A Randomized, Placebo-Controlled Study of Rifabutin Added to a Regimen of Clarithromycin and Ethambutol for Treatment of Disseminated Infection with Mycobacterium avium Complex

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Current guidelines suggest that disseminated Mycobacterium avium complex (MAC) infection be treated with a macrolide plus ethambutol or rifabutin or both. From 1993 to 1996, 198 AIDS patients with MAC bacteremia participated in a prospective, placebo-controlled trial of clarithromycin (500 mg b.i.d.) plus ethambutol (1,200 mg/d), with or without rifabutin (300 mg/d). At 16 weeks, 63% of patients in the rifabutin group and 61% in the placebo group \((P = .81)\) had responded bacteriologically. Changes in clinical symptoms and time to survival were similar in both groups. Development of clarithromycin resistance during therapy was similar in the two groups; of patients who had a bacteriologic response, however, only 1 of 44 (2%) receiving rifabutin developed clarithromycin resistance, vs. 6 of 42 (14%) in the placebo group \((P = .055)\). Thus, rifabutin had no impact on bacteriologic response or survival but may protect against development of clarithromycin resistance in those who respond to therapy.
of ethambutol and clofazamine alone [21]. In view of these promising findings, we conducted a prospective trial of treatment of MAC bacteremia, in which rifabutin or a matching placebo was added to a regimen of clarithromycin and ethambutol.

Methods

Study population. HIV-positive patients were eligible for the study if they were ≥12 years old and had a documented blood culture that was positive for MAC or a not-yet-specified acid-fast bacillus, within 90 days prior to randomization. Patients were also required to have two blood cultures performed within 14 days of randomization, and if neither was positive were quantified as cfu per mL of blood. Mycobacteria were acid-fast bacillus, within 90 days prior to randomization. Patients were also required to have a Karnofsky score of ≥50, or had an estimated life expectancy of <16 weeks. Patients were allowed to have received previous antimycobacterial therapy, but not within 7 days before the baseline blood cultures.

At baseline, patients needed serum aminotransferase levels <10× the upper limit of normal, a bilirubin level <3× the upper limit of normal, a serum creatinine value ≤3.0 mg/dL, an absolute neutrophil count >500/mm³, and a platelet count >50,000/mm³. Patients were excluded who were pregnant or lactating, had a Karnofsky score of <50, or had an estimated life expectancy of <16 weeks. Patients were allowed to have received previous antimycobacterial therapy, but not within 7 days before the baseline blood cultures.

The protocol was reviewed and approved by each site’s institutional review board, and all patients or their guardians gave written informed consent.

Study design. Patients were randomized to receive either rifabutin (300 mg once daily) or a matching placebo. All patients received 500 mg of clarithromycin twice daily and 1,200 mg of ethambutol per day (patients weighing ≤50 kg received 800 mg/d). Patients were evaluated at weeks 2 and 4 and every 4 weeks thereafter until a common closing date. At each visit, the patient’s history was recorded and a physical examination, complete blood cell count, and renal and liver function evaluations were performed. Two blood cultures for MAC were performed at weeks 8 and 16, and one blood culture was performed at other visits. Patients could discontinue taking medications temporarily because of adverse effects or permanently because of recurrence of adverse effects, life-threatening toxicity, or the need for additional (nonstudy) antimycobacterial therapy.

The primary endpoint was the proportion of patients in each treatment group who, at week 16, had a bacteriologic response, defined as negative blood cultures for MAC or a >2-log₁₀ decrease in cfu per mL of blood. Patients who did not have a microbiologic response before week 16 and were not available at week 16 were counted as treatment failures; patients who had a bacteriologic response before week 16 and were not available at week 16, however, were not counted as treatment responses. For patients who had negative cultures at week 16, a relapse was defined by any subsequent single blood culture with ≥10 cfu/mL or by any two positive cultures. For patients without negative blood cultures but a >2-log₁₀ decrease in cfu/mL at week 16, a relapse was defined as an increase in cfu to a level <2 log₁₀ below the baseline. A second primary objective was to compare, at week 16, the abatement of clinical symptoms in each group.

Bacteriologic evaluation. Blood cultures for MAC were processed at the National Jewish Center for Immunology and Respiratory Medicine, in Denver. The blood was concentrated, lysed, and plated, as previously described [22]. The organisms were quantified as cfu per mL of blood. Mycobacteria were identified with the AccuProbe (Gen-Probe, San Diego). Antimicrobial susceptibility testing was performed with 7H12 broth, by means of a previously described radiometric method [23]. Clarithromycin resistance was defined as an MIC of ≥32 µg/mL.

Statistical analysis. The primary efficacy evaluation was based on the incidence of (and time to) bacteriologic response and negative cultures by week 16. Kaplan-Meier methodology was used to estimate the time-to-bacteriologic-response and time-to-negative-blood-culture distributions for each treatment group. The log-rank test was then used to compare the estimated distributions. Chi-square statistics were used to make comparisons with respect to incidence at weeks 8 and 16.

Additional efficacy analyses were based on clinical symptoms associated with MAC bacteremia at weeks 8 and 16: fever (absent or present), night sweats (≤mild or >mild), and abdominal pain (≤mild or >mild).

Clinical symptoms and categorical baseline characteristics were examined with a χ² test, and continuous baseline characteristic variables were assessed with a one-way ANOVA F-test.

The major analysis was an intention-to-treat analysis including all patients who had at least one positive blood culture for MAC at baseline. A second, during-treatment analysis excluded patients who died within the first 15 days, received study medication for <30 days, or had an interruption in study medication for >30 days in the first 16 weeks, for reasons other than clinical failure or adverse event. The results of the during-treatment analysis were similar to those of the intention-to-treat analysis and are not presented in this article.

Results

From December 1993 to September 1996, patients were followed at 47 sites in the United States, Canada, and Mexico. The study cohort consisted of 198 patients for whom at least one blood culture was positive for MAC at baseline. The rifabutin arm of the study had 102 patients, and the placebo, 96; in addition, all patients received clarithromycin and ethambutol.
As shown in table 1, the patients were predominantly male, with sex with a male as the main HIV-risk behavior, and the mean CD4 cell count was 20/mm³.

The bacteriologic response to the two regimens was similar (table 2). The groups were well matched at baseline: the median quantity of MAC in blood cultures was 18 cfu/mL for patients receiving rifabutin and 24 cfu/mL for patients assigned to placebo (P = .19). At 8 weeks, 58% of persons in each group were found to have a bacteriologic response (P = .95); by week 16, 63% of patients in the rifabutin group and 61% in the placebo group had responded (P = .81). Of patients available for blood cultures at week 16, 73% in each group achieved negative cultures for MAC. The median time to bacteriologic response was 30 days in the rifabutin group and 56 days in the placebo group (log-rank P = .47). The median time to negative blood cultures was 55 days in the rifabutin group and 64 days in the placebo group (log-rank P = .32).

As shown in table 3, fever was present in almost all patients at baseline and responded similarly to the two regimens. Night sweats and abdominal pain were more common in the placebo group at baseline and responded well to both regimens. Overall survival did not differ between the two groups (log-rank P = .87). Patients receiving rifabutin had a median survival of 398 days, and those in the placebo group had a median survival of 439 days.

Clarithromycin resistance was present at baseline in four patients who received rifabutin and in three who received placebo. Only one of these patients, who was in the placebo group, developed in vitro resistance to clarithromycin and relapsed at week 40. Bacteriologic response at week 16, 1 of 44 (2%) in the rifabutin group demonstrated resistance to clarithromycin, vs. 6 of 42 (14%) in the placebo group (P = .055). Only one patient in this study had a bacteriologic relapse—an individual in the placebo group who developed in vitro resistance to clarithromycin and relapsed at week 40.

Of the 223 patients dosed, the only significant laboratory abnormality associated with the three-drug regimen was a higher proportion of patients who had leukopenia (<1,000 WBCs/mm³) during the study (18%, vs. 8% in the placebo group; P < .05), although no patient permanently discontinued taking a study drug because of neutropenia. There was no difference between the two study groups in terms of the number of patients developing other hematologic, renal, or liver abnor-

### Table 1. Baseline characteristics of study participants.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data per recipient group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td></td>
<td>.78</td>
</tr>
<tr>
<td>Male (%) Male</td>
<td>89</td>
<td>.42</td>
</tr>
<tr>
<td>Race White</td>
<td>70</td>
<td>.80</td>
</tr>
<tr>
<td>Black</td>
<td>28</td>
<td>.00</td>
</tr>
<tr>
<td>HIV risk behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men having sex with men</td>
<td>71</td>
<td>.29</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>7</td>
<td>.12</td>
</tr>
<tr>
<td>Heterosexual partner</td>
<td>17</td>
<td>1.00</td>
</tr>
<tr>
<td>Mean values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karnofsky score (%)</td>
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<td>.34</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62</td>
<td>.51</td>
</tr>
<tr>
<td>CD4 cell count (no./mm³)</td>
<td>20</td>
<td>.31</td>
</tr>
</tbody>
</table>

### Table 2. Bacteriologic results of blood cultures, per recipient group.

<table>
<thead>
<tr>
<th>Endpoint variable</th>
<th>Rifabutin (n = 102)</th>
<th>Placebo (n = 96)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>18 (3–167)</td>
<td>24 (3–185)</td>
<td>.19</td>
</tr>
<tr>
<td>Week 8</td>
<td>46/80 (58%)</td>
<td>47/81 (58%)</td>
<td>.95</td>
</tr>
<tr>
<td>Bacteriologic</td>
<td>38/78 (49%)</td>
<td>36/68 (53%)</td>
<td>.61</td>
</tr>
<tr>
<td>Eradication</td>
<td>44/70 (63%)</td>
<td>42/69 (61%)</td>
<td>.81</td>
</tr>
<tr>
<td>Week 16</td>
<td>40/55 (73%)</td>
<td>37/51 (73%)</td>
<td>.98</td>
</tr>
</tbody>
</table>

### Table 3. Symptoms of disseminated MAC infection in the recipient groups.

<table>
<thead>
<tr>
<th>Time point, symptom</th>
<th>Rifabutin (n = 102)</th>
<th>Placebo (n = 96)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>92</td>
<td>93</td>
<td>.90</td>
</tr>
<tr>
<td>Fever</td>
<td>46</td>
<td>61</td>
<td>.03</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23</td>
<td>35</td>
<td>.06</td>
</tr>
<tr>
<td>Week 8</td>
<td>42</td>
<td>43</td>
<td>.89</td>
</tr>
<tr>
<td>Night sweats</td>
<td>11</td>
<td>12</td>
<td>.86</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12</td>
<td>17</td>
<td>.43</td>
</tr>
<tr>
<td>Week 16</td>
<td>37</td>
<td>39</td>
<td>.86</td>
</tr>
<tr>
<td>Fever</td>
<td>7</td>
<td>10</td>
<td>.62</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
<td>13</td>
<td>.93</td>
</tr>
</tbody>
</table>

NOTE: cfu = colony forming units of Mycobacterium avium complex; IQR = interquartile range.
* Eradication or a ≥2-log₁₀ decrease in cfu/mL, from baseline.
† Data represent the number of patients achieving end point/number of patients with end-point data available.

As shown in table 3, fever was present in almost all patients at baseline and responded similarly to the two regimens. Night sweats and abdominal pain were more common in the placebo group at baseline and responded well to both regimens. Overall survival did not differ between the two groups (log-rank P = .87). Patients receiving rifabutin had a median survival of 398 days, and those in the placebo group had a median survival of 439 days.

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Of the 223 patients dosed, the only significant laboratory abnormality associated with the three-drug regimen was a higher proportion of patients who had leukopenia (<1,000 WBCs/mm³) during the study (18%, vs. 8% in the placebo group; P < .05), although no patient permanently discontinued taking a study drug because of neutropenia. There was no difference between the two study groups in terms of the number of patients developing other hematologic, renal, or liver abnor-
malities. Rash was reported for 16 patients receiving rifabutin and 19 receiving placebo \((P = .49)\), and uveitis was reported for 4 patients receiving rifabutin and 2 receiving placebo \((P = .44)\).

**Discussion**

In this study, rifabutin, when added to a regimen of clarithromycin and ethambutol for the treatment of MAC bacteremia, did not improve the clearance of organisms, abatement of clinical symptoms, or survival rate. Among patients who did have a bacteriologic response, however, those who received rifabutin were less likely to develop in vitro resistance to clarithromycin.

The importance of clarithromycin resistance has been demonstrated in this study as well as in other published series \([14, 15, 24, 25]\). In this study, of seven persons who had clarithromycin resistance at baseline, only one had a treatment response at week 16. Furthermore, the only relapse occurred in a person who developed clarithromycin resistance during treatment. The strong correlation between development of clarithromycin resistance and clinical failure was first demonstrated in a study of clarithromycin monotherapy for disseminated MAC infection \([14]\): in vitro resistance to clarithromycin developed in 46% of patients and was associated with recrudescence of symptoms and increases in cfu of MAC in the blood.

More recently, May et al. compared a regimen of clarithromycin, rifabutin, and ethambutol with a regimen of clarithromycin and clofazimine for the treatment of disseminated MAC infection \([24]\): resistance to clarithromycin developed in 23 patients, only two of whom were receiving the three-drug regimen; furthermore, the development of in vitro resistance was strongly correlated with clinical failure. Additional evidence of the clinical importance of in vitro clarithromycin resistance has been provided by Dube et al. \([25]\); again, patients who developed in vitro resistance were likely to manifest clinical failure.

Clarithromycin and rifabutin have been shown to be synergistic in vitro against MAC \([26]\). The clinical ability to use these drugs together, however, has been limited by drug toxicities, due in part to the pharmacokinetic interactions of the two drugs. In a study of prophylaxis for MAC infection, patients receiving rifabutin and clarithromycin had significantly more adverse events than patients taking either drug alone \([27]\). Of particular significance was the development of uveitis in 8.5% of patients in the combination-treatment group. The occurrence of uveitis has also been reported when clarithromycin and rifabutin have been used together for the treatment of MAC infection in both HIV-positive and HIV-negative patients \([24, 28, 29]\).

Rifabutin at a daily dose of 600 mg has been shown to be more effective than rifabutin at a lower dose for treating patients with disseminated MAC infection \([28]\) but has also been associated with a higher incidence of uveitis \([29, 30]\). In our study, a daily dose of 300 mg of rifabutin was chosen to decrease the incidence of uveitis. This lower dose, however, may have reduced the efficacy of the combination regimen. Another factor that may have lessened any additive benefit of rifabutin is the pharmacokinetic interaction of this agent with clarithromycin. Among HIV-negative patients treated for MAC pulmonary infection, the mean serum level of clarithromycin was 5.4 \(\mu g/mL\) among those receiving 500 mg of clarithromycin twice daily, which was reduced to 2.0 \(\mu g/mL\) when rifabutin was added at a dosage of 600 mg daily \([31]\). In a pharmacokinetic study of HIV-positive patients, the addition of rifabutin at a dosage of 300 mg daily resulted in a 44% decrease in the area under the concentration-time curve of clarithromycin for persons receiving 500 mg of clarithromycin every 12 hours \([32]\). Therefore, any potential gain in the clearance of MAC bacteremia in our study by the addition of rifabutin may have been offset by a reduction in serum clarithromycin levels.

A number of studies have helped to clarify the initial treatment regimen for AIDS patients with disseminated MAC infection. It is essential that a macrolide be included in the regimen, and some data support the use of azithromycin \([33, 34]\), although clarithromycin has been evaluated more extensively \([13\text{–}15, 24, 25, 28, 35]\). In order to reduce the development of resistance to the macrolide, at least one additional drug must be employed. Clofazimine has not been effective in preventing resistance \([24, 25, 35]\) and may result in increased mortality when used in the treatment of MAC infection \([35]\). The most recent national guidelines state that in the treatment of MAC, clarithromycin should be used with either ethambutol or rifabutin or both \([36]\).

We conclude that the regimen of clarithromycin and ethambutol was as effective as the same two drugs given with rifabutin. Since among those patients who responded bacteriologically there was a trend toward development of clarithromycin resistance in the two-drug group, one must question whether using rifabutin in addition to these two drugs would have long-term benefit. Clarithromycin and rifabutin may be equivalent to or better than clarithromycin and ethambutol, and the former regimen is currently being evaluated. Since rifabutin does not reduce azithromycin blood levels \([37]\), as it does clarithromycin levels, the combination of azithromycin and rifabutin may have additive effects, as has been shown in a study of prophylaxis with these two drugs for MAC infection \([38]\). Therefore, the role of rifabutin for patients whose regimens contain azithromycin, as well as for persons infected with macrolide-resistant organisms, needs further investigation.

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