

Treatment of *Mycobacterium avium-intracellulare* complex Lung Disease With a Macrolide, Ethambutol, and Clofazimine*

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Background: *Mycobacterium avium-intracellulare* (MAC) causes progressive lung disease. Recommended treatment regimens include a macrolide and a rifamycin, but drug intolerance and relapse after treatment is completed often limit successful therapy.

Methods: Consecutive individuals referred for treatment of MAC lung disease were treated with a regimen that included either clarithromycin, 500 mg bid, or azithromycin, 250 mg/d, on weekdays; ethambutol, 15 mg/kg/d; and clofazimine, 100 mg/d. The intention was to treat patients for a minimum of 12 months. The diagnosis of MAC lung disease was confirmed by multiple positive sputum culture findings in patients with typical symptoms and radiologic findings.

Results: Thirty patients (27 women and 3 men; mean age, 70 ± 9.4 years [SD]) were treated. A total of 22 of the patients reported adverse effects from clarithromycin or azithromycin. Intolerance of clarithromycin resulted in the withdrawal of four patients before sputum conversion. The remaining patients continued treatment for an average of 10 months, and sputum findings converted to negative in all 26 patients (87%). One patient died of unrelated causes while still receiving therapy, and five patients (19%) relapsed an average of 17 months after treatment was completed.

Conclusions: Treatment with a macrolide, ethambutol, and clofazimine was successful in 20 of 30 patients (67%) with MAC lung disease and is a reasonable alternative to rifamycin-containing regimens. (CHEST 2003; 124:1482-1486)

Key words: azithromycin; bronchiectasis; clarithromycin; clofazimine; ethambutol; *Mycobacterium avium*

Abbreviations: MAC = *Mycobacterium avium-intracellulare*; NTM = nontuberculous mycobacteria

Mycobacterium avium-intracellulare (MAC) is the most common nontuberculous mycobacteria (NTM) pathogen in the United States.¹ Previously, it was assumed that MAC colonized the lungs of patients with underlying disease. It is now recognized that this organism causes progressively destructive lung disease, sometimes over a period of years.² Two patterns of pulmonary disease are seen in adult patients without HIV infection. Fibrocavi-

tary disease that has clinical and radiologic similarities to tuberculosis is seen in patients with a history of tobacco and/or alcohol abuse, usually male patients with underlying COPD, bronchiectasis, silicosis, previously active tuberculosis, chronic aspiration, or immunosuppression. More recently, it has been recognized that MAC causes nodular bronchiectasis, a condition seen primarily in elderly women without an obvious immunodeficiency disorder; if untreated, the condition can progress to respiratory failure and death.²⁻⁴ Treatment of MAC lung disease with antituberculous medications including isoniazid, rifampin, ethambutol, pyrazinamide, streptomycin, or other aminoglycosides, cycloserine, fluoroquinolones, and ethionamide has been disappointing. Reported sputum conversion-to-negative rates with antituberculous therapy have been variable; ranging from 25 to 90%.⁵⁻⁸ These regimens have also been associated with a high relapse rate.⁹ Localized pulmonary disease with MAC has also been treated surgically in patients with adequate pulmonary func-

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tion reserve, but it has a significant morbidity and some associated mortality.^{10,11}

The University of Texas group based at Tyler, TX, and others¹²⁻²¹ have shown that both clarithromycin and azithromycin are active against MAC lung disease in patients without HIV infections either when administered alone or in combination with other medications. To avoid the emergence of resistant organisms, it is recommended that MAC lung disease be treated with a macrolide in combination with two or three other medications. The American Thoracic Society statement on the diagnosis and treatment of disease caused by NTM, published in 1997, recommends that MAC pulmonary disease be treated with a combination of a macrolide, either clarithromycin or azithromycin; a rifamycin, either rifabutin or rifampin; and ethambutol until sputum culture findings have been negative for at least 1 year.²² It also recommends that streptomycin be administered for the first 8 weeks of therapy to facilitate a rapid decline in the number of organisms. Unfortunately, long-term treatment with these medications is not well tolerated by the elderly. Studies¹⁵⁻¹⁷ with intermittent therapy have been undertaken to attempt to reduce drug intolerance, but side effects remain a limiting factor.

Rifabutin is the more active rifamycin against MAC, but side effects believed to be of an immune nature, including the development of polyarthralgias, anterior uveitis, and leukopenia, may be severe enough to require withdrawal of the drug.²³⁻²⁶ Rifampin is not as active against MAC as rifabutin but causes fewer adverse effects. Unfortunately, it affects the metabolism of other drugs through its action on the hepatic cytochrome P-450 system.¹³ Both rifabutin and rifampin lower serum levels of clarithromycin and its 14-hydroxy metabolite.²⁷ Most patients with MAC lung disease are elderly and may have comorbid conditions that are adversely affected by drug interactions with rifampin. Clarithromycin is a cytochrome P-450 3A4 isoenzyme inhibitor and may increase serum levels of several drugs including rifabutin.²⁸ Drug/drug interactions involving clarithromycin may account for some of the intolerance of this drug in the elderly. Aminoglycosides are administered by injection and have serious side effects including renal failure and ototoxicity that can be manifested as hearing loss or vestibular dysfunction.²²

This article reports the results of treatment with a regimen containing ethambutol and clofazimine as companion drugs to clarithromycin or azithromycin for treatment of MAC lung disease in patients without HIV infection, sparing them the need for treatment with and the potential side effects of the rifamycins and aminoglycosides. Clofazimine was

chosen as the second companion drug because the provincial tuberculosis laboratory used to report sensitivities for NTM isolates and local MAC isolates were uniformly sensitive to it. Another advantage is that it is generally well tolerated, even in the elderly.

MATERIALS AND METHODS

Patient Selection

Patients with NTM infection are referred to the central tuberculosis clinic in the Calgary Health Region. All patients without HIV infection with MAC lung disease were included in the analysis. The diagnosis of MAC lung disease was based on a typical clinical and radiologic picture associated with a minimum of three positive sputum culture findings or two positive culture findings if at least one was smear-positive in agreement with the 1997 American Thoracic Society statement on NTM.²² History of prior treatment with tuberculosis medication, records of prior acid-fast bacilli smear and culture results, and patient demographic information were recorded.

Patients referred to the Calgary Health Region Tuberculosis Clinic with MAC lung disease who were ≥ 18 years were considered for inclusion. Patients could be inpatients or outpatients. Exclusion criteria included macrolide intolerance or allergy, pregnancy, inadequate contraception, known infection with a macrolide-resistant organism, and risk factors for or known HIV positivity. Patients were eligible for inclusion in the analysis regardless of previous MAC therapy as long as the pretreatment isolate was not macrolide resistant.

Specimen Preparation

Unless sputum was readily produced, it was induced using 5% nebulized saline solution. Sputum specimens were decontaminated with equal amounts of 4% sodium hydroxide. Sputum specimens were examined with a rhodamine-auramine fluorescent stain, and positive smears were confirmed with Ziehl-Neelsen staining. All specimens were cultured. Cultured specimens were checked weekly for a minimum of 7 weeks. All sputum specimens demonstrating growth underwent Ziehl-Neelsen staining and were examined with DNA probes. MAC probe-positive specimens were reported and were sent for sensitivity testing. Susceptibility testing was done in our provincial laboratory by the standardized method recommended by the National Committee for Laboratory Standards.²⁹

Therapy

All patients were treated with clarithromycin, 500 mg bid po, or azithromycin 250 mg/d po, on weekdays, together with ethambutol, approximately 15 mg/kg/d po, and clofazimine 100 mg/d po. The aim was to provide the treatment regimen for a total of 1 year or at least 6 months after the sputum culture finding became negative, whichever was longer. To be included in the analysis, all patients had been followed up for at least 6 months after stopping treatment.

Drug Safety Tests

Prior to initiation of drug therapy and at each subsequent clinic visit, patients were questioned about problems and symptoms. Patients were instructed about potential side effects prior to

initiating therapy and questioned about these at each visit during therapy. Patients were instructed to contact the clinic, which was open 5 days per week, with any concerns or symptoms between visits. Blood work including a CBC count, differential cell count, and liver function tests were done at baseline and every 2 months while receiving therapy for safety reasons. Eye examinations were performed at baseline and repeated at 2-month intervals. Patients were only given a 1-month supply of medication and came to the clinic to receive monthly refills, at which time medication containers were checked to verify adherence to the prescribed regimen. Records were kept of sputum culture results and side effects.

Statistical Analysis

Group results are expressed as mean \pm SD. Comparisons between groups were done by paired *t* tests for continuous variables and by χ^2 analysis for categorical data.

RESULTS

A total of 30 patients (3 men and 27 women) fulfilled the criteria for inclusion in the analysis. The age range of the patients was 47 to 87 years (mean age, 70 ± 9.4 years [SD]). None of the patients had previously been treated for MAC disease. All but three of the patients had a minimum of three positive sputum culture findings for MAC. The three exceptions had a least two positive sputum culture findings, with at least one positive sputum smear for acid-fast bacilli. The results of MAC susceptibility testing are shown in Table 1. The provincial laboratory no longer does susceptibility testing to clofazimine.

Four patients failed to complete a 4-month course of treatment because of intolerable side effects; in none of these subjects did the sputum findings convert to negative for MAC (Fig 1). The four patients with treatment failure were significantly older than the rest of the patients (82 years vs 68 years, $p = 0.004$). The remaining 26 patients completed an average of 10 months of treatment; in all, the sputum culture finding converted to negative. One patient died of unrelated causes after sputum conversion and before completing treatment. The remaining 25 patients have been followed up for an average of 19 months. In 5 of these 25 patients, the

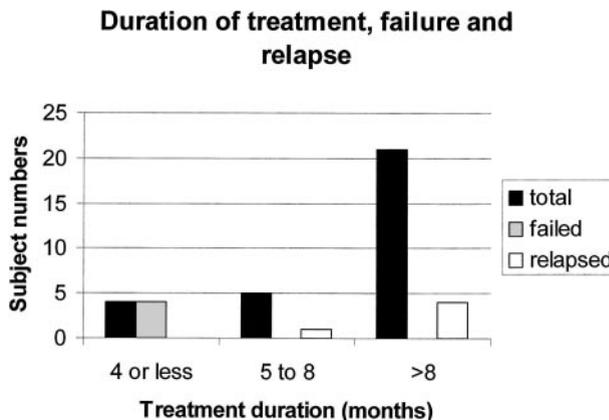


FIGURE 1. Duration of treatment, failure, and relapse. Total number of subjects (black column), number who failed therapy (gray column), and number of subjects who relapsed (white column) among those treated for ≤ 4 months, 5 to 8 months, and > 8 months. One subject who was treated for > 8 months converted to negative and did not relapse but died of other causes.

sputum culture finding again became positive for MAC an average of 17 months after stopping treatment (Fig 1). In each case, the organism in the patients who relapsed was sensitive to macrolides, and retreatment with the same regimen again resulted in the sputum finding converting to negative. There was no apparent difference in the relapse rates between the clarithromycin and azithromycin-treated patients. In those whose treatment was successful, the average duration of follow-up was 20 months after stopping treatment.

A total of 22 of the 30 patients reported side effects that they attributed to the macrolide. Side effects were attributed to clarithromycin by 16 of 19 patients and to azithromycin by 6 of 11 patients, with a trend favoring azithromycin ($p = 0.08$). The side effects from clarithromycin necessitated a change to azithromycin in four patients. One of these patients and another three of those starting with clarithromycin discontinued therapy prematurely and failed to convert to negative. The other three patients were successfully treated after changing to azithromycin. Only one patient failed to tolerate azithromycin and successfully changed to clarithromycin. There was a trend toward treatment completion (≥ 1 year) for those who were receiving azithromycin at the end of their treatment period: 7 of 14 patients receiving azithromycin compared with 3 of 16 patients receiving clarithromycin ($p = 0.07$).

Three patients complained about the change in skin color associated with clofazimine. Two patients complained of visual disturbance, necessitating withdrawal of ethambutol in one patient.

Table 1—Sensitivity of MAC Isolates to Different Antibiotics*

Drugs	Sensitive	Intermediate	Resistant
Clarithromycin	28	2	0
Ciprofloxacin	6	3	21
Ethambutol	15	13	2
Rifabutin	5	15	10

*Data are presented as No.

DISCUSSION

This analysis shows that treatment with a regimen that includes a macrolide, either clarithromycin, 500 mg bid, or azithromycin 250 mg/d, on weekdays, in combination with ethambutol, 15 mg/kg/d, and clofazimine, 100 mg/d, achieved similar sputum conversion rates in patients with MAC lung disease but was easier to administer and required less monitoring than previously published macrolide-containing regimens.¹²⁻²¹ Currently, macrolides are the most effective medications for treatment of MAC infections but need to be administered with other classes of medications to prevent the development of resistance.^{12,13} Most previously published regimens have included both a rifamycin and an aminoglycoside, classes of medications that have a variety of serious side effects and are difficult to administer. Our regimen of a macrolide in combination with ethambutol and clofazimine, was relatively well tolerated and achieved sputum conversion to negative and relapse rates that were at least as good as any of the previously published macrolide-containing regimens.

Research trials of MAC lung disease are difficult to perform because of the small number of patients in any one center. MAC lung disease is slowly progressive, and responses to treatment are relatively slow.^{2-4,22} It is hard to compare the published studies too closely since patient selection criteria, sputum criteria for diagnosis, surveillance during and after the completion of therapy, and criteria for defining a successful outcome differ.³ Some studies included patients who had been treated previously for MAC and some included patients with defined immunodeficiency disorders. Gender proportions, and pattern and extent of lung disease also varied in different studies. In most of the published clinical trials of treatment with macrolides, a large proportion of the patients required a change from the planned treatment protocol because of side effects.

The most common complaint related to the use of clarithromycin was taste perversion, which was most often associated with loss of appetite and with nausea.^{19,30} These were the complaints of the four patients in whom treatment failed. Patients receiving azithromycin generally complained of diarrhea, with nausea and dyspepsia being less common. These side effects were often not severe and generally resolved with continued use of the drug.³¹

All patients who were able to tolerate a minimum of 5 months of treatment converted their sputum to negative, whereas none of the four who were unable to tolerate 4 months of therapy converted their sputum findings to negative. Five of the 26 patients relapsed an average of 17 months after stopping therapy. The relapse rate with this regimen was

comparable to the results of other macrolide-containing regimens.^{12,13,19}

In the patients who relapsed, the MAC organisms retained their susceptibility to clarithromycin and azithromycin, and all converted their sputum findings to negative with retreatment. It may be that apparent relapse actually represents reinfection rather than relapse. Genetic studies³² have demonstrated that a single strain of MAC tends to persist in patients with fibrocavitary lung, whereas different strains are found over time in patients with fibronodular bronchiectasis. Most of our patients and those in other reports of macrolide-containing regimens have the fibronodular bronchiectasis form of MAC lung disease. The long-term success of both this and other regimens will need to be assessed by studies with longer follow-up periods.

It is uncertain why some people without an obvious immunodeficiency disorder or preceding lung disease acquire MAC lung disease. A study³³ compared cytokine profiles in patients with MAC lung disease to control subjects who were infected with MAC, as determined by a positive delayed-type hypersensitivity response to MAC sensitin, and a negative tuberculin skin test reaction, but who were healthy. The monocytes from the control subjects produced higher concentrations of interferon- γ and tumor necrosis factor- α , cytokines that have been shown to contribute to host defenses against tuberculosis and MAC in animals.³³ Patients with cystic fibrosis also appear to be predisposed to NTM infection including MAC lung disease.³⁴ It is likely that those who may be predisposed to MAC infection will continue to be at risk for infection whether they do or do not have underlying lung disease.³³ These patients should be followed up indefinitely, as was formerly the case for patients with a history of tuberculosis, and treated again if necessary.

It appears that MAC lung disease, especially fibronodular bronchiectasis, is becoming more common.^{1,2} This may be due to the aging of the population and/or a greater awareness of the role of MAC in the pathogenesis of bronchiectasis. As the awareness of the role of MAC increases, especially in patients with chronic respiratory symptoms, the reported prevalence will probably increase. Patients with bronchiectasis, especially when it occurs late in life or primarily affects the lingula and/or the right middle lobe, should have sputum sent for mycobacterial culture.³⁵

Most studies of the treatment of MAC lung disease have been case series because of the small numbers treated in any one institution. An exception was the British Thoracic Society study published in 2001.⁸ Unfortunately, it was conceived before the newer macrolides were available, and the results are

no longer relevant. Hopefully, further multicenter trials will be undertaken both to better understand the natural history of this condition and to help define optimal therapy for this condition.

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