Azithromycin Activity Against *Mycobacterium avium* Complex Lung Disease in Patients Who Were Not Infected with Human Immunodeficiency Virus

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We initiated a prospective trial of an azithromycin-containing regimen for the treatment of human immunodeficiency virus–negative patients with *Mycobacterium avium* complex (MAC) lung disease; the initial 4 months of therapy were with azithromycin (600 mg/d) alone. The primary study endpoint was microbiological response measured at 4 and 6 months of therapy. Of 29 patients enrolled in the study, 23 completed therapy. Fifty-two percent of these 23 patients were male, and 65% were smokers. All 23 patients were older than 45 years of age; 83% had bilateral disease, and 48% had fibrocavitary disease. Macrolide (clarithromycin)–susceptible MAC isolates were recovered from these 23 patients before treatment. Cultures of sputum from 38% of these patients became negative, and the positivity of cultures of sputum from 76% of these patients was significantly reduced. Sixty-eight percent of sputum cultures were strongly positive (>200 colonies) before therapy, while only 27% were strongly positive after therapy. Although most patients continued to receive 600 mg of azithromycin/d, the high incidence of gastrointestinal side effects (76%) and altered hearing (41%) suggests the need for lower or less frequent dosing. Macrolide (clarithromycin) resistance did not develop in any MAC isolates during monotherapy. These results, which demonstrate that azithromycin is active against MAC pulmonary disease, provide a rationale to include this drug in the initial multidrug regimens recommended for the treatment of this disease.

Mycobacterium avium complex (MAC) is a frequent and difficult-to-treat cause of mycobacterial lung disease in HIV-negative patients. Sputum samples converted to negative at initial rates that were reported to be 40%–90% in association with treatment with multiple antituberculous drugs, although sustained sputum conversion to negative has been achieved only in 40%–50% of patients treated with these therapeutic regimens [1–6]. The introduction of newer agents with better in vitro activity against MAC should improve the outlook for successful treatment of MAC lung disease.

The new macrolide clarithromycin has significant in vitro activity against MAC. Human trials have shown that clarithromycin is effective as prophylaxis for disseminated MAC disease [7]; this agent has clinical and microbiological activity as monotherapy and in drug combinations for the treatment of MAC pulmonary disease and disseminated MAC disease [7–12]. We recently demonstrated that initial therapy with clarithromycin for 4 months was effective against MAC lung disease in immunocompetent (HIV-negative) patients [10]; this was the first time that a single agent was shown to be active against MAC pulmonary disease. Although effective microbiologically, clarithromycin has been associated with both significant toxicity and drug-drug interactions [8, 13–17]. Clarithromycin monotherapy for both disseminated and pulmonary disease has also been associated with the development of in vitro resistance and subsequent treatment failure [8, 10].

Monotherapy with azithromycin, an azalide, has activity against disseminated MAC disease [18], and a once-weekly dose of 1,200 mg has been shown to be effective for prophylaxis against disseminated MAC disease [18a]. The safety of long-term administration of azithromycin has not been tested, and it is unknown whether it would be effective as a single agent or in a multiple-drug regimen for the treatment of chronic MAC lung disease. Significant unknown risk factors of azithromycin therapy are the effect of accumulation of this drug in tissues during long-term administration and the possible associated toxicity. Azithromycin is not known to inhibit the cytochrome P-450 system and has not been implicated in significant drug-drug interactions [14]. Azithromycin excretion is unchanged with decreasing renal function, unlike clarithromycin (which is partially excreted by the kidneys).

In addition, azithromycin has a long half-life (~70 hours) that is conducive to intermittent administration. Therefore, azithromycin has some pharmacologic advantages over clarithromycin for long-term administration. Because of the close structural similarities between the azalide azithromycin and macrolides, azithromycin will be included as a macrolide in further discussion.

We initiated a prospective, open, controlled, noncomparative trial of an azithromycin-containing regimen as therapy for HIV-

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Informed consent was obtained from the patients, and the guidelines for human experimentation of the Human Subjects Committee of the University of Texas Health Center at Tyler were followed in the conduct of this study.

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negative patients with MAC lung disease; the initial 4 months of treatment were with azithromycin alone. This article will focus on the first 6 months of therapy with this treatment regimen.

Methods

Patients and disease. Patients older than 18 years of age who had MAC lung disease that was diagnosed at the University of Texas Health Center at Tyler or who were referred there because of the disease between April 1993 and September 1994 were considered for therapy. Diagnostic criteria for lung disease included cultures of two or more sputum samples that yielded moderate to large numbers of organisms and a chest radiograph revealing abnormalities consistent with mycobacterial lung disease that were in agreement with the most recent criteria of the American Thoracic Society [19]. Features of the pretreatment chest radiograph, history of antimycobacterial therapy, results of prior microscopic examinations and cultures for acid-fast bacilli (AFB), and information on patient demographics were recorded.

Study criteria. Inclusion criteria for treatment included culture positivity of sputum for MAC prior to any drug treatment or at the time of enrollment 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, clarithromycin or azithromycin allergy, life-threatening illness with no prior therapy for MAC lung disease, and risk factors or known positivity for HIV. Patients were considered for treatment regardless of prior therapy for MAC infection as long as the MAC isolate recovered before treatment was susceptible to macrolides. Informed consent was obtained under a protocol approved by the Human Subjects Committee of the University of Texas Health Center at Tyler and by the U.S. Food and Drug Administration under an Investigational New Drug application.

Therapy. Patients were to receive 600 mg of azithromycin (a special formulation provided by Pfizer Pharmaceuticals, Groton, CT) daily for 4 months; the drug was administered when the patients had empty stomachs. Before completion of 4 months of monotherapy, additional drugs could be added to the therapeutic regimens for patients for whom cultures became negative. At the end of 4 months, additional drugs were added to the therapeutic regimens for all remaining patients regardless of the status of their sputum cultures. These drugs were ethambutol (25 mg/[kg · d] for 2 months and then 15 mg/[kg · d]), rifabutin (300–600 mg/d), and streptomycin (given two to three times per week for 2 months).

AFB smear evaluations and cultures. Generally, three sputum specimens were collected on consecutive days at enrollment into the study, one to two specimens were obtained every 4 weeks during therapy, three consecutive daily specimens were taken at completion of monotherapy (these specimens were not obtained if the sputum had already converted to negative), and one to two specimens were collected monthly during therapy with multiple drugs. Sputum samples were decontaminated by using routine methods [20]. Sputum smears were stained by the fluorochrome technique, and semiquantitative examinations of these smears for AFB (0 to ++++) were performed as previously described [10]. Cultures with Middlebrook 7H10 agar were quantitated from 0 to ++++ by means of published standards and as previously described [10, 21]. Subsequent samples from patients whose initial sputum specimens were contaminated with bacteria (especially *Pseudomonas aeruginosa*) were processed a second time with oxalic acid [20]. In addition, samples were also inoculated onto plates with Middlebrook 7H10 agar and 10 μg of tobramycin/mL. Organisms were identified as MAC with use of a commercial nucleic acid probe (Accuprobe, Gen-Probe, San Diego).

The results of the last three examinations of sputum smears for AFB and the last three cultures of sputum for AFB before (or within 4 weeks of) starting azithromycin monotherapy and before (or within 4 weeks of) the addition of other drugs to the therapeutic regimen were recorded for each patient. Sputum conversion was defined as three consecutive negative cultures; the time of conversion was defined as the date of the first of the three negative sputum cultures. A definite microbiological response was a reduction in colony count from +++ or ++++ to + or countable colonies on three successive sputum cultures. Smaller decreases in colony counts were considered as an improvement in the patient's condition without sputum conversion, whereas no change in colony counts was considered as no response. The percentage of patients for whom these results were found at 4 and 6 months of therapy was calculated and recorded.

Susceptibility testing. A MAC isolate recovered before treatment, selected isolates recovered during treatment, and an isolate recovered from the last three cultures during single-drug therapy were subcultured once on Middlebrook 7H10 agar. MICs of clarithromycin and azithromycin were then determined by the broth microdilution test with use of twofold dilutions of the drugs in Mueller-Hinton broth with 5% oleic acid, albumin, and dextrose and 2-week incubations as previously described [10, 22, 23]. Isolates were considered to be macrolide-susceptible if the MIC of clarithromycin was ≤ 8 μg/mL and macrolide-resistant if the MIC of clarithromycin was ≥ 32 μg/mL. Each isolate was frozen at −70°C for future analysis.

Drug tolerance and safety tests. At baseline and during each clinic visit, patients were questioned about problems and symptoms (especially gastrointestinal, auditory, and vestibular symptoms). Laboratory safety tests consisted of determinations of baseline measurements of liver enzymes (including glutamyl transpeptidase and alkaline phosphatase), blood urea nitrogen level, serum creatinine level, and complete blood cell count. The liver enzyme levels were retested at 2-week intervals for 3 months and then once a month thereafter. An increase in liver enzyme levels was considered to be present if during

therapy the levels rose to twice the upper limits of normal if the baseline values were normal or to twice the baseline values if the baseline values were abnormal. Routine audiograms were also obtained at baseline and when there was any subjective decrease in auditory acuity.

Statistical analysis. The culture results for azithromycin responders and nonresponders before and at the end of therapy were compared by means of the χ^2 test with Yates' correction for small sample sizes and Fisher's exact test; the results of azithromycin monotherapy in this study and clarithromycin monotherapy in a previous study [10] were also compared by means of these analyses. Differences were considered significant at a P value of $\leq .05$.

Results

Patients. Twenty-nine patients who met the study criteria were enrolled. Six patients discontinued therapy within 16 weeks: 2 had possible adverse events, 3 were noncompliant (failed to submit sputum samples for AFB smear evaluation and/or did not keep follow-up appointments), and 1 died of unrelated problems. The remaining 23 patients completed the 4 months of initial monotherapy and the 2 months of subsequent combination therapy. Safety and drug tolerance data were available for all 29 patients, whereas drug efficacy data were available only for the 23 patients who completed 6 months of therapy.

Demographics. Information for the 23 patients is shown in table 1. Patients were predominantly male (52%), older than 45 years of age (100%), and former or current smokers (65%; 4 of 11 women and 11 of 12 men). Routine chest radiographs revealed that 48% of these patients had fibrocavitary disease, and 83% had bilateral disease. Prior antituberculous therapy, mostly with isoniazid, rifampin, ethambutol, and streptomycin, for at least 6 months had failed for seven patients. The remaining 16 patients had received antituberculous therapy for <3 months. No patient had received a regimen that included clarithromycin or azithromycin. At least one sputum smear from 20 patients (87%) was positive for AFB, with a mean of 13 positive smears from the seven patients who had received prior therapy and a mean of seven positive smears from the 16 patients with no history of prior therapy. Cultures of sputum from all patients were positive for MAC before evaluation for study eligibility. The mean number of cultures positive for MAC was 18 for the group of previously treated patients and 12 for the group of untreated patients.

Therapy. Twenty-eight patients received 600 mg of azithromycin once daily. Because of low body mass and previous intolerance to clarithromycin, one patient's therapy was started at 300 mg/d. Dosages for two patients receiving 600 mg/d were decreased to 300 mg/d because of side effects. The 23 patients who completed 6 months of therapy received initial monotherapy for a mean of 3.8 months (range, 2.5–5.25 months).

AFB smear evaluations and cultures. The 23 patients were divided into four groups on the basis of microbiological response. The first three groups consisted of 16 patients who had definite responses to therapy. Sputum from eight of these patients (group 1, patients 1–8) converted to negative during monotherapy. The results of AFB smears and cultures of five patients (group 2, patients 9–13) improved during monotherapy, and sputum from these patients converted to negative within 6 months after the start of azithromycin therapy (i.e., after the addition of other drugs). The results of AFB smears and cultures of three patients (group 3, patients 14–16) improved during initial monotherapy, but cultures of sputum from these patients were still positive at 6 months.

Smears of 31 (69%) of 45 pretreatment sputum samples from the 16 azithromycin responders were positive for AFB, while smears of only 11 (24%) of 45 samples obtained at the end of therapy were positive for AFB ($P = .001$). Thirty-six percent of pretreatment isolates were strongly positive (+++ or ++++) for AFB on smears, whereas only 2% of posttreatment isolates were strongly positive. There were no significant differences in the results of AFB smear evaluations between the azithromycin responders and the previously described clarithromycin responders [10]. Cultures of 40 (91%) of 44 pretreatment samples were positive compared with only 16 (34%) of 47 samples obtained at the end of therapy ($P = .001$). Again, there were no significant differences in AFB culture results between the azithromycin responders and the previously described clarithromycin responders [10]. The differences among patients for whom cultures were strongly positive (+++ or ++++ or >200 colonies) were equally striking. Semiquantitative cultures of 30 (68%) of 44 pretreatment samples were strongly positive compared with four (9%) of 47 samples obtained at the end of therapy ($P = .01$).

The fourth group included the remaining seven patients who were azithromycin nonresponders. The AFB smear evaluations for these seven patients showed reduced positivity, but there were no declines in culture positivity. The nonresponders were more likely to have received prior therapy (4 [57%] of 7) than were the responders (3 [19%] of 16) or the patients for whom sputum converted to negative (2 [15%] of 13).

The results of AFB smear evaluations and cultures for the 23 patients from whom macrolide-susceptible isolates were recovered (responders and nonresponders) who completed therapy are summarized in table 2. Sputum smears were more often negative for AFB after therapy than before therapy, although this difference did not reach statistical significance ($P = .06$). On the basis of evaluations of AFB smears, the response to azithromycin monotherapy was not significantly different than the response to clarithromycin monotherapy in patients from whom macrolide-susceptible isolates were recovered. The total number of negative cultures was significantly greater after therapy (52%) than before therapy (9%) ($P = .0002$). Similarly, when strongly positive (>200 colonies) sputum cultures were assessed, 68% were positive before therapy compared with only 27% at the end of monotherapy ($P = .008$).

Table 1. Summary of data on the microbiological efficacy of azithromycin monotherapy for 23 patients with MAC lung disease.

Patient types, group/ patient no.	Age (y)/sex	Radiographic disease		Prior antituberculous therapy*	No. of positive AFB smears/ no. of positive cultures of sputum	Pretherapy MIC (μg/mL)	
		Cavitary	Bilateral			Clarithromycin	Azithromycin
Azithromycin responders							
Group 1							
1	64/F	+	−	No	10/12	2	16
2	66/F	−	+	No	2/2	1	8
3	62/F	−	+	No	0/3	8	−
4	74/F	−	+	No	2/22	4	−
5	71/F	−	+	No	9/10	1	8
6	79/M	−	+	No	6/9	4	−
7	79/M	−	+	No	0/2	16	−
8	56/M	+	+	Yes	15/18	4	32
Group 2							
9	74/F	−	+	Yes	6/12	2	16
10	80/F	+	+	No	10/12	1	8
11	76/F	−	−	No	7/15	4	8
12	56/M	+	−	No	12/14	1	8
13	63/M	+	−	No	5/11	2	8
Group 3							
14	65/F	+	+	Yes	25/34	2	8
15	54/M	+	+	No	15/18	8	−
16	46/M	0	+	No	10/18	2	16
Azithromycin nonresponders							
Group 4							
1	65/F	−	+	Yes	9/11	0.5	2
2	65/M	+	+	Yes	28/29	4	16
3	68/F	−	+	No	6/20	2	8
4	70/M	−	+	Yes	0/10	4	64
5	75/M	−	+	No	4/11	4	−
6	80/M	+	+	No	16/16	4	−
7	61/M	+	+	Yes	11/11	8	−

NOTE All patients received therapy with azithromycin-containing regimens for at least 6 months. AFB = acid-fast bacilli; group 1 = patients whose sputum converted to negative during monotherapy; group 2 = patients for whom the results of sputum tests improved during monotherapy and for whom sputum converted to negative within 6 months after the start of therapy; group 3 = patients for whom the results of sputum tests improved during monotherapy and for whom sputum was still positive at 6 months of therapy; group 4 = patients for whom the results of sputum cultures did not improve during monotherapy and for whom sputum cultures were still positive at 6 months of therapy; MAC = *Mycobacterium avium* complex; + = present; − = absent.

* Administered for a minimum of 6 months.

The results of an overall comparison of the microbiological responses associated with azithromycin monotherapy and clarithromycin monotherapy are outlined in table 3 [10]. There were no significant differences between the azithromycin and clarithromycin treatment groups in terms of the total number of responders and the number of patients for whom sputum converted to negative at the end of monotherapy or at 6 months. Macrolide (clarithromycin) resistance did not develop in any of the isolates during azithromycin monotherapy but did develop in isolates from three patients receiving clarithromycin monotherapy. This difference did not reach statistical significance because of the relatively small numbers of patients in each group.

Susceptibility testing. Macrolide susceptibility was based on in vitro clarithromycin susceptibility. No pretreatment isolates were clarithromycin-resistant (table 1). None of the isolates from patients who completed therapy became macrolide-resistant during monotherapy with azithromycin. No additional isolates became macrolide-resistant with the addition of multiple drugs during the 6 months of treatment.

Drug tolerance and safety tests. Side effects potentially related to azithromycin were relatively common (table 4). Of 29 patients originally enrolled in the study, 26 reported at least one adverse event. The most common side effects were gastrointestinal; these effects occurred in 76% of all 29 patients and 87% of the 23 patients who completed the study Loose stools and/or diarrhea was the most common gastrointestinal side effect; it occurred in 65% of patients who completed the study. Both patients who withdrew from the study because of side effects did so because of gastrointestinal symptoms. For most patients, however, gastrointestinal symptoms were generally mild and intermittent and lasted only 1–2 days at a time.

Subjective decreases in hearing while receiving azithromycin therapy occurred in 41% of all patients enrolled in the study

Table 2. Results of AFB examinations of sputum smears and of cultures of sputum specimens from 23 patients from whom macrolide-susceptible MAC isolates were recovered before and at the conclusion of monotherapy with azithromycin.

Test, result	No. (%) of samples in each specified group*		
	Pretherapy	Posttherapy	*P* value
AFB smear evaluation†			
Negative	21 (32)	38 (61)	NS (.06)
+ or ++	19 (29)	14 (23)	NS (.06)
+++ or ++++	25 (38)	10 (16)	NS (.06)
No. positive/no. tested	44/65 (68)	24/62 (39)	NS (.09)
AFB culture†			
Negative	6 (9)	33 (52)	.0002
1–49 colonies	8 (12)	7 (11)	NS
+ or ++	7 (11)	7 (11)	NS
+++ or ++++	44 (68)	17 (27)	.008
No. positive/no. tested	59/65 (91)	31/64 (48)	.04

NOTE. AFB = acid-fast bacilli; MAC = *Mycobacterium avium* complex; NS = not significantly different.

* Three consecutive sputum samples were obtained from each patient during each period.

† For numerical equivalent of each group, see text.

and in 52% of patients who completed the study. Serial audiograms were obtained for all 23 patients who completed therapy; a decrease in hearing in patients who were receiving azithromycin monotherapy before the administration of streptomycin was documented by audiograms for three of these patients. Two of these three patients required a decrease in the dosage of azithromycin to 300 mg/d during the 6 months of therapy. Following the modification of the azithromycin dose, hearing returned to the baseline status for these two patients. Tinnitus and dizziness were also common but were not associated with acute changes in hearing and did not limit doses.

Results of liver function tests were normal for all 29 patients at enrollment into the study. There were no significant rises in liver enzyme levels during therapy. All 29 patients had a baseline level of serum creatinine of <1.5 mg/dL.

Discussion

This study demonstrates that azithromycin alone is effective for reducing the positivity of sputum cultures for AFB for patients with MAC pulmonary disease. The positivity of sputum smears for AFB was also reduced, although this reduction did not reach statistical significance. Sputum converted to negative in 38% of the 23 patients from whom macrolide-susceptible isolates were recovered before treatment and who completed the study; a significant decline in the positivity of sputum from another 38% of these patients was shown.

Because of the threat of in vitro drug resistance, azithromycin should never be used as monotherapy for MAC disease. Current recommendations are for the inclusion of a macrolide (azithromycin or clarithromycin) in multidrug regimens for the treatment of MAC lung disease. In addition to clarithromycin, azithromycin has now been shown to have activity against MAC lung disease in a clinical trial [10]. Azithromycin monotherapy produced microbiological responses comparable with those of clarithromycin monotherapy and in general was reasonably tolerated by patients.

As in the previous clarithromycin trial [10], this was not a randomized, multidrug or placebo comparative trial. The single-group (noncomparative) study design was again adopted for several reasons. There was a perceived need to obtain experience with azithromycin as quickly as possible since the drug is already marketed and there is essentially no information available about its clinical usefulness, safety, or appropriate dosing in the treatment of chronic lung disease. To embark on a randomized comparison of multidrug regimens with and without azithromycin seemed premature without this information.

In addition, the previous experience with clarithromycin monotherapy in this setting suggested a strong likelihood of safety and success. The 4-month monotherapy design maximized the opportunity to assess activity and toxicity yet limited the time during which selection of resistant organisms might occur. If the efficacy of azithromycin was comparable with that of clarithromycin (as was the case), then blinded compara-

Table 3. Comparison of results from trials of clarithyromycin and azithromycin as monotherapy for MAC lung disease.

Parameter	Clarithromycin*	Azithromycin†	*P* value
No. of patients for whom monotherapy was intended	30	29	
No. who completed monotherapy (susceptible to clarithromycin)	19	23	NS
No. of responders to monotherapy/ total no. treated (%)	15/19 (79)	16/23 (70)	NS
No. for whom sputum converted to negative/total no. treated (%)			
After monotherapy	11/19 (58)	8/23 (35)	NS
After 6 mo	14/19 (74)	14/21 (67)	NS
No. for whom macrolide resistance developed at 6 mo/total no. treated (%).	3/19 (16)	0/24	NS

NOTE. MAC = *Mycobacterium avium* complex; NS = not significantly different.

* Data are from [10]

† Data are from this study.

Table 4. Adverse events in patients with MAC lung disease treated daily with 600 mg of azithromycin monotherapy.

Variable	No. of patients enrolled in the study (n = 29)	No. of patients who completed therapy (n = 23)
One or more adverse events	26	22
Withdrawn from study because of adverse event	2	0
Dose decreased because of adverse event	3	3
Side effect		
Bitter taste	8 (6)*	8
Gastrointestinal	22	20
Anorexia	9 (6)	9
Nausea	6 (1)	5
Vomiting	3	2
Loose stools and/or diarrhea	17 (1)	15
Abdominal pain	10	10
Gas, belching	3 (1)	3
Auditory and/or vestibular		
Decreased hearing		
Subjective worsening	12	12
Worsening by audiogram	3	3
Tinnitus	11 (7)	11
Dizziness and/or poor balance	9 (6)	9
CNS		
Insomnia	7 (2)	7
Headache	4	3
Weakness	3	3
Miscellaneous	13 (4)	13
Abnormal liver enzyme levels	0 (4)	0

NOTE. MAC = *Mycobacterium avium* complex.

* Numbers in parentheses represent the number of patients with similar symptoms before therapy.

tive trials of multidrug regimens containing these two macrolides would be both feasible and desirable.

We chose clarithromycin as the drug representing macrolide susceptibility since the range of its MICs has been studied in much greater detail and no breakpoints of azithromycin for MAC isolates have been determined yet. It is clear that MAC isolates that are resistant to clarithromycin do not respond in vivo to macrolide therapy [8, 10]. Despite the use of initial azithromycin monotherapy, macrolide (clarithromycin) resistance did not develop in any MAC isolates from our patients within the 6-month observation period. However, as expected, macrolide resistance did develop in isolates from some patients receiving azithromycin therapy after the 6-month study period during multidrug treatment (authors' unpublished data).

Acquired resistance to clarithromycin has been described in isolates from patients with MAC lung disease who received both initial clarithromycin monotherapy and combination therapy as well as in isolates from patients with AIDS and disseminated MAC disease who were treated with clarithromycin monotherapy or combination therapy with other agents [7–11].

The incidence rates of resistance in the two previously reported trials of clarithromycin treatment for MAC lung disease (15% and 20%, respectively) [10, 11] are lower than that reported for clarithromycin treatment of disseminated MAC infection (>50%) [8], presumably because the total number of organisms associated with lung disease is lower and because more patients received combination therapy. The genetic mechanism of resistance to azithromycin and clarithromycin in MAC appears to be the same (i.e., mutations involving A-2058 or A-2059 in the binding site of macrolides on the 23 S rRNA gene) [24, 25]; therefore, isolates resistant to one macrolide are cross-resistant to the other, regardless of the companion drugs utilized [27]. Performance of in vitro macrolide susceptibility testing is important for patients who have previously received or are not responding to macrolide-containing regimens [27].

Azithromycin did not have an obvious microbiological effect in ~24% of the patients who received initial monotherapy or subsequent short-term combination therapy. None of these patients missed clinic appointments, and they all stated that they took their medicine regularly. We did not detect any differences between in vitro macrolide susceptibility of MAC isolates recovered before treatment from azithromycin responders and nonresponders. The nonresponders tended to have more extensive cavitary disease, although the difference was not uniform.

Because the number of study participants was small, it is difficult to be certain if any differences between responders and nonresponders would be significant in a larger study. Clearly, these patients represent an important group for future studies. It is interesting that the nonresponders (4 [57%] of 7) were more likely to have received prior antimycobacterial therapy than were patients whose sputum converted to negative within the 6-month observation period (2 [15%] of 13), an observation previously noted with clarithromycin therapy [10, 12].

The conditions of patients receiving azithromycin monotherapy universally improved from a symptomatic standpoint, regardless of their microbiological response. Changes in clinical symptoms were not used as endpoints in this study, however. The difficulty in quantifying cough, sputum volume, and sputum consistency discouraged the use of symptomatic status as a parameter of clinical response. Other symptoms, such as fever, night sweats, and recent weight loss, were relatively infrequent in these elderly patients and, hence, were not likely to be useful.

Side effects associated with 600 mg of azithromycin/d were common but generally were not limiting during the 6 months of therapy. Subsequent follow-up has shown that long-term administration of this dose is intolerable for most patients, with the need for dosage adjustment because of the auditory and/or gastrointestinal symptoms (B. A. Brown, D. E. Griffith, W. M. Girard, et al., unpublished observations). Concomitant administration of azithromycin and streptomycin would dictate very close follow-up for possible auditory toxicity. Although 600 mg of azithromycin/d is effective microbiologically, preliminary results suggest that smaller doses (e.g., 300 mg/d) or intermittent dosing (e.g., 600 mg three times per week) of azithromycin

is as effective for and much better tolerated by the generally low body weight elderly patients with MAC lung disease who are usually seen (authors' unpublished data). Current ongoing trials are focused on intermittent therapy. Overall, the optimal dosing strategy for azithromycin as treatment for MAC pulmonary disease has yet to be determined.

Azithromycin and clarithromycin are the only two drugs proven to be active as single agents against MAC lung disease. It must be stressed, however, that multidrug therapy is required for long-term conversion of sputum to negative in cases of MAC lung disease and for avoidance of the development of in vitro macrolide resistance, observations already noted in reports of disseminated MAC disease [7–9, 9a]. The newer macrolides appear to be the cornerstone of this multidrug therapy. It is hoped that ongoing clinical trials will identify the most effective, least toxic combination of drugs to be used with the macrolides in multidrug therapeutic regimens for MAC pulmonary disease.

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References

1. Dutt AK, Stead WW. Long-term results of medical treatment in Mycobacterium intracellulare infection. Am J Med **1979**;67:449–53.
2. Davidson PT, Khanijo V, Goble M, Moulding TS. Treatment of disease due to *Mycobacterium intracellulare*. Rev Infect Dis **1981**;3:1052–9.
3. Etzkorn ET, Aldarondo S, McAllister CK, Matthews J, Ognibene AJ. Medical therapy of *Mycobacterium avium-intracellulare* pulmonary disease. Am Rev Respir Dis **1986**;134:442–5.
4. Ahn CH, Ahn SS, Anderson RA, Murphy DT, Mammo A. A four-drug regimen for initial treatment of cavitary disease caused by *Mycobacterium avium* complex. Am Rev Respir Dis **1986**;134:438–41.
5. Hornick DB, Dayton CS, Bedell GN, Fick RB Jr. Nontuberculous mycobacterial lung disease: substantiation of a less aggressive approach. Chest **1988**;93:550–5.
6. Reich JM, Johnson RE. *Mycobacterium avium* complex pulmonary disease: incidence, presentation, and response to therapy in a community setting. Am Rev Respir Dis **1991**;143:1381–5.
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. Chaisson RE, Benson CA, Dube MP, et al. Clarithromycin therapy for bacteremic *Mycobacterium avium* complex disease: a randomized, double-blind, dose-ranging study in patients with AIDS. Ann Intern Med **1994**;121:905–11.
9. Dautzenberg B, Saint Marc T, Meyohas MC, et al. Clarithromycin and other antimicrobial agents in the treatment of disseminated *Mycobacterium avium* infections in patients with acquired immunodeficiency syndrome. Arch Intern Med **1993**;153:368–72.

9a. Shafron 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.

10. Wallace RJ Jr, Brown BA, Griffith DE, et al. Initial clarithromycin monotherapy for *Mycobacterium avium-intracellulare* complex lung disease. American Journal of Respiratory and Critical Care Medicine **1994**;149:1335–41.
11. Dautzenberg B, Piperno D, Diot P, Truffot-Pernot C, Chauvin J-P, the Clarithromycin Study Group of France. Clarithromycin in the treatment of *Mycobacterium avium* lung infections in patients without AIDS. Chest **1995**;107:1035–40.
12. Wallace RJ Jr, Brown BA, Griffith DE, et al. Clarithromycin regimens for pulmonary *Mycobacterium avium* complex: the first 50 patients. American Journal of Respiratory and Critical Care Medicine **1996**;153:1766–72.
13. Wallace RJ Jr, Brown BA, Griffith DE. Drug intolerance to high-dose clarithromycin among elderly patients. Diagn Microbiol Infect Dis **1993**;16:215–21.
14. Periti P, Mazzei T, Mini E, Novelli A. Pharmacokinetic drug interactions of macrolides. Clin Pharmacokinet **1992**;23:106–31.
15. The DATRI Study Group. Coadministration of clarithromycin alters the concentration-time profile of rifabutin [abstract no. A2]. In: Program and abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy (Orlando). Washington, DC: American Society for Microbiology, **1994.**
16. Griffith DE, Brown BA, Girard WM, Wallace RJ Jr. Adverse events associated with high-dose rifabutin in macrolide-containing regimens for the treatment of *Mycobacterium avium* complex lung disease. Clin Infect Dis **1995**;21:594–8.
17. Wallace RJ Jr, Brown BA, Griffith DE, Girard W, Tanaka K. Reduced serum levels of clarithromycin in patients treated with multidrug regimens including rifampin or rifabutin for *Mycobacterium avium–M. intracellulare* infection. J Infect Dis **1995**;171:747–50.
18. Young LS, Wiviott L, Wu M, Kolonoski P, Bolan R, Inderlied CB. Azithromycin for treatment of *Mycobacterium avium-intracellulare* complex infection in patients with AIDS. Lancet **1991**;338:1107–9.

18a. Havlir 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.

19. American Thoracic Society. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. Am Rev Respir Dis **1990**;142:940–53.
20. Roberts GD, Koneman EW, Kim YK. Mycobacterium. In: Balows A, Hausler WJ Jr, Herrmann KL, Isenberg HD, Shadomy HJ, eds. Manual of clinical microbiology. 5th ed. Washington, DC: American Society for Microbiology, **1991**:304–39.
21. Hawkins JE, Wallace RJ Jr, Brown BA. Antibacterial susceptibility tests: mycobacteria. In: Balows A, Hausler WJ Jr, Herrmann KL, Isenberg HD, Shadomy HJ, eds. Manual of clinical microbiology. 5th ed. Washington, DC: American Society for Microbiology, **1991**:1138–52.
22. 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.
23. 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.
24. Meier A, Kirschner P, Springer B, et al. Identification of mutations in 23S rRNA gene of clarithromycin-resistant *Mycobacterium intracellulare*. Antimicrob Agents Chemother **1994**;38:381–4.
25. Meier A, Heifets L, Wallace RJ Jr, et al. Molecular mechanisms of clarithromycin resistance in *Mycobacterium avium:* observation of multiple 23S rDNA mutations in a clonal population. J Infect Dis **1996**;174:354–60.
26. Heifets L, Mor N, Vanderkolk J. *Mycobacterium avium* strains resistant to clarithromycin and azithromycin. Antimicrob Agents Chemother **1993**;37:2364–70.