Azithromycin-Containing Regimens for Treatment of Mycobacterium avium Complex Lung Disease


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Ninety-two patients were assessable in 3 consecutive, open, noncomparative, prospective, controlled, single-center trials of the use of multidrug regimens that contain azithromycin for treating pulmonary Mycobacterium avium complex (MAC) disease. Azithromycin was provided at a dose of 300–600 mg per day with oral companion drugs administered daily (regimen A, 29 patients); 600 mg 3 times weekly (t.i.w.), with oral companion drugs administered daily (regimen B, 20 patients); and 600 mg t.i.w., with oral companion drugs administered t.i.w. (regimen C, 43 patients). All regimens included rifabutin (or rifampin) and ethambutol as companion drugs as well as initial streptomycin. Treatment success was defined as 12 months of negative cultures while on therapy. Treatment failure was defined as sputum culture positivity after at least 6 months of therapy. Of the patients in each regimen who reached study end points, 17 of 29 (59%) were in regimen A, 11 of 20 (55%) were in regimen B, and 28 of 43 (65%) were in regimen C met the treatment success criterion. There were no statistically significant differences in outcome between the 3 regimens. These studies demonstrate the effectiveness of daily and t.i.w. regimens containing azithromycin for treatment of MAC lung disease.

Macrolide and azalide antibiotics, including clarithromycin and azithromycin, are currently the most important component of multidrug treatment regimens for pulmonary and disseminated Mycobacterium avium complex (MAC) disease [1–3]. We previously reported initial results after 6 months of therapy from 3 consecutive, open, concomparative, prospective, controlled, single-center trials of azithromycin-containing regimens (ACRs) as therapy for HIV-negative patients with MAC lung disease [4, 5]. The first report evaluated initial responses to a daily administration of azithromycin monotherapy and a multidrug ACR; the second report evaluated initial responses to administration of 2 intermittent multidrug regimens containing azithromycin for MAC lung disease. These studies suggested that during the first 6 months of therapy, azithromycin has significant activity, comparable to clarithromycin, when used either on a daily or intermittent (3 times weekly, or t.i.w.) basis in multidrug regimens for MAC lung disease.

We report on the long-term results of the 3 ACRs in HIV-negative patients with pulmonary MAC disease. The goal of these ongoing clinical trials is to identify...
Patients and disease. Patients aged >18 years diagnosed with MAC lung disease or referred to the University of Texas Health Center at Tyler (UTHCT) were considered for therapy. Diagnostic criteria for lung disease included ≥2 sputum samples that contained moderate-to-large numbers of organisms on culture and an abnormal chest radiograph consistent with mycobacterial lung disease, in agreement with the most recent criteria of the American Thoracic Society [1]. Features of the pretreatment chest radiograph, history of antituberculosis drug therapy, records of acid-fast bacilli smears, and culture results and patient demographic information were recorded. Patients were considered to have been on previous therapy if they received ≥6 months’ treatment with antituberculosis drugs with or without a macrolide. Patients were considered to be current smokers if they continued to smoke while on MAC therapy and former smokers if they had stopped smoking before entering into the trial.

Study criteria. Inclusion criteria included the presence of culture-positive sputum for MAC before any drug treatment or at the time of entrance into the study and patient reliability and availability for long-term follow-up. Patients could be either hospital inpatients or outpatients. Exclusion criteria included pregnancy, inadequate birth control, macrolide allergy, life-threatening illness with no previous therapy for MAC lung disease, resistance to macrolides in a pretreatment MAC isolate, and identified risk factors or known seropositivity for HIV. Patients were considered for inclusion into the study, regardless of previous therapy for MAC, as long as the pretreatment MAC isolate was macrolide susceptible. Informed consent was obtained under a protocol approved by the UTHCT Human Subjects Investigation Committee and by the US Food and Drug Administration under Investigational New Drug applications for azithromycin and rifabutin. All patients who met inclusion criteria, signed an informed consent form and received study medications are included in the intent-to-treat category.

Therapy. The 3 azithromycin treatment protocols are outlined in table 1. All medications were self-administered. Patient compliance was evaluated by direct patient questioning and monitoring of medication prescription refills. All patients initially received a 300-mg or 600-mg tablet of azithromycin (a special dosage formulation of azithromycin provided by Pfizer Pharmaceuticals) taken either daily or t.i.w. on Monday, Wednesday, and Friday, 2 h before or after a meal. In addition, patients received companion drugs either daily or t.i.w. Orally administered companion drugs were taken on an empty stomach, and to encourage compliance, patients were asked to take all of the medicine at one time.

Regimen A consisted of azithromycin 300–600 mg/day (dosage based on age and weight); ethambutol, 25 mg/kg/day for 2 months, then 15 mg/kg/day; rifabutin, 300 mg/day (provided by Pharmacia & Upjohn) or rifampin, 600 mg/day; and streptomycin, usually included for the first 2 months of therapy given 2–3 times weekly with dosage adjusted for age, weight, and renal function. Regimen B consisted of azithromycin, 600 mg t.i.w., with daily administration of oral companion medications as outlined in regimen A. Regimen C consisted of t.i.w. administration of all oral drugs in the regimen, including ethambutol, 25 mg/kg, and rifabutin, 300–600 mg (dosage based on patient body weight), or rifampin, 600 mg. The initial choice of rifabutin or rifampin was dictated by the availability of rifabutin. Streptomycin was also usually included for the first 2 months of therapy, given 2–3 times per week with dosage adjusted for age, weight, and renal function. All patients considered in this analysis received 3 orally administered drugs (azithromycin, ethambutol, and rifabutin or rifampin) throughout the study.

Acid-fast bacilli smears and cultures. Generally, 3 daily

### Table 1. Protocols for treatment of Mycobacterium avium complex lung disease using regimens that contain azithromycin.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Azithromycin regimen²</th>
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<tbody>
<tr>
<td></td>
<td>A</td>
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<tr>
<td>Azithromycin</td>
<td>300–600 mg/day</td>
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<tr>
<td>Ethambutol</td>
<td>25 mg/kg/day for 2 months, then 15 mg/day</td>
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<tr>
<td>Rifabutin</td>
<td>150–300 mg/day</td>
</tr>
<tr>
<td>Streptomycin²</td>
<td>500–1000 mg b.i.w. or t.i.w. for the first 2 mo</td>
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**NOTE.** b.i.w., 2 times weekly; MWF, Monday, Wednesday, and Friday; t.i.w., 3 times weekly.

² Regimen A consisted of oral administration of all drugs daily. Regimen B consisted of azithromycin on MWF and oral administration of other drugs daily. Regimen C consisted of oral administration of drugs on MWF.

² Streptomycin dosage was individualized on the basis of age, weight, and renal function.
sputum specimens (1 specimen per day for 3 days) were collected at entrance into the study, and at least 1 specimen was taken every 4 weeks during therapy. Sputum samples were decontaminated with N-acetyl-L-cysteine and sodium hydroxide (NALC/NaOH) [6]. Semiquantitative acid-fast bacilli smears (fluorochromes method) were performed at a magnification of ×200, as described elsewhere [7]. Samples were plated on Middlebrook 7H10 agar and into BACTEC 12B broth (Becton-Dickenson). Cultures that used solid media were quantitated from no growth to 4+ by use of published standards and as described elsewhere [7]. For patients whose initial sputum specimens were contaminated (especially with Pseudomonas aeruginosa), subsequent samples were processed initially with NALC/NaOH, then processed a second time with oxalic acid [6]. In addition, samples were also inoculated onto a 7H10 agar plate containing 10 µg/mL of tobramycin. Organisms were identified as MAC with a commercial nucleic acid probe (AccuProbe; GenProbe).

Sputum conversion was defined as 3 consecutive cultures negative for MAC (both solid media and BACTEC) with the time of conversion the date of the first of 3 negative sputum cultures. Treatment success was defined as 12 consecutive months of negative cultures while the patient was on therapy. Failure to respond to treatment was defined as persistently positive sputum cultures (failure to convert sputum cultures to negative) after at least 6 months of therapy. Patients were dropped from the study and classified as noncompliant if they did not keep follow-up appointments and did not obtain medication refills before completing 6 months of therapy.

**Macrolide susceptibility testing.** Clarithromycin was used as the class drug for testing macrolide and azalide susceptibility. A pretreatment isolate of MAC and selected isolates on treatment were subcultured once on 7H10 agar. Clarithromycin MICs were then performed with broth microdilution with 2-fold drug dilutions in Mueller-Hinton broth supplemented with 5% oleic acid, albumin, and dextrose; pH 7.4; and 2-week incubation, as described elsewhere [8, 9]. Isolates were considered to be macrolide-azalide susceptible if they had clarithromycin MICs ≤8 µg/mL and resistant if they had MICs ≥32 µg/mL. Each isolate was frozen at −70°C for future use.

**Drug tolerance and safety tests.** Patients were questioned about problems and symptoms (especially gastrointestinal, auditory, and vestibular symptoms) at entry and on each clinic visit. In addition, a study coordinator was available 5 days each week by telephone. Laboratory safety tests consisted of baseline liver enzymes (including a glutamyl transpeptidase and alkaline phosphatase), blood urea nitrogen, serum creatinine, and complete blood count. The liver enzyme test and complete blood count were done at monthly intervals for 6 months. An increase in liver enzymes was considered to be present if the enzymes rose during therapy to twice the upper limits of normal (if baseline values were normal), or if they rose to twice the baseline value if they were already abnormal. Routine audiograms were also performed on entry for the first 31 patients and for any patient who had a subjective decrease in auditory acuity. Rifabutin was discontinued if the patient’s WBC count fell below 2 × 10^3 cells/mm³, or the absolute granulocyte count fell below 1 × 10^3 cells/mm³, or the platelet count fell below 1 × 10^3 platelets/mm³.

Visual acuity and red-green color discrimination were tested on entry, at monthly intervals, and whenever the patient complained of a sudden change in vision (blurred vision). In the latter circumstance, the ethambutol was discontinued and consultation with the patient’s ophthalmologist was sought. Patients unable to tolerate rifabutin (patients who experienced fever, chills, nausea, vomiting, or leukopenia) were switched to rifampin, 600 mg. Patients unable to tolerate either rifamycin or ethambutol were dropped from the study. If patients were unable to tolerate 600 mg of azithromycin, we decreased the dose to 300 mg. Patients unable to tolerate 300 mg of azithromycin 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 an unpaired t test with a 2-tailed P value. Comparison of culture results in patients who did or did not respond before and at the end of therapy and comparison with previous clarithromycin treatment groups were done by χ² analysis and Fisher’s exact test with Yates’s correction for small sample sizes. Significance was determined at P < .05.

**RESULTS**

A total of 103 HIV-negative patients were enrolled in the 3 ACRs (table 2) in the intent-to-treat category: 32 in regimen A, 22 in regimen B, and 49 in regimen C. There were no differences demographically (mean age at enrollment, sex, smoking history, or type of MAC lung disease) between the intent-to-treat patients in these 3 treatment regimens (table 2) or compared with patient populations from our previous treatment trials [7, 10]. Eleven patients (11%) were excluded because of noncompliance. Ninety-two patients (89%) reached study end points, either negative cultures for 12 months while they were receiving therapy or persistently positive cultures after at least 6 months of therapy. Of the patients in each regimen who reached study end points, 59% in regimen A, 55% in regimen B, and 65% in regimen C met the treatment success criterion (table 2).

All patients who met the treatment success criterion had symptomatic improvement in cough and fatigue, and most had radiographic improvement, although for cost reasons, serial CT scans that would have provided more detailed results were not performed. There were no statistically significant differences in
<table>
<thead>
<tr>
<th>Variable</th>
<th>Azithromycin regimen</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients enrolled (intent-to-treat)</td>
<td>32       22     49     103</td>
<td></td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>15/17 (1:1.1)        11/11 (1:1) 24/25 (1:1.1) 50/53 (1:1.1)</td>
<td></td>
</tr>
<tr>
<td>Type of lung disease, no. (%)</td>
<td>Midlung nodular bronchiectasis 21 (66) 13 (59) 34 (69) 68 (66)</td>
<td></td>
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<tr>
<td></td>
<td>Upper lobe fibrocavitary 11 (34) 9 (41) 15 (31) 35 (34)</td>
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<tr>
<td></td>
<td>Cigarette smoker (current or former) 23 (72) 14 (64) 32 (65) 69 (67)</td>
<td></td>
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<tr>
<td>Age at enrollment, y</td>
<td>Range 45–87 45–89 41–89 41–89</td>
<td></td>
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<tr>
<td></td>
<td>Mean ± SD 62 ± 12 62 ± 13 61 ± 14 62 ± 13</td>
<td></td>
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<tr>
<td>Treatment outcome</td>
<td>Total assessable 29 20 43 92</td>
<td></td>
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<tr>
<td></td>
<td>Converted with 12 months of negative cultures, no. (%)^a 17 (59) 11 (55) 28 (65) 56 (61)</td>
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</tr>
<tr>
<td></td>
<td>Failed to respond, with positive sputum after 6 mo, no. (%)^b 12 (41) 9 (45) 15 (35) 36 (39)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Noncompliant, dropped from study^b 3 2 6 11</td>
<td></td>
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</table>

^a Percentages calculated based on total assessable.
^b Dropped out of the study before 6 months of follow-up.

outcome between the 3 ACRs (table 3). However, treatment outcomes with regimens A and B were significantly different from a study published elsewhere [10] that used a daily clarithromycin regimen with identical companion drugs; regimen C was not significantly different from any comparison regimen (table 3).

Twenty-seven patients (29%) from the 3 regimens received rifampin instead of rifabutin as part of the initial treatment regimen. As observed in previous studies from this institution, there were no statistically significant differences in outcome between patients who received rifabutin and those who received rifampin in any of the 3 regimens [4, 5, 7, 10].

There were also no significant demographic differences in the parameters in table 2 between the patients who met the treatment success criterion and the patients who did not. Of the 36 patients from all 3 regimens who failed to respond to therapy, 11 (30%) had a history of alcohol abuse during therapy and 26 (72%) were current or former smokers, versus 9 (16%) of the 56 patients who successfully completed therapy (P = .02). Of the patients who had received previous therapy, only 9 (38%) of 24 were successfully treated in this trial, compared with success with 46 (68%) of 68 of those patients with no previous therapy (P = .01). There was no significant difference in the dropout rates between patients who had failed previous therapy and patients who were not previously treated.

In general, azithromycin was tolerated well, both on a daily and intermittent basis. However, 6 patients in regimen A (21%) required a decrease in azithromycin dose, 5 because of decreased auditory acuity, and 1 because of gastrointestinal symptoms. Two patients (10%) in regimen B and 2 patients (5%) in regimen C (1 patient from each regimen because of decreased auditory acuity and 1 patient from each regimen because of gastrointestinal symptoms) required azithromycin dosage adjustment (P < .02 compared with regimen A). Four patients from regimen A, all of whom received 4 months of initial azithromycin monotherapy, developed macrolide-resistant MAC isolates. No MAC isolate from patients receiving intermittent azithromycin in combination with rifabutin and ethambutol, without an initial course of monotherapy, developed macrolide resistance.

As was the case in previous studies, rifabutin was the drug most frequently associated with adverse events (gastrointestinal symptoms, arthralgia, fever, chills, and leukopenia). For patients initially placed on rifabutin, 37% in regimen A, 37% in regimen B, and 32% in regimen C required rifabutin dosage adjustment or discontinuation. Two patients in regimen A who received daily...
ethambutol experienced deterioration of visual acuity sufficiently severe to require discontinuation of ethambutol.

### DISCUSSION

Three ACRs for MAC lung disease were evaluated in open, prospective, noncomparative trials. The treatment regimen in which all medications were given on an intermittent basis yielded results comparable to those obtained with a daily clarithromycin-containing regimen (CCR). Two other ACRs that included a daily treatment component did not achieve the same level of success. One of these regimens, including daily azithromycin, was also associated with significantly more azithromycin-related toxicity. Additionally, as we have consistently observed, previous unsuccessful therapy for MAC lung disease was a significant predictor for failure to respond to treatment, even in the presence of macrolide-susceptible MAC isolates [4, 5, 10].

Theoretically, azithromycin should be a good drug for treatment of MAC lung disease. Levels of azithromycin that exceed the MIC for MAC are not obtainable in the serum; however, they can be achieved intracellularly and specifically within the macrophage [11–14]. Intracellular levels of azithromycin are also maintained up to 2–3 weeks after dosing; therefore, intracellular pathogens, such as MAC, would be exposed to high levels of azithromycin for substantial periods of time. The sustained concentration of azithromycin in phagocytic cells undoubtedly contributes to its efficacy when it is administered on an intermittent basis, which is an important consideration for reducing treatment costs of MAC lung disease. Azithromycin has little significant metabolism through the cytochrome P-450 hepatic enzyme system, and therefore azithromycin has low potential for drug interactions.

Overall, azithromycin appears to have some pharmacologic advantages over clarithromycin for long-term intermittent administration, which is why we initially chose azithromycin as the basis for intermittent regimens to treat pulmonary MAC disease. It is therefore surprising that at least some ACRs appear to be less effective than CCRs that used similar companion medications.

There are few studies directly comparing the efficacy of ACRs and CCRs for the treatment of either pulmonary or disseminated MAC lung disease. Ward et al. [15] compared azithromycin, 600 mg/day plus ethambutol versus clarithromycin, 1000 mg/day, plus ethambutol in the treatment of MAC bacteremia in AIDS patients. Patients were evaluated every 4 weeks for 16 weeks. Fifty-nine patients were enrolled, but only 37 patients (21 in the clarithromycin study arm and 16 in the azithromycin study arm) were available for determination of quantitatively defined bacteremia and clinical outcomes. The proportion of patients with clearance of bacteremia at the final study visit (at 16 weeks) was 37.5% in the study’s azithromycin arm and 85.7% in the study’s clarithromycin arm ($P = .007$). Additionally, the estimated median time to clearance of bacteremia was significantly different for the 2 treatment groups: 4.4 weeks for the clarithromycin arm versus >16 weeks for the azithromycin arm. There was no difference between the 2 treatment arms in clinical (symptomatic) response. Both azithromycin and clarithromycin were tolerated well, with few side effects, and no patient required discontinuation of either drug. In this relatively brief study period, only 1 patient in the study’s clarithromycin arm developed macrolide-resistant MAC. Ward et al. [15] do not offer explanations for the differences in microbiologic response between ACRs and CCRs.

In a larger, more recent multinational study, Dunne et al. [16] compared azithromycin, 250 mg/day, azithromycin, 600 mg/day, and clarithromycin, 1000 mg/day (each combined with ethambutol) in the treatment of disseminated MAC infection in 246 HIV-infected patients. The azithromycin, 250 mg/day arm was discontinued early because clearance of bacteremia was lower than in the other 2 arms. After 24 weeks of therapy and through the last follow-up visit, no significant differences were found in the likelihood of development of 1 or 2 negative cultures, the likelihood of relapse, or the mortality rate between

### Table 3. Treatment outcome for azithromycin regimens compared with a trial of daily clarithromycin with the same companion drugs from the same study site.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Azithromycin regimen</th>
<th>Clarithromycin regimen</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>No. of assessable patients</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Converted with 12 mo of negative cultures, no. (%)</td>
<td>17⁵ (59)</td>
<td>11³ (55)</td>
</tr>
<tr>
<td>Developed macrolide resistance, no. (%)</td>
<td>4 (14)⁴</td>
<td>0</td>
</tr>
</tbody>
</table>

⁴ Derived from [2].
⁵ No statistical difference compared with the other 3 regimens.
⁶ Five of these patients received at least 3 mo of initial clarithromycin monotherapy.
patients receiving azithromycin (600 mg/day) versus clarithromycin (1000 mg/day). None of the MAC isolates from patients who experienced relapse who had received azithromycin were resistant in vitro to macrolides. In contrast to the study by Ward et al. [15], the study by Dunne et al. [16] suggests that in combination with ethambutol, azithromycin, 600 mg/day, provided microbiologic efficacy in disseminated MAC disease similar to that of clarithromycin.

In our studies of patients with MAC lung disease, it is not likely that administration of an inadequate dose of azithromycin was responsible for the difference in treatment outcome compared to CCRs. Serum levels were measured in patients in regimen A and in general were \( \geq 0.5 \) mg/mL, with a strong correlation between high serum levels and adverse side effects [17]. Similarly, the difference probably is not due to the choice of companion medications in ACRs and CCRs. One possible explanation is that achievable blood levels exceeding the MIC for MAC can be obtained with clarithromycin, which may be important for treatment outcome [7, 10, 18]. This explanation is perhaps most persuasive for the outcomes in patients with MAC bacteremia who were described by Ward et al. [15]. It is a less intuitively appealing explanation for a chronic process, such as MAC lung disease, in which the pathogen and the treatment agent are both primarily intracellular. Another possibility is that clarithromycin is more active in vivo against MAC than azithromycin.

Overall, the differences in efficacy between ACRs and CCRs for treatment of MAC lung disease are relatively small (table 3) [10]. It is unclear why there was not a significant difference in MAC disease response at 6 months between ACRs and CCRs, but a significant difference at the end of therapy [4, 5]. It is also unclear why the intermittent azithromycin regimen (regimen C) was the most effective azithromycin regimen. These studies are relatively small, and in the absence of a large head-to-head trial between ACRs and CCRs for treatment of MAC lung disease, it is difficult to make definitive statements about the superiority of one agent over the other for producing long-term sputum conversion. It is possible, for instance, that the observed differences between the azithromycin and clarithromycin trials could be due to a factor that was not revealed because patients were not randomized in these studies. Last, this study does not address MAC disease relapses or MAC reinfection after completion of therapy, which could be different with the 2 agents. Studies to look at these issues in patients enrolled in these trials are ongoing.

The toxicity of azithromycin, and ototoxicity specifically, diminished dramatically with intermittent administration of azithromycin. As in previous studies, most drug-related toxicity in all 3 regimens was due to rifabutin [4, 5, 10]. The number of patients requiring rifabutin dosage adjustment was similar to that with clarithromycin-containing regimens [10]. It is noteworthy that the initial rifabutin doses, 300 mg/day or 600 mg t.i.w., used in these studies were higher than are now generally used (150 mg/day or 300 mg t.i.w.). As has also been observed in previous studies having patients with MAC lung disease, there was no significant difference in outcome between patients who received rifampin versus those who received rifabutin [4, 5, 10, 19]. Recent studies of disseminated MAC infection in AIDS patients suggest that rifabutin plus 2 companion drugs (including a macrolide) does not increase the clearance of bacteremia in these patients when compared with the 2 companion drugs alone [16, 20]. Such studies have not been done in pulmonary MAC disease. As is the case for azithromycin and clarithromycin, there has not been a prospective head-to-head trial comparing rifabutin with rifampin in macrolide-containing regimens for MAC lung disease. Given the frequent adverse events seen with rifabutin and the apparent lack of therapeutic advantage, it is difficult to enthusiastically endorse administration of rifabutin rather than rifampin routinely.

Given the findings in this study, intermittent (t.i.w.) administration should be the preferred method of administration for MAC lung disease treatment regimens that use azithromycin. In addition to the efficacy of this approach, there is a significant potential cost reduction with intermittent t.i.w. administration. Assuming an average-sized individual (70 kg) for dosing considerations, the yearly pharmacy acquisition cost at our hospital for a daily azithromycin, rifabutin, and ethambutol regimen is approximately $4400, compared with $2800 for the same 3 drugs administered on a t.i.w. basis. In addition, if rifampin is used in place of rifabutin, the annual pharmacy acquisition cost for the t.i.w. regimen is further reduced, to approximately $2400. We have also had initial success with an intermittent (t.i.w.) CCR for treatment of MAC lung disease [21]. If this success is maintained, then intermittent therapy for MAC lung disease would be preferable with both azithromycin- and clarithromycin-based treatment regimens.

References
6. Roberts GD, Koneman EW, Kim YK. Mycobacterium. In: Balows A,
Azithromycin for MAC Lung Disease