exceedingly rapidly; skin lesions consistently improved after eight doses with continuing progressive resolution over the 2 months of the trial, and no important side effects/toxicities were noted.1

Herein we describe the results of two additional lepromatous patients treated with moxifloxacin and assessed in a similar manner.

**Materials and Methods**

The first patient was a 30 year-old male with clinical and histopathologic (method of Ridley and Jopling9) features of polar LL leprosy with an average bacteriologic index (6 sites) of 4.4, and the second patient was a 45 year-old male, also with LL leprosy with an average bacteriologic index of 5.3. The protocol for this study was approved by a local Institutional Review Board accredited by the National Institutes of Health of the United States and written informed consent obtained from the participants.

The two patients were hospitalised during the course of the trial, observed daily, and administered directly observed therapy with an initial 400 mg dose of moxifloxacin on day 1, no therapy for the next 7 days, and a daily moxifloxacin dose of 400 mg from days 8 to 56. The methods utilised in this study to monitor clinical response, side effects/toxicities, and *M. leprae* sensitivity and serial viability obtained from skin biopsies performed prior to therapy and on days 7, 14, 28 and 56 both from four foot-pad pools and 10 or more single-foot harvests were the same as those of our recently published clinical trial of moxifloxacin in leprosy.1 Mouse foot-pad studies employed the standard method of Shepard,10 and statistical analysis of single-foot harvests utilised the method of Spearman and Karber.11

**Results**

Clinical improvement and regression of skin lesions, as determined by review of clinical photographs, was found subtle yet discernable in both patients by day 7, after a single dose of moxifloxacin. This improvement in both patients was more evident by day 14, and progressive improvement was observed on days 28 and 56.

In both patients prior to therapy, *M. leprae* was viable and fully susceptible to all three levels of dapsone and moxifloxacin (data not shown). The data on *M. leprae* viability are presented in the Table 1.

Though after the initiation of therapy, some viable *M. leprae* were detected in both patients by single-foot harvests on day 7 and day 14, a single dose of moxifloxacin resulted in significant killing (*P* < 0.001) in both patients, 70% killing in the first patient and 97% killing in the second. Significant (*P* < 0.001) killing by an additional 1 week of daily therapy (day 14) was obtained in both patients, this being an additional 99% in the first patient and 95% in the second. In both patients greater than 99% of *M. leprae* had been killed on days 14, 28, and 56, and in both patients no viable *M. leprae* were detected in any four-foot or single-foot harvests by day 28, as well as day 56.
Table 1. *M. leprae* viability

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Day</th>
<th>8 months</th>
<th>12 months</th>
<th>5000</th>
<th>500</th>
<th>50</th>
<th>Percent of viable <em>M. leprae</em> (%)</th>
<th>Percent of organisms killed by treatment (%)</th>
<th>P value (versus Day 0)</th>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>29/29</td>
<td>12/15</td>
<td>17/22</td>
<td>8·16</td>
<td></td>
<td>&lt;0·001</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>+</td>
<td>+</td>
<td>13/13</td>
<td>10/10</td>
<td>1/19</td>
<td>2·46</td>
<td>70</td>
<td>&lt;0·001</td>
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<tr>
<td></td>
<td>14</td>
<td>–</td>
<td>–</td>
<td>4/20</td>
<td>0/18</td>
<td>0/20</td>
<td>2·46</td>
<td>&gt;99</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>–</td>
<td>–</td>
<td>0/18</td>
<td>0/17</td>
<td>–</td>
<td>0·03</td>
<td>&gt;99</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>–</td>
<td>–</td>
<td>0/15</td>
<td>–</td>
<td>–</td>
<td>0·02</td>
<td>&gt;99</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>31/31</td>
<td>19/20</td>
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<td>14</td>
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<td>2/17</td>
<td>0/20</td>
<td>0/18</td>
<td>0·03</td>
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<td>0·02</td>
<td>&gt;99</td>
<td>&lt;0·001</td>
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Neither patient experienced significant side effects/toxicities nor any clinical laboratory abnormalities. The first patient developed a mild reversal reaction in the skin without neuritis on day 44 which did not require corticosteroid therapy and resolved in 7 days.

**Discussion**

In these two MB patients treated with moxifloxacin we found, as we had in the eight patients previously reported, that moxifloxacin killed *M. leprae* exceedingly rapidly and in a single dose, cleared skin lesions quickly and was well tolerated. In our previous report, we made the case that the rapid bactericidal activity found for moxifloxacin against *M. leprae* was almost unique, being matched previously only by rifampicin, thus providing for the first time a second truly bactericidal agent to treat leprosy. In the treatment of tuberculosis short-course chemotherapy has demonstrably required two or more bactericidal agents,\(^\text{12–14}\) and by analogy, moxifloxacin paired with rifampicin, and perhaps another agent, presents the same promise in leprosy—a new generation of MDT which might provide a more reliable cure, shorter duration of therapy, and be efficacious for all forms of leprosy. Standard MDT for tuberculosis is currently administered for a minimum of 6 months; this duration is considered undesirably long, and currently shorter regimens, including moxifloxacin are being tested. Similarly, the 1-year treatment for MB leprosy is operationally difficult and results in significant compliance issues. Unfortunately, we\(^\text{15}\) and others\(^\text{16}\) have found that MB relapse following both WHO MDT and other intensive short-course regimens may not begin to occur for 5 years after the completion of therapy, and in our\(^\text{15}\) experience, the majority of relapses occurred ten years after the completion of therapy. Thus, we recommend to leprosy policy-makers to accelerate the initiation of a trial of short-course therapy of a few months for MB leprosy with a rifampicin/moxifloxacin-based regimen. Also, as a higher rate of rifampicin resistance has been found in relapsed leprosy as compared to previously untreated disease,\(^\text{17}\) the rate of rifampicin-resistant relapsed leprosy being quite variable, in one locale as much as 20%,\(^\text{17}\) a moxifloxacin-based regimen surely would be most applicable to patients experiencing a relapse after the completion of WHO MDT.

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**Contributors**

Fe Eleanor F. Pardillo – Clinician in charge of clinical trial
Jasmin Burgos – Managed and conducted mouse studies
Tranquilino T. Fajardo – Clinician involved in the clinical trial
Eduardo Dela Cruz – Managed vivarium and mouse studies
Rodolfo M. Abalos – Dermatopathology
Rose Maria D. Paredes – Conducted mouse studies
Cora Evelyn S. Andaya – Conducted mouse studies
Robert H. Gelber – Designed trial, managed its execution, analysed data and prepared manuscript.
References


