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Long-term Follow-up of *Mycobacterium avium* Complex Lung Disease in Patients Treated With Regimens Including Clofazimine and/or Rifampin

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BACKGROUND: *Mycobacterium avium* complex (MAC) lung disease requires prolonged treatment with multiple antibiotics. Drug intolerances and interactions are common with the current recommended treatment. There is limited information on outcomes with alternative medications.

METHODS: Retrospective review including adult patients with MAC lung disease who were treated and monitored for at least 6 months posttreatment. The aim was to evaluate the clinical and microbiologic outcomes in patients treated with regimens including clofazimine and/or rifampin.

RESULTS: One hundred and seven patients were included (79% were female; mean age, 67 years). Sputum samples were smear positive in 54% of patients. The majority (84%) were treated with clofazimine in combination with a macrolide and ethambutol. Fourteen patients (13%) were treated with rifampin, macrolide, and ethambutol. Most patients (95%) converted from positive to negative sputum culture results in an average of 4.5 $\pm$ 4.2 months (range, 0-30 months). A significantly greater proportion of patients treated with clofazimine converted to negative culture results compared with those treated with rifampin (100% vs 71%; $P = .0002$). Microbiologic relapse occurred in 52 of 107 patients (49%). Thirty-six percent of patients required retreatment. There was no difference in microbiologic relapse or re-treatment rates between the two treatment groups.

CONCLUSIONS: The majority of patients with MAC lung disease achieve negative sputum culture results. Re-treatment is needed in approximately one-third of patients. In this cohort, both initial outcomes and re-treatment rates were at least as good in patients treated with clofazimine-containing regimens as in patients receiving rifampin-containing regimens. Clofazimine should be considered as an alternative drug for the treatment of MAC lung disease.

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KEY WORDS: clofazimine; *Mycobacterium avium* complex; nontuberculous mycobacteria

ABBREVIATIONS: ATS/IDSA = American Thoracic Society/Infectious Diseases Society of America; MAC = *Mycobacterium avium* complex; NTM = nontuberculous mycobacterial

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Mycobacterium avium complex (MAC) is the most common nontuberculous mycobacterium isolated worldwide.[1] Approximately half (52%) of all nontuberculous mycobacterial (NTM) isolates in North America are members of *M avium* complex.[1] MAC exists in the environment, likely inhabiting biofilms in municipal water sources, household plumbing, and soil.[2-4] In many countries, the prevalence of NTM infection is increasing, and MAC lung disease leads the way.[1,5-8] Approximately one-third to one-half (33%-47%) of patients with positive respiratory culture results are reported to fulfill American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) diagnostic criteria for NTM lung disease.[9-11] MAC causes chronic lung disease in both immunocompetent and immunocompromised hosts, with and without preexisting lung disease.[12]

Patients with NTM lung disease, in particular those with cavitary disease and/or poor lung function, have been shown to have significantly impaired health-related quality of life.[13,14] Although treatment is not always necessary, patients with progressive symptoms, radiologic changes, and/or persistently positive culture results frequently clinically benefit from medical therapy.[15,16] Most treatment outcome reports have focused on microbiologic results, but there are few data on how many patients require re-treatment.

Treatment of MAC lung disease remains challenging. The most recent ATS/IDSA guidelines recommend triple therapy (ie, macrolide, ethambutol, and rifampin) for a minimum of 12 months after culture conversion.[11] Therapy is prolonged and expensive, and is frequently associated with drug-related adverse events. Drug intolerance and drug-drug interactions are problematic and often limit the use of first-line medications.[17,18] Information on second-line agents, such as fluoroquinolones, inhaled amikacin, and clofazimine, is limited.[19-21]

The aim of this study was to evaluate the microbiologic and clinical outcomes, primarily re-treatment rates, in patients with MAC lung disease treated with regimens including clofazimine and/or rifampin.

Materials and Methods

Patient Population

All patients treated at the Calgary Tuberculosis Clinic (Calgary, AB, Canada) from January 1, 1990 to December 31, 2009 for pulmonary nontuberculous mycobacterial infections were reviewed (Fig 1). Patients were included in the study if (1) they were 18 years of age or older; (2) they met ATS/IDSA diagnostic criteria for MAC lung disease including (a) pulmonary symptoms, (b) the presence of multifocal bronchiectasis and multiple small nodules on chest radiograph or high-resolution CT scan of the chest and appropriate exclusion of alternative diagnoses, and (c) two or more sputum cultures, or one bronchoalveolar lavage culture, or one lung tissue biopsy specimen that was positive for *Mycobacterium avium* complex; and (3) they received a minimum of 6 months of multidrug treatment (including a macrolide) and ≥ 6 months of follow-up posttreatment or continual treatment for > 2 years.[11] Treatment was initiated during the previously described time frame. The decision to use clofazimine or rifampin was at the discretion of the treating physician. Clofazimine was often chosen if there were relative contraindications to the use of rifampin, such as drug interactions and/or concerns about side effects. Patients with a diagnosis of HIV were excluded. None of the patients had been previously treated for MAC. Patients were monitored until March 31, 2013. Approval for this study was obtained from the University of Calgary Conjoint Health Research Ethics Board (E-23071). Eighteen patients reported in this study were previously included in a study by Field and Cowie[19] published in 2003.

Data

Demographic, clinical, microbiologic, radiologic, and treatment data were collected at baseline and during follow-up from all patients with MAC lung disease through retrospective medical record review. Chest radiograph and CT scan reports at or near the time of diagnosis were reviewed and radiographic abnormalities (bronchiectasis, nodular opacities, cavities, and airspace consolidation) were recorded. If any of these radiographic abnormalities were seen in both lungs, the patient was considered to have bilateral disease. Unless sputum was readily produced by spontaneous expectoration, sputum samples were induced by

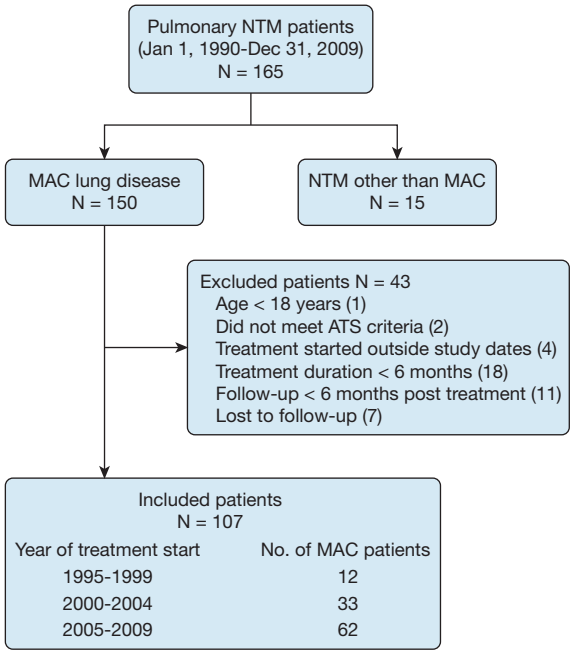

Figure 1 – *Patient identification flow diagram. ATS = American Thoracic Society; MAC =* Mycobacterium avium *complex; NTM = nontuberculous mycobacterial.*