Macrolide/Azalide Therapy for Nodular/Bronchiectatic *Mycobacterium avium* Complex Lung Disease

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BACKGROUND: There is no large study validating the appropriateness of current treatment guidelines for *Mycobacterium avium* complex (MAC) lung disease. This is a retrospective single-center review evaluating the efficacy of macrolide/azalide-containing regimens for nodular/bronchiectatic (NB) MAC lung disease.

METHODS: Patients were treated according to contemporary guidelines with evaluation of microbiologic responses. Macrolide susceptibility of MAC isolates was done at initiation of therapy, 6 to 12 months during therapy, and on the first microbiologic recurrence isolate. Microbiologic recurrence isolates also underwent genotyping for comparison with the original isolates.

RESULTS: One hundred eighty patients completed > 12 months of macrolide/azalide multidrug therapy. Sputum conversion to culture negative occurred in 154 of 180 patients (86%). There were no differences in response between clarithromycin or azithromycin regimens. Treatment regimen modification occurred more frequently with daily (24 of 30 [80%]) vs intermittent (2 of 180 [1%]) therapy ($P = .0001$). No patient developed macrolide resistance during treatment. Microbiologic recurrences during therapy occurred in 14% of patients: 73% with reinfection MAC isolates, 27% with true relapse isolates ($P = .03$). Overall, treatment success (ie, sputum conversion without true microbiologic relapse) was achieved in 84% of patients. Microbiologic recurrences occurred in 74 of 155 patients (48%) after completion of therapy: 75% reinfection isolates, 25% true relapse isolates.

CONCLUSIONS: Current guidelines for macrolide/azalide-based therapies for NB MAC lung disease result in favorable microbiologic outcomes for most patients without promotion of macrolide resistance. Intermittent therapy is effective and significantly better tolerated than daily therapy. Microbiologic recurrences during or after therapy are common and most often due to reinfection MAC genotypes.

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ABBREVIATIONS: AFB = acid-fast bacilli; MAC = *Mycobacterium avium* complex; MR = microbiologic recurrence; NB = nodular/bronchiectatic; NTM = nontuberculous mycobacteria; tiw = three times weekly; UTHSCT = University of Texas Health Science Center, Tyler

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Introduction of the macrolide clarithromycin and the closely related azalide azithromycin in the early 1990s was associated with significant improvement in the therapy of *Mycobacterium avium* complex (MAC) infections.[1-4] Several single-center, uncontrolled trials and one prospective randomized trial of MAC lung disease therapy demonstrated favorable treatment responses to macrolide/azalide-based regimens.[3-13] These studies are difficult to compare, as doses of the macrolide/azalide, choices of companion drugs, and definitions of sputum conversion and disease relapse varied.[3-13] Additionally, patients with MAC disease characterized by nodules and bronchiectasis (nodular/bronchiectatic [NB] MAC disease) and those with disease characterized by upper lobe fibronodular and fibrocavitary disease were analyzed together, which is questionable from a pathophysiologic perspective.[14-16]

A further complicating factor emerged with the recognition that patients with NB disease can be infected with multiple MAC genotypes and that microbiologic recurrences (MRs) during or after therapy may be the result of new MAC genotypes and presumed reinfection rather than true disease relapse.[17,18] We report results of a consistent protocol for treatment of MAC lung disease at a single center using a microbiologic end point and contemporary diagnostic and MAC lung disease treatment standards.[19,20]

FOR EDITORIAL COMMENT SEE PAGE 244

Materials and Methods

Patients treated at The University of Texas Health Science Center, Tyler, (UTHSCT), Texas, for NB MAC lung disease not previously reported are included in this report. The clinical treatment outcome studies, retrospective chart reviews, and maintenance of a database were approved by the Institutional Review Board of UTHSCT (Institutional Review Board #760, #11-009).

Daily therapy consisted of rifampin 600 mg or rifabutin 150 mg, ethambutol 15 mg/kg, clarithromycin 1,000 mg in divided doses or 15 mg/kg for patients weighing $<$ 50 kg, or azithromycin 250 mg. Three times weekly (tiw) therapy consisted of rifampin 600 mg or rifabutin 150 to 300 mg, ethambutol 25 mg/kg, and clarithromycin 1,000 mg in divided doses, or azithromycin 500 mg. Medication choices and frequency of dosing were at the discretion of the investigator.

Three routine expectorated sputum cultures for acid-fast bacilli (AFB) were collected at initiation of therapy. For patients unable to produce sputum by spontaneous expectoration, sputum induction was performed with nebulized hypertonic saline with directions for home use. Sputum samples were collected monthly from patients receiving therapy and then every 1 to 2 months for the length of follow-up. Patients initially diagnosed bronchoscopically did not routinely undergo repeat bronchoscopies, as most patients were successful in submitting samples after induction.

Sputum samples were processed in the UTHSCT clinical laboratory using standard decontamination procedures, fluorochrome microscopy, solid media culture on a biplate of Middlebrook 7H10 agar with and without antibiotics, and a broth culture (BACTEC 960; Becton, Dickinson and Company; ESP; Thermo Fisher Scientific) as previously described.[4,5] MAC isolates were identified using AccuProbe (Hologic Gen-Probe Inc). Semiquantitative AFB smear and culture results for each submitted clinical specimen during and after therapy were recorded as previously described.[4,5]

Macrolide/azalide susceptibilities were performed at initiation of therapy, at 6 to 12 months while receiving therapy, or on the first MR isolate. Susceptibilities used broth microdilution according to contemporary guidelines.[21,22] Clarithromycin was used as the class drug for both macrolide and azalide susceptibility.

Sputum conversion was defined as three or more consecutive negative AFB cultures over a minimum of 3 months. In patients unable to expectorate, a single culture-negative bronchoscopically obtained specimen was also considered conversion. The primary treatment end point was 12 months of negative cultures for the initial MAC genotype(s). A single positive culture during therapy after sputum conversion did not change the duration of therapy if other monthly cultures were negative. Failure to convert sputum to culture negative with 12 months of macrolide/azalide therapy was considered treatment failure.

Two or more positive AFB cultures for MAC after sputum conversion constituted MR. Patients with positive cultures receiving therapy after sputum conversion or after successful completion of therapy had genotyping performed on three pretreatment MAC isolates and all MR isolates. Two or more positive MR cultures for the pretreatment genotype were considered a true relapse. Two or more positive cultures for a new genotype(s) were considered reinfection. If genotyping was not performed, two or more positive cultures after sputum conversion were considered a probable true relapse. Treatment success was defined as 12 months with negative sputum cultures while receiving therapy without isolation of a true relapse MAC isolate.

Genotyping was performed using pulsed-field gel electrophoresis as previously described.[17,18] Definitions of isolates as indistinguishable (no band differences), probably related (four to six band differences), or unrelated (more than seven band differences) were the same as in previous studies.[17,18] Restriction enzymes used were *Xba*I and AseI or *Dra*I.

Group data are expressed as means and SD. Comparison of outcomes between patient treatment groups was done with Fisher exact test or Pearson χ^2 test. The binomial test was used to compare the frequencies of new infections vs true relapse in episodes with subsequent MR. Analysis of other clinical variables between groups was done with the *t* test for equality of means after evaluation of the data with Levene test for equality of variances. Two-tailed *P* values were used for all *t* tests. Significance of all comparisons was determined with a *P* value $<$ .05. IBM SPSS Statistics, version 21 was used to calculate these values.

Results

Two hundred seven consecutively treated patients were started on MAC therapy for NB MAC lung disease during the study period. Twenty-seven patients were excluded from the main analysis because they did not receive at least 12 months of macrolide/azalide-based therapy, leaving 180 patients who met the inclusion criteria for analysis. Fifty-five of 180 patients (31%) received $>$ 6 months macrolide-based therapy prior to treatment at our facility. Twenty-one patients (15%) received