Early Results (at 6 Months) with Intermittent Clarithromycin-Including Regimens for Lung Disease Due to *Mycobacterium avium* Complex

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We initiated a prospective noncomparative trial of treatment for lung disease due to *Mycobacterium avium* complex (MAC) in human immunodeficiency virus–negative patients, with a regimen of clarithromycin (1000 mg), rifabutin (300–600 mg), and ethambutol (25 mg/kg) administered 3 times per week. Fifty-nine patients were enrolled. Twelve (20%) were lost to follow-up, and 6 (10%) developed clarithromycin intolerance. The remaining 41 patients (69%) completed the initial 6 months of therapy. The sputum of 32 of these patients (78%) converted to negative. When results were compared with the sputum response rates at 6 months in previous studies with a regimen including daily clarithromycin and regimens including intermittent (3 times per week) azithromycin with the same companion drugs, no differences in treatment responses were evident. Adverse reactions related to rifabutin were a major problem, and for 24 (41%) of 59 patients the dosage was decreased or the drug was withdrawn. Intermittent (3 times per week) administration of clarithromycin appears to be as effective as daily administration in effecting sputum conversion in pulmonary MAC disease.

The introduction of more potent antimicrobials, such as the newer macrolides and rifabutin, with relatively long tissue and intracellular half-lives has raised the possibility of intermittent therapy as prophylaxis for disseminated *Mycobacterium avium* complex (MAC) disease or for established disseminated or pulmonary MAC disease. With the availability of such potent drugs for tuberculosis, intermittent therapy has become standard for drug-susceptible disease. Recent studies have shown that administration of azithromycin once a week is effective for preventing disseminated *M. avium* disease in patients with advanced HIV disease and that a 3-times-per-week regimen (Monday, Wednesday, Friday) that includes azithromycin appears as effective as daily regimens for pulmonary MAC disease in HIV-negative patients [1, 2].

No similar studies with clarithromycin have been reported. Intermittent therapy offers multiple potential advantages over daily therapy, including decreased cost and the potential for directly observed therapy. Drug-related side effects also remain a major problem in treatment of pulmonary MAC disease, and for 40% of patients, dosage of at least 1 oral drug is altered or discontinued during daily therapy with a macrolide-including 3-drug oral regimen [3].

We initiated a single-center, open, noncomparative, prospective trial of treatment for MAC lung disease with a 3-times-per-week clarithromycin-including regimen. We sought to determine whether thrice-weekly treatment would produce results similar to those previously reported following trials of daily treatment with a clarithromycin-including regimen or 1 that included azithromycin 3 times per week, which was performed in the same institution in a demographically similar patient population and with the same companion drugs [2, 3].

Methods

Patients and disease definitions. Patients aged >18 years with MAC lung disease who were referred to the University of Texas Health Center at Tyler or whose disease was diagnosed there were considered for therapy. Diagnostic criteria for lung disease included chest radiographic abnormalities consistent with mycobacterial lung disease; ≥2 culture-positive sputum samples, of which at least 1 was smear-positive for acid-fast bacilli (AFB); ≥3 smear-negative, culture-positive samples (or a single bronchoalveolar lavage sample if the patient was unable to produce sputum) in the previous year; and agreement with the most recent diagnostic criteria of the American Thoracic Society [4].

Features of the pretreatment chest radiograph, history of antimycobacterial drug therapy, records of prior AFB smears and cultures, and patient demographic information were recorded. Patients were considered to have received prior therapy if they had received treatment for ≥6 months with antimycobacterial drugs, with or without a macrolide. Patients were considered current smokers if

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Informed consent was obtained from patients, and human experimentation guidelines were followed as established by the institutional review board of the University of Texas Health Center at Tyler, Texas.

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they continued to smoke during therapy for MAC disease or former smokers if they had stopped smoking before enrollment in the trial.

Study criteria. Criteria for enrollment included a sputum culture positive for MAC, either prior to any drug treatment or at the time of enrollment in the study, and a patient’s reliability and availability for long-term follow-up. Patients could be either hospital inpatients or outpatients. Exclusion criteria included pregnancy, inadequate birth control, known allergy or intolerance to any of the study drugs, life-threatening illness with no prior therapy for MAC lung disease, resistance of a pretreatment MAC isolate to macrolides, and/or identified risk factors or known positivity for HIV.

Patients were considered for enrollment regardless of prior therapy for MAC, as long as the pretreatment MAC isolate was macrolide-susceptible. Informed consent was obtained under a protocol approved by the Human Subjects Investigation Committee at the University of Texas Health Center at Tyler and by the United States Food and Drug Administration under investigational new drug applications (for clarithromycin and rifabutin).

Therapy. All patients were initially to receive 1000 mg of clarithromycin (Abbott Laboratories, Abbott Park, IL) 3 times per week, usually on Monday, Wednesday, and Friday. In addition, patients received companion drugs, including ethambutol (25 mg/kg) and rifabutin (150–300 mg; generally, 150 mg for body weight <55 kg and 300 mg for body weight >55 kg), also 3 times per week. Patients were encouraged to take all of the medicine with a meal and were instructed how to take the medicine by a study coordinator. Patients and family caregivers were encouraged to buy labeled pill boxes holding 1 week’s supply to help them remember when to take medicines. Medicines were to be administered until patients were culture-negative for 12 months. The results of therapy for the first 6 months of this regimen are reported.

AFB smears and cultures. Generally, 3 daily sputum specimens were collected at enrollment in the study, in addition to at least 1 specimen every 4 weeks during therapy. Sputum samples were decontaminated with Na-acetyl-L-cysteine sodium hydroxide (NACL/NaOH) by routine methods [5]. Semiquantitative AFB smears (fluorochrome method) were performed at a magnification of ×200, as described elsewhere [6].

Specimens were plated on Middlebrook 7H10 agar and onto BACTEC 12B medium (Becton-Dickinson, Cockeysville, MD). Cultures in solid media were quantitated from no growth to 4+ by use of published standards, as described elsewhere [6]. For patients whose initial sputum specimens were contaminated with bacteria, especially Pseudomonas aeruginosa, subsequent samples were processed initially with NACL/NaOH and then processed a second time with oxalic acid [5]. Organisms were identified as MAC by use of a commercial nucleic acid probe (AccuProbe; GenProbe, San Diego).

Sputum conversion was defined by 3 consecutive negative cultures (in both solid media and BACTEC), with the time of conversion considered to be the date of the first of the 3 negative sputum culture results. A definite microbiological response was a reduction in colony count in 3 successive sputum cultures, from 3+ or 4+ to 1+ or countable colonies. Lesser degrees of decrease in colony counts were considered to represent improvement without sputum conversion, whereas no change in colony counts was considered as a lack of response. The percentage of patients in each of these categories at 6 months was recorded.

Susceptibility testing. A pretreatment isolate of MAC and selected isolates recovered during treatment were tested for susceptibility to clarithromycin by means of broth microdilution with 2-fold drug dilutions in cation-supplemented Mueller-Hinton broth with 5% oleic acid albumin dextrose (pH, 7.4) and 2 weeks’ incubation, as described elsewhere [7, 8]. Isolates were considered macrolide-susceptible if the clarithromycin MIC was <8 μg/mL and macrolide-resistant if the MIC was ≥32 μg/mL. Each isolate was frozen at −70°C for future needs.

Drug tolerance and safety tests. Patients were questioned about problems and symptoms (especially gastrointestinal) at baseline and on each clinic visit. In addition, a study coordinator was available 5 days per week by telephone. Patients were encouraged to continue taking medicines despite adverse reactions, and medicines were withdrawn only as a last resort. Laboratory safety tests consisted of baseline determinations of the following values: liver enzymes (including glutamyl transpeptidase and alkaline phosphatase), serum urea, nitrogen, serum creatinine, and complete blood cells.

The liver enzyme values and complete blood cell counts were determined at monthly intervals for 6 months. Liver enzyme levels were considered abnormal if they increased during therapy to twice the upper limits of normal (if baseline values were normal) or to twice the baseline value if they were already abnormal. Rifabutin was withdrawn if the patient’s WBC count fell below 2 × 10^3/mm^3, the absolute granulocyte count fell below 1 × 10^3/mm^3, or the platelet count fell below 1 × 10^3/mm^3.

Visual acuity and red-green color discrimination were tested at baseline, at monthly intervals, and whenever the patient complained of a sudden change in vision (blurred vision). In the latter circumstance, ethambutol was withdrawn and the patient’s ophthalmologist was consulted. Patients unable to tolerate rifabutin (because of fever, chills, nausea, vomiting, or leukopenia) were switched to rifampin (600 mg). Patients unable to tolerate either rifampin or ethambutol were dropped from the study. Patients unable to tolerate 1000 mg of clarithromycin had the dose decreased to 500 mg. Patients unable to tolerate 500 mg of clarithromycin were dropped from the study.

Statistical analysis. Group results are expressed as mean ± SD. Comparison of characteristics between patients with and without sputum conversion and between treatment groups was done by means of an unpaired Student’s *t*-test with a two-tailed *P* value. Comparison of culture results for responders and nonresponders before and at the end of therapy and comparison of results with previous azithromycin and clarithromycin treatment groups at 6 months were done with χ^2^-analysis and the Fisher’s exact test with Yates’ correction for small sample sizes. Significance was determined at *P* < .05.

Results

Patients. Fifty-nine patients, 24 men and 35 women (mean age ± SD, 63 ± 14 years), were enrolled in the study. Their ages, sex, and type of clinical disease are listed in tables 1 and 2. There were no significant differences among the entire intent-to-treat population, the patients who completed 6 months of
therapy, and those patients excluded because they did not complete 6 months of therapy.

Therapy and drug tolerance. Eighteen patients (31%), 8 men and 10 women (mean age ± SD, 57 ± 15.2 years) did not complete 6 months of therapy. Twelve (21%) were nonadherent to the regimen and/or clinic visits and/or were lost to follow-up. The sputum of 3 of those patients converted to negative before they were dropped from the study. Six patients (10%) had intolerable side effects, usually rash or gastrointestinal symptoms, related to the clarithromycin and thus were dropped from the study.

The remaining 41 patients (69%), 16 men and 25 women (mean age ± SD, 64 ± 11.4 years) completed the first 6 months of therapy. Twenty-four of these patients (59%) were current or recent smokers. Five of the 41 patients (13%) required a decrease in the dosage of clarithromycin to 500 mg 3 times per week, and 1 required a decrease to 250 mg 3 times per week. Four of 5 of these patients weighed ≤55 kg. Seventeen patients (29%) required a decrease in rifabutin dose because of intolerable adverse events, usually gastrointestinal or musculoskeletal symptoms, whereas 7 patients (12%) had sufficiently severe rifabutin-related adverse events to necessitate the replacement of rifabutin with rifampin in the medication regimen. No patient was intolerant of ethambutol or required a decrease in dosage.

Thirteen of 59 patients (22%) enrolled in the study discontinued taking 1 drug, either clarithromycin or rifabutin, because of drug-related adverse events. In addition, 22 of 59 patients (37%) required a decrease in the dose of either clarithromycin or rifabutin because of drug-related adverse events. This incidence of drug-related adverse events was not significantly different from that encountered with the same medications when administered daily [3].

For 32 patients (78%), 12 men and 20 women (mean age ± SD, 64 ± 10.9 years), including 18 (56%) current or former smokers, conversion of sputum to negative occurred within the first 6 months of therapy. This included 18 (82%) of 22 patients with primarily midlung nodular disease/bronchiectasis evident on a chest radiograph and 14 (74%) of 19 patients with primarily upper-lobe fibrocavitary disease (P > .05). Thirty-one patients had received no significant previous therapy against MAC, but the sputum of 26 (84%) of these patients converted to negative, whereas sputum conversion occurred in only 6 (60%) of the 10 patients with significant previous therapy (P > .05). All patients (100%) whose sputum became negative had symptomatic improvement, including decreased cough and sputum production. In addition, all of these patients had radiographic improvement.

For 9 patients (22%) who completed 6 months of therapy, sputum did not convert to negative. These patients did not differ significantly in age, sex ratio, or type of lung disease from the patients whose sputum converted. Three of those patients met criteria for improvement without sputum conversion. Seven of 9 patients (78%) whose sputum did not convert did have symptomatic improvement, with decreased cough and sputum production. These 7 patients also had radiographic improvement. The 2 patients without symptomatic improvement had no radiographic change. There were no significant differences in clinical response between patients with or without microbiological response.

The sputum conversion rate with the intermittent clarithromycin regimen was not statistically different from the 6-month sputum conversion rates for a daily multidrug clarithromycin-including regimen (83%) or for an intermittent azithromycin-including multidrug regimen (62%) (table 3).

Susceptibility testing. Three of the 59 patients had clarithromycin-resistant isolates at enrollment and were dropped from the study. None of the isolated strains developed clarithromycin resistance in the 6-month study period.

Discussion

This is the second multidrug treatment trial for pulmonary MAC infection to demonstrate the utility and efficacy of intermittent therapy [2]. This study demonstrates that multidrug regimens that include clarithromycin and are given intermittently can be effective in converting sputum to culture-negative for patients with pulmonary MAC disease. The overall sputum conversion rate in the study was 78% for all patients completing 6 months of therapy with 3 drugs, and the conversion rate was 84% among patients without prior drug therapy. These results are similar to our findings at 6 months in 2 previous studies, one involving 4 months of daily single-drug therapy with clarithromycin (followed by administration of clarithromycin with the same companion drugs on a daily basis for 2 months) and the other involving an intermittent azithromycin-including multidrug regimen [2, 6].

One anticipated benefit of intermittent administration was an improvement in drug tolerance, compared with that seen with daily treatment regimens. Unfortunately, this has not occurred, despite the use of the same medications but at lower weekly doses [3].

With regard to tolerance of clarithromycin, the current intermittent regimen was generally well tolerated; 13% of patients required an adjustment in the dosage of clarithromycin, and
10% required discontinuation of therapy because of a clarithromycin-related adverse event. More troublesome for patients than clarithromycin, from the perspective of adverse events, was rifampin. Although rifampin is effective in multidrug regimens for treatment of disseminated and pulmonary MAC infection [2, 3, 9], it is also associated with frequent and severe adverse events [10, 11]. In the current study, 41% of patients needed to have their dosages decreased because of rifabutin-related adverse reactions.

An additional potential problem is the effect of rifabutin on clarithromycin metabolism and clarithromycin serum levels, which it reduces by almost 50% [12]. Substituting rifampin for rifabutin is not necessarily desirable, because it has an even more profound effect on clarithromycin serum levels, reducing them by almost 90% [12]. Gordin et al. recently published results of a trial comparing clarithromycin and ethambutol with rifabutin, clarithromycin, and ethambutol for treatment of disseminated MAC infection [13]. There was no difference in rates of bacteriologic response or survival between the regimens with or without rifabutin. The regimen that included rifabutin was associated less frequently than clarithromycin and ethambutol with the emergence of macrolide- (clarithromycin-) resistant MAC isolates.

With respect to MAC pulmonary disease, which usually occurs in frail elderly patients, it would clearly be of interest to investigate the efficacy of a regimen of clarithromycin plus ethambutol without a rifamycin (especially rifabutin), which should be easier for patients to tolerate. The clinician should be advised that such a trial has never been performed for patients with MAC lung disease, and ethambutol alone may well be insufficient to prevent the development of clarithromycin resistance, especially in patients with upper-lobe cavitary disease and large numbers of organisms. It is our opinion that this 2-drug regimen should not be used, especially in the latter situation, until it is studied by clinical trial. The absence of any treatment regimen for macrolide-resistant MAC disease makes the development of such resistance a major, perhaps insurmountable, clinical issue.

For 9 patients (22%) who completed 6 months of therapy, conversion of sputum to negative did not occur. Treatment failures appeared to mirror the demographics of the study patient population as a whole, including age, sex, and smoking status. Because none of these patients received their medications by directly observed therapy, nonadherence with the treatment regimen cannot be excluded as the cause of the treatment failure, although it seems an unlikely explanation in all cases. As in previous studies, we could not identify a significant difference between treatment failures and responses with regard to patients’ severity of illness at presentation [2, 3, 14].

As we have also previously observed, the treatment failure group did have a higher incidence of previous MAC therapy (with or without a macrolide) that did not impact in vitro MAC susceptibility to macrolides. Sputum became negative for only 6 (60%) of 10 patients who had prior drug therapy (i.e., for \( \geq 6 \) months) but for 26 (84%) of 31 who did not receive prior therapy. Although this difference did not reach statistical significance in this study, it is a difference noted in all pulmonary MAC treatment trials, regardless of the macrolide-including

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
<th>No. (%) who completed</th>
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<tbody>
<tr>
<td></td>
<td>Intent to treat</td>
<td>Excluded</td>
</tr>
<tr>
<td>No. of patients</td>
<td>59</td>
<td>18 (33)</td>
</tr>
<tr>
<td>No prior therapy (&lt;6 mo)</td>
<td>42</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Prior therapy (( \geq 6 ) mo)</td>
<td>17</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Sex, M/F (M : F)</td>
<td>24/35 (1 : 1.5)</td>
<td>8/10 (1 : 1.2)</td>
</tr>
<tr>
<td>Type of lung disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midlung nodular bronchiectasis</td>
<td>29 (49)</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Upper-lung fibronodular or fibrocavitary disease</td>
<td>30 (51)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Age at enrollment, y</td>
<td></td>
<td>31±88</td>
</tr>
<tr>
<td>Range</td>
<td>63±14</td>
<td>64±11.4</td>
</tr>
</tbody>
</table>

NOTE. Data are no. of patients, no. (%), or no./no. examined (%). There was no statistical difference in the sputum conversion rates for the 3 regimens (P>0.18).

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Table 3. Sputum conversion rates at 6 months with clarithromycin (3 times per week), compared with these in 2 trials at the same study site that utilized azithromycin (3 times per week) or clarithromycin (daily) with the same companion drugs.

<table>
<thead>
<tr>
<th>Patient parameter</th>
<th>Clarithromycin</th>
<th>Azithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily(^a)</td>
<td>3 \times W(^b)</td>
</tr>
<tr>
<td>Enrolled (intent to treat)</td>
<td>50</td>
<td>59</td>
</tr>
<tr>
<td>Dropped from study</td>
<td>11 (22)</td>
<td>18 (30)</td>
</tr>
<tr>
<td>Completed 6 mo of therapy</td>
<td>39</td>
<td>41</td>
</tr>
<tr>
<td>Sputum conversion at 6 mo</td>
<td>24/29(^e)</td>
<td>32/41 (78)</td>
</tr>
<tr>
<td>Developed macrolide resistance ( \leq 6 ) mo</td>
<td>3/29(^f)</td>
<td>0/39 (0)</td>
</tr>
</tbody>
</table>

| NOTE. Data are no. of patients, no. (%), or no./no. examined (%). There was no statistical difference in the sputum conversion rates for the 3 regimens (P>0.18).
| \(^a\) See [3].
| \(^b\) Three times per week: Monday, Wednesday, and Friday.
| \(^c\) See [2].
| \(^d\) Time of conversion known for only 29 patients.
| \(^e\) Developed in all 3 during a course of initial clarithromycin monotherapy.

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regimen employed [2, 3, 6, 14], and a difference that was statistically significant in 1 of these studies [2]. This observation may be an indication that some of these patients have yet unidentified factor(s) (including possible nonadherence) that defeat macrolide-including treatment regimens.

An effective intermittent treatment regimen for pulmonary MAC disease is important for a number of reasons enumerated elsewhere [2]. Perhaps most important, macrolide-including regimens are expensive, and intermittent therapy could dramatically decrease the cost of these regimens, which typically are administered for 12–24 months. For instance, the acquisition cost at our pharmacy for 1 year of daily doses of clarithromycin (1000 mg/d), rifabutin (300 mg/d), and ethambutol (1200 mg/d) is ~US$5700. In contrast, the pharmacy acquisition cost for 1 year of 3-times-per-week doses of clarithromycin (1000 mg), rifabutin (300 mg), and ethambutol (1600 mg) is ~US$2700. Clearly, the difference in retail cost to the patient would be much greater. The high cost of these treatment regimens is at least as important as their potential toxicity as a barrier for their widespread use for people with pulmonary MAC disease.

Recent studies in our institution have shown that ~50% of patients with MAC lung disease have upper-lobe cavitary disease, a form of disease often identified in male alcoholics [15]. Intermittent administration would also allow directly observed therapy to eliminate nonadherence as a mechanism of treatment failure.

It is also possible that intermittent therapy with a clarithromycin-including regimen will have utility for management of disseminated MAC disease. Azithromycin given once weekly is effective as treatment of disseminated MAC disease, and the advantages listed above for intermittent treatment of pulmonary MAC disease are also pertinent for disseminated MAC disease [1].

Because of its long half-life and concentration in phagocytes and tissues, clarithromycin appears to be a suitable agent for long-term intermittent treatment of chronic infections, such as mycobacterial diseases. Although we did not compare them directly in a head-to-head fashion, we found that clarithromycin-including regimens, either daily or intermittent, are associated with consistently better but not always statistically significantly different sputum conversion rates than are regimens including azithromycin. A recent direct comparison of clarithromycin- and azithromycin-including regimens in the treatment of disseminated MAC infection in AIDS patients demonstrated superior efficacy of the clarithromycin-including regimen [16]. The long-term consequences of these observations on the treatment of MAC lung disease are unclear.

References