Initial (6-Month) Results of Three-Times-Weekly Azithromycin in Treatment Regimens for *Mycobacterium avium* Complex Lung Disease in Human Immunodeficiency Virus–Negative Patients

David E. Griffith, Barbara A. Brown, David T. Murphy, William M. Girard, Leslie Couch, and Richard J. Wallace, Jr.

Departments of Medicine, Microbiology, and Pathology, and Center for Pulmonary Infectious Disease Control, University of Texas Health Center, Tyler, Texas

Two consecutive, open, prospective trials of intermittent azithromycin (600 mg), usually given Monday, Wednesday, and Friday (TIW) for *Mycobacterium avium* complex (MAC) lung disease were initiated in human immunodeficiency virus–negative patients. Regimen A consisted of TIW azithromycin and daily ethambutol (15 mg/kg/day), daily rifabutin (300 mg/day), and initial twice weekly (BIW) streptomycin. Regimen B consisted of TIW azithromycin, TIW ethambutol (25 mg/kg/dose), TIW rifabutin (600 mg/dose), and initial BIW streptomycin. Of 19 patients enrolled in regimen A who completed at least 6 months of therapy, 14 (74%) had sputum samples become culture-negative. Of 39 patients enrolled in regimen B who completed at least 6 months of therapy, 24 (62%) had sputum conversion. These sputum conversion rates are comparable to previous rates at 6 months in patients receiving daily clarithromycin- or azithromycin-containing regimens. No resistance to azithromycin emerged with either regimen. This is the first study to demonstrate the efficacy of intermittent administration of medication for MAC lung disease.

Azithromycin and clarithromycin have significant activity against pulmonary and disseminated *Mycobacterium avium* complex (MAC) disease [1–5] and are effective as prophylaxis against disseminated MAC [6, 7]. Both drugs have significant activity as single agents and in multidrug regimens for the treatment of pulmonary MAC disease [1–3]. These drugs represent the most important recent pharmacologic advance in the treatment of MAC diseases [8]. Although azithromycin is an azalide, because of its structural similarities to macrolides, it will be included as a macrolide in subsequent discussions.

An important challenge at this point is to utilize these expensive and sometimes toxic antimycobacterial agents in the most efficient and cost-effective way possible. The treatment of tuberculosis was revolutionized by the use of intermittent drug administration regimens that allowed less expensive, shorter, and better supervised regimens. Several drugs that are already in use for treatment of MAC lung disease have shown efficacy in intermittent regimens for tuberculosis, including ethambutol, streptomycin, rifampin, and rifabutin. Several features of azithromycin suggest that it also would be effective in an intermittent regimen. Azithromycin has a very long half-life, up to 70 h, and it is concentrated in phagocytes and tissues, including the lung [9, 10]. Intermittent azithromycin, 1200 mg on a once-weekly basis, has been shown to be effective as chemoprophylaxis against disseminated MAC [6]. We therefore undertook an open, noncomparative, prospective, single-center trial of two regimens that both included three-times-weekly (TIW) azithromycin for pulmonary MAC disease and report here the results of the first 6 months of treatment from these trials.

Materials and Methods

Patients and disease. Patients >18 years of age referred to or diagnosed with MAC lung disease at the University of Texas Health Center (Tyler) were considered for therapy. Diagnostic criteria for lung disease included ⩾2 sputum samples with at least 1 smear-positive for acid-fast bacilli (AFB) or ⩾3 positive cultures in 1 year and abnormal chest radiograph findings consistent with mycobacterial lung disease, in agreement with the most recent criteria of the American Thoracic Society [11]. Features of the pretreatment chest radiograph, history of prior antituberculous drug therapy, records of prior AFB smear and culture results, and patient demographic information were recorded. Patients were considered to have received prior therapy if they received ⩾6 months of treatment with antituberculous drugs with or without a macrolide.

Study criteria. Inclusion criteria included the presence of sputum culture-positive for MAC prior to 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 hospital inpatients or outpatients. Exclusion criteria included pregnancy, inadequate birth control measures, azithromycin allergy or intolerance, life-threatening illness with no prior therapy for MAC lung disease, resistance of a pretreatment MAC isolate to macrolides, and identified risk factors or known positivity for human immunodeficiency

Received 3 October 1997; revised 9 February 1998.

Presented in part: American Thoracic Society annual meeting, San Francisco, April 1997 (Am J Respir Crit Care Med, A334).

Informed consent was obtained from patients following guidelines for human experimentation of the Human Subjects Investigation Committee of the University of Texas Health Center and by the Food and Drug Administration under an Investigational New Drug application.

Financial support: Pfizer Laboratories; Pharmacia; Upjohn.

Reprints or correspondence: Dr. David E. Griffith, P.O. Box 2003, UTHCT, Tyler, TX 75710.

The Journal of Infectious Diseases 1998; 178:121–6

0022–1899/98/7801–0015$02.00

Table 1. Sputum MAC culture results at 6 months for patients receiving intermittent azithromycin regimens compared with results from patients receiving other macrolide-containing regimens for the treatment of pulmonary MAC disease.

	Daily		Intermittent azithromycin (no initial monotherapy)	
No.	Clarithromycin* (initial monotherapy)	Azithromycin† (initial monotherapy)	Regimen A	Regimen B
Completed 6 months of therapy	19	23	19	39
No. with surgical resection	4/39 (10%)	0	1 (5%)	3 (8%)
Sputum conversion at 6 months	14/19 (74%)	14/21 (67%)	14/19 (74%)‡	24/39 (62%)§
Sputum conversion/improvement at 6 months	15/19 (79%)	16/21 (76%)	17/19 (89%)‡	30/39 (77%)§
Developed macrolide resistance within 6 months	3 (16%)	0	0	0

* Daily clarithromycin monotherapy (for 4 months) followed by addition of multiple daily medications (2 trials).
† Daily azithromycin monotherapy (for 4 months) followed by addition of multiple daily medications (1 trial).
‡ $P > .05$ compared with regimen B and other macrolide-containing regimens.
§ $P > .05$ compared with regimen A and other macrolide-containing regimens.

virus. Patients were considered for inclusion regardless of prior therapy for MAC as long as the pretreatment MAC isolate was macrolide-susceptible.

Therapy. All patients were to receive 600 mg of azithromycin (special dosage formulation of azithromycin provided by Pfizer Pharmaceuticals [Groton, CT]) taken TIW (usually Monday, Wednesday, and Friday) 2 h before or after a meal. In addition, patients received companion drugs in one of two regimens. Patients were recruited first to regimen A and then consecutively (not randomized) to regimen B (results with regimen A were sufficiently encouraging that regimen B was instituted).

Regimen A consisted of 25 mg/kg/day ethambutol for 2 months followed by 15 mg/kg/day ethambutol, 300 mg/day rifabutin, and streptomycin, usually included for the first 2 months of therapy, given two to three times weekly with dosage adjusted for age and weight (500–1000 mg).

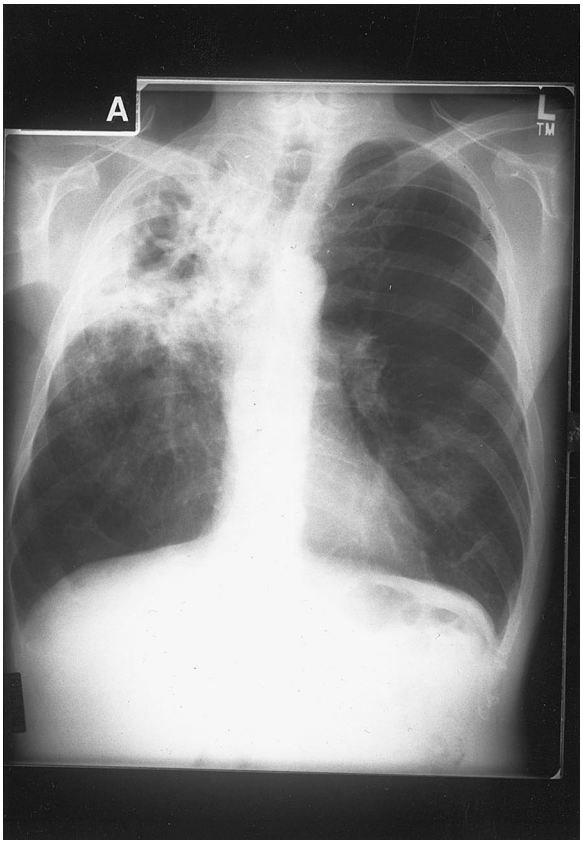
Regimen B consisted of all oral drugs in the regimen administered on a TIW basis, including 25 mg/kg ethambutol and 300–600 mg of rifabutin (dosage based on patient body weight). Streptomycin was also usually included for the first 2 months of therapy and was given two to three times per week, with dosage adjusted for age and weight (500–1000 mg). The results for the first 6 months of therapy with each regimen are reported.

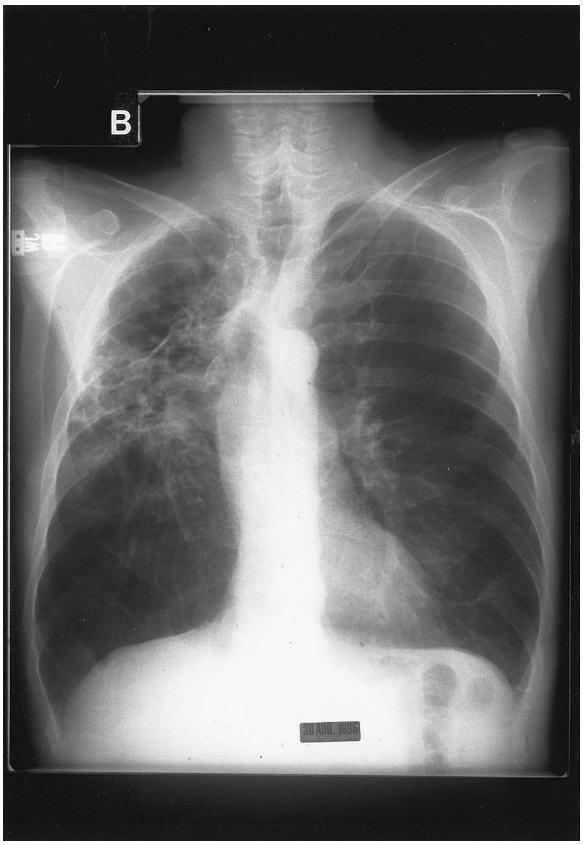
AFB smears and cultures. Generally, 3 daily sputum specimens were collected at entrance into the study, and at least 1 specimen was collected every 4 weeks during therapy. Sputum samples were decontaminated with *N*-acetyl-L-cysteine sodium hydroxide (NALC/NaOH) using routine methods [12]. Semiquantitative AFB smears (fluorochrome method) were performed at magnification ×200 as previously described [2]. Cultures on Middlebrook 7H10 agar were quantitated from no growth to 4+, using published standards and as previously described [2]. For patients whose initial sputum specimens were contaminated (especially by *Pseudomonas aeruginosa*), subsequent samples were processed initially with NALC/NaOH and then processed a second time with oxalic acid [12]. In addition, samples were also inoculated onto a 7H10 agar plate containing 10 μg/mL tobramycin. Organisms were identified as MAC using a commercial nucleic acid probe (AccuProbe; GenProbe, San Diego).

Sputum conversion was defined as 3 consecutive negative cultures, with the time of conversion being the date of the first of the 3. A definite microbiologic response was a reduction in colony count on 3 successive sputum cultures from 3+ or 4+ to 1+ or countable colonies. Lesser degrees of decrease in colony counts were considered improvement without sputum conversion, whereas no change in colony counts was considered as no 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 from patients receiving treatment were subcultured on 7H10 agar. Clarithromycin (and usually azithromycin) MICs were then performed, using broth microdilution with 2-fold drug dilutions in Mueller-Hinton broth supplemented with 5% oleic acid–albumin and dextrose. At pH 7.4, plates were incubated for 2 weeks in room air, as previously described [13, 14]. Isolates were considered to be macrolide-susceptible if the MIC for clarithromycin was ≤ 8 μg/mL and macrolide-resistant if the MIC was ≥ 32 μg/mL. A MIC of 16 mg/mL was considered intermediate. Each isolate was frozen at −70°C for future needs.

Drug tolerance and safety tests. Patients were questioned about problems and symptoms (especially gastrointestinal, auditory, and vestibular) at baseline and at each clinic visit, both verbally and by use of a written questionnaire. In addition, a study coordinator was available 5 days per week by telephone. Laboratory safety tests measured baseline liver enzymes (including a glutamyl transpeptidase and alkaline phosphatase), blood urea nitrogen, serum creatinine, and complete blood cell count. The liver enzymes and complete blood cell count were retested monthly for 6 months. Liver enzymes were considered to be increased if the enzymes rose 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. Routine audiograms were also performed at baseline for the first 31 patients. Audiograms were performed during therapy upon any subjective decrease in auditory acuity for all patients enrolled in the study.





Statistical analysis. Group results are expressed as means ± SD. Comparison of patient characteristics between treatment groups, intermittent azithromycin regimen A or regimen B, and previous daily azithromycin and clarithromycin regimens was done using an unpaired *t* test with a two-tailed *P* value. Comparison of culture results in responders and nonresponders before and at the end of therapy and comparison with previous azithromycin and clarithromycin treatment groups at 6 months were done using a χ^2 analysis and Fisher's exact test with Yates's correction for small sample sizes. Significance was determined at $P \leq .05$.

Results

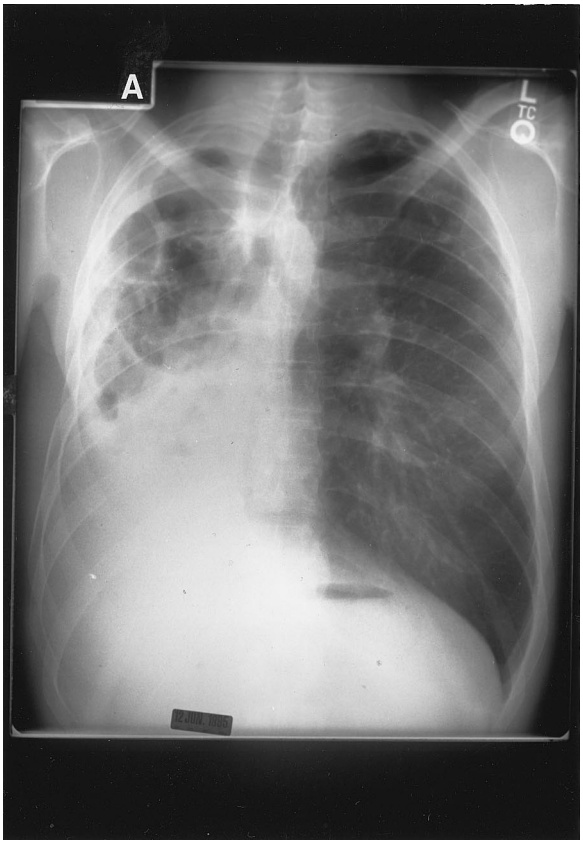
Regimen A. Twenty-one patients were enrolled in regimen A; 19 completed at least 6 months of therapy. Four (21%) had received >6 months of therapy previously, with or without a macrolide. Eight (42%) of these 19 were women (mean age, 66.1 ± 11.8 years), and 11 (58%) were men (mean age, 62.8 ± 16.2 years). Two patients were dropped prior to completion of 6 months of therapy, 1 because of noncompliance and 1 because of gastrointestinal symptoms (primarily diarrhea). Of the women, 33% were current or former smokers (>20 pack years), and 90% of the men were current or former smokers.

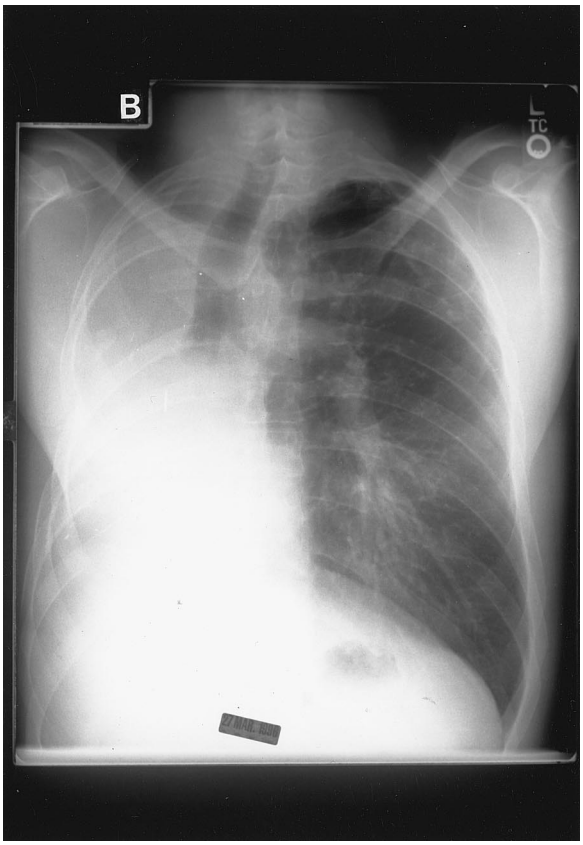
Fourteen (74%) of 19 patients had their sputum culture convert to negative within the first 6 months of therapy (mean time to sputum conversion, 4.4 ± 1.6 months). One patient also had a right upper lobectomy. Three patients (16%) had microbiologic improvement in their sputum cultures without conversion to negative. These 6 patients also had symptomatic improvement. Overall, 17 (89%) of 19 patients had either sputum culture conversion or improvement. Two patients had neither symptomatic improvement nor improvement of sputum AFB cultures.

In general, the TIW 600-mg dose of azithromycin was well tolerated in regimen A and was reduced to 300 mg in only 4 patients, primarily because of loose stools. All but the 2 patients without improvement in sputum cultures who received regimen A had symptomatic improvement while receiving protocol medications. Comparison of these results at 6 months with other macrolide-containing regimens for the treatment of pulmonary MAC disease is shown in table 1.

Regimen B. Forty-seven patients were enrolled in regimen B, the TIW multidrug regimen. The following 8 patients received <6 months of medication: 3 men, due to noncompliance; 1 woman, due to death unrelated to MAC disease; and 4 (3 men and 1 woman) due to intolerable gastrointestinal symptoms (primarily diarrhea). The remaining 39 patients received at least 6 months of medication. Nine (23%) had received >6 months of therapy previously, with or without a

Figure 1. **A**, Chest radiograph of 60-year-old man with rapidly progressive cavitary infiltrate in right upper lobe and multiple 4+ smear- and culture-positive (for MAC) sputum samples. **B**, After 6 months of therapy with intermittent azithromycin, rifampin, and ethambutol, sputum had become smear- and culture-negative.





macrolide. Of these 39 patients, 21 (54%) were women (mean age, 66.3 ± 13.8 years), and 18 (46%) were men (mean age, 56.4 ± 14 years). Six (28%) women were current or former smokers; 16 (89%) men were current or former smokers.

Within the first 6 months of therapy, 24 patients (62%) receiving regimen B had sputum become culture-negative (mean time to conversion, 3.9 ± 1.5 months; table 1; figure 1 shows radiographic findings). Three of these patients also had surgical resection of severely affected lung tissue, including two right pneumonectomies and one right upper lobectomy (figure 2). An additional 6 patients (15%) met criteria for improvement as indicated by improvement in sputum cultures. Overall, 30 (77%) of 39 patients either had their sputum become culture-negative or had improvement in sputum culture results within the first 6 months of therapy with this regimen. Regimen B is compared with regimen A and with previous macrolide-containing regimens in table 1. Of 39 patients, 9 (23%) had no change in their sputum culture results within the first 6 months of therapy. These patients included 4 men (ages 53.4 ± 14.1 years), 75% of whom were current or former smokers, and 5 women (ages 76.8 ± 11.4 years), 20% of whom were current or former smokers.

Regimens A and B. There were no significant differences in patient characteristics between regimens A and B. Similarly, there were no significant differences in patient characteristics between either intermittent azithromycin regimen A or regimen B and the patients who previously received daily clarithromycin or azithromycin regimens (data not shown) [1, 2].

All patients had clarithromycin-susceptible MAC isolates at the beginning of therapy. Thirteen patients were considered to have had significant prior drug therapy, with or without a macrolide, prior to entry into either intermittent azithromycin protocol. Sputum conversion occurred in 5 (46%) of 13 (2/4 from regimen A, 3/9 from regimen B) patients with previous therapy versus 33 (73%) of 45 (12/15 from regimen A, 21/30 from regimen B) patients without previous therapy ($P = .04$).

Six patients (2 from regimen A, 4 from regimen B; 3 women, 3 men) required a decrease in azithromycin dosage to 300 mg TIW, 3 on the basis of intolerable gastrointestinal symptoms (abdominal bloating, diarrhea, and/or nausea) and 3 on the basis of decreased auditory acuity and/or tinnitus. Symptoms resolved in all patients with the decrease in azithromycin dosage. On retesting, no patient on either of the intermittent multidrug regimens (azithromycin dose of 300 mg or 600 mg) had emergence of a macrolide-resistant MAC isolate.

Discussion

This is the first multidrug treatment trial for either pulmonary or disseminated MAC infection to utilize intermittent therapy.

Figure 2. **A**, Chest radiograph of 36-year-old man with destruction of right lung due to progressive, cavitary MAC lung disease (4+ culture-positive sputum sample). **B**, Conversion of sputum to culture–negative (for acid-fast bacilli) after resection of right lung and administration of intermittent azithromycin, rifampin, and ethambutol.

This study demonstrates that multidrug regimens including azithromycin, given intermittently, can be effective for converting sputum to culture negativity in patients with pulmonary MAC disease. The overall sputum conversion rate at 6 months in this study was 71% for regimen A and 62% for regimen B, both similar to our findings in two previous studies involving 4 months of daily single-drug therapy (followed by 2 months of the same daily multiple drugs) utilized in these trials with either clarithromycin (74% sputum conversion rate) or azithromycin (58% sputum conversion rate). The current intermittent regimen was generally well tolerated with only a small percentage (14%) of patients requiring azithromycin dosage adjustment and no patients requiring discontinuation of therapy because of an azithromycin-related adverse event.

Although all patients had clarithromycin-susceptible isolates at entry into the study, 11% of patients in regimen A and 24% of patients in regimen B had no microbiologic improvement during 6 months of therapy. Treatment failures were equally divided between men and women and appeared to mirror the demographics of the study patient population as a whole, including age and smoking status. Because none of these patients received their medications by directly observed therapy, noncompliance with the treatment regimen cannot be excluded as the cause of the treatment failure, although it seems an unlikely explanation in all cases. These patients tended to have severe disease; however, significant differences between those with treatment failures and responders in this regard are difficult to quantitate. Those with treatment failures did have a higher incidence of previous macrolide therapy that did not impact in vitro MAC susceptibility to macrolide but may be an indication that some of these patients have an as yet unidentified factor that defeats treatment with even good drug regimens. In support of this concept, only 5 (38%) of 13 patients from both treatment protocols who had significant prior therapy had sputum conversion, whereas 33 (73%) of 45 patients without previous therapy had sputum conversion, a difference that was statistically significant. In all of our MAC treatment trials, we have found that patients with significant previous drug therapy have a uniformly higher incidence of treatment failure regardless of the macrolide-containing regimen [1–3]. It is also possible that some patients will respond to therapy after 6 months of medication, although none of the patients reported here who had treatment failure at 6 months had subsequent sputum conversion while receiving this drug treatment protocol (unpublished data).

An effective intermittent treatment regimen for pulmonary MAC disease is important for a number of reasons, including lower (relative) cost, potentially better compliance, and a lower incidence of adverse events or toxicity. Macrolide-containing regimens are expensive but appear to be the most effective regimens available for treating pulmonary MAC disease [8]. Intermittent therapy could dramatically decrease the cost of these regimens, which are typically administered for 12–24 months. As the pharmacy budgets of state departments of health become more limited, the priority for disease treatment will understandably be directed toward tuberculosis. More and more, the cost of treatment for MAC disease will fall to the individual. Minimizing cost will be imperative to make these treatment regimens a realistic option for people with pulmonary MAC disease.

Patient compliance would also likely improve with intermittent drug administration. Alcoholism is a major risk factor for the upper lobe fibrocavitary (tuberculosis) type of MAC disease and almost certainly increases the incidence of noncompliance. For some patients whose therapy is failing for unclear reasons, intermittent administration will allow directly observed therapy to eliminate noncompliance as a mechanism of treatment failure. These benefits of intermittent therapy have long been recognized in the treatment of tuberculosis. Intermittent medication administration also lowers the required total weekly dose of both azithromycin and rifabutin, which will decrease the adverse events associated with chronic administration of these medications, another important factor in patient compliance [15, 16].

It is also possible that intermittent therapy with an azithromycin-containing regimen will have utility for treatment of disseminated MAC disease. Azithromycin given once weekly is effective as prophylaxis against disseminated MAC infection [6], and the advantages listed above for intermittent therapy of pulmonary MAC disease are all pertinent for disseminated MAC disease as well [6].

Because of long half-life and concentration in phagocytes and tissues, azithromycin would appear to be an almost ideal agent for long-term intermittent administration of chronic infections such as mycobacterial diseases. When given daily, azithromycin appears to have early (first 6 months) activity comparable to that of clarithromycin against pulmonary MAC disease [1]. It remains to be seen if azithromycin will be as effective as clarithromycin in multidrug regimens given over long periods of time.

References

1. Griffith DE, Brown BA, Girard WM, Murphy DT, Wallace RJ Jr. Azithromycin activity against *Mycobacterium avium* complex lung disease in patients who were not infected with human immunodeficiency virus. Clin Infect Dis **1996**;23:983–9.
2. Wallace RJ Jr, Brown BA, Griffith DE, et al. Initial clarithromycin monotherapy for *Mycobacterium avium-intracellulare* complex lung disease. Am J Respir Crit Care Med **1994**;149:1335–41.
3. Wallace RJ Jr, Brown BA, Griffith DE, Girard WM, Murphy DT. Clarithromycin regimens for pulmonary *Mycobacterium avium* complex: the first 50 patients. Am J Respir Crit Care Med **1996**;153:1766–72.
4. Chaisson RE, Benson CA, Dube MP, et al. Clarithromycin therapy for bacteremic *Mycobacterium avium* complex disease. Ann Intern Med **1994**;121:905–11.
5. Shafran SD, Singer J, Zarowny DP, et al. A comparison of two regimens for the treatment of *Mycobacterium avium* complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. N Engl J Med **1996**;335:377–83.
6. Halvir DV, Dube MP, Sattler FR, et al. Prophylaxis against disseminated *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin, or both. N Engl J Med **1996**;335:392–8.

7. Pierce M, Crampton S, Henry D, et al. A randomized trial of clarithromycin as prophylaxis against disseminated *Mycobacterium avium* complex infection in patients with advanced acquired immunodeficiency syndrome. N Engl J Med **1996**;335:384–91.
8. Bates JH. *Mycobacterium avium* disease: progress at last. Am J Respir Crit Care Med **1996**;153:1737–8.
9. Eisenberg E, Barza M. Azithromycin and clarithromycin. In: Remington JS, Swartz MN, eds. Current clinical topics in infectious diseases. Vol. 14. Cambridge, MA: Blackwell Scientific Publications, **1994**:52–78.
10. Kanatani MS, Guglielmo BJ. The new macrolides—azithromycin and clarithromycin. West J Med **1994**;160:31–7.
11. Wallace RJ Jr, Glassroth J, Griffith DE. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. Am J Respir Crit Care Med **1997**;156(suppl):S1–25.
12. Roberts GD, Koneman EW, Kim YK. *Mycobacterium*. In: Balows A, Hausler WJ Jr, Hermann KL, Isenberg HD, Shadomy HJ, eds. Manual of clinical microbiology. 5th ed. Washington, DC: American Society for Microbiology, **1991**:304–39.
13. Brown BA, Wallace RJ Jr, Onyi GO. Activities of clarithromycin against eight slowly growing species of nontuberculous mycobacteria, determined by using a broth microdilution MIC system. Antimicrob Agents Chemother **1992**;36:1987–90.
14. Wallace RJ Jr, Nash DR, Steele LC, Steingrube V. Susceptibility testing of slowly growing mycobacteria by a microdilution MIC method with 7H9 broth. J Clin Microbiol **1986**;24:976–81.
15. Brown BA, Griffith DE, Girard W, Levin JL, Wallace RJ Jr. Relationship of adverse events to serum drug levels in patients receiving high-dose azithromycin for mycobacterial lung disease. Clin Infect Dis **1997**;24:958–64.
16. Griffith DE, Brown BA, Wallace RJ Jr. Varying dosages of rifabutin affect white blood cell and platelet counts in human immunodeficiency virus–negative patients who are receiving multidrug regimens for pulmonary *Mycobacterium avium* complex disease. Clin Infect Dis **1996**;23:1321–2.