Short Course Antimicrobial Therapy for Adult Patients with Mycobacterium Avium Complex (MAC) Pulmonary Infection: A Pilot Study

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Abstract

Rationale: Patients with pulmonary infections due to Mycobacterium avium complex (MAC) are treated with multiple antimicrobial agents administered simultaneously for a period of at least one year after conversion of sputum cultures from positive to negative. However, this therapy is often poorly tolerated. Additionally, repeat infections upon discontinuation of therapy commonly occur and often necessitate subsequent prolonged courses of therapy. Shorter courses of drug therapy would likely diminish the morbidity of treatment but could potentially result in the development of antibiotic resistance. We hypothesized that a 3 months course of antimicrobial therapy for MAC would not induce macrolide resistance and be well tolerated, while providing clinical benefit to patients. This pilot study was conducted to test this hypothesis in a small number of patients.

Methods: We treated adults with MAC pulmonary disease associated with multifocal bronchiectasis and multiple small nodules with a 3 months course of triple antibiotic therapy including a macrolide antibiotic (clarithromycin or azithromycin). The development of macrolide resistance was the primary outcome assessed. Secondary outcomes included drug tolerability, quality of life (QOL) assessments, and temporal changes in pulmonary function tests (PFT) and high resolution computed tomography (HRCT) scans.

Measurements and main results: Thirteen adult patients with MAC pulmonary infection were recruited and begun on antimicrobial therapy; 12 completed 3 months of treatment; 11 had 6 months follow-up. No participant developed evidence of macrolide resistant MAC. HRCT findings at 6 months were stable or improved relative to baseline in most participants (8/11 and 9/11, respectively). The symptom score on the St. George Respiratory Questionnaire (SGRQ) improved at the conclusion of drug administration at 3 months in 10 of 12 patients and there was improvement on the mental subscale of the SF-12 at 6 months.

Conclusions: We demonstrated preliminary supporting evidence that a 3 months course of triple drug therapy in adult patients with MAC pulmonary infections does not induce macrolide resistance and that it may be associated with improved QOL and radiographic stability.

Implications: A three month course of multiple drug therapy for patients with MAC pulmonary infections may offer an alternative to standard prolonged drug therapy. Subsequent periodic, short courses of therapy may be needed if re-infection occurs.

Keywords: Clarithromycin; Pulmonary infections; Drug therapy; Multifocal bronchiectasis

Abbreviations: MAC: Mycobacterium Avium Complex; PFT: Pulmonary Function Test; HRCT: High Resolution Computed Tomography; QOL: Quality of Life; SGRQ: St. George Respiratory Questionnaire; NTM: Nontuberculous Mycobacteria; AFB: Acid Fast Bacilli; ESR: Erythrocyte Sedimentation Rate; SF-12: short form 12; IQR: Interquartile Range; NTM: Nontuberculous Mycobacterium; BMI: Body Mass Index; FEV1: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity

Introduction

Although the incidence of pulmonary tuberculosis is declining in developed countries, lung disease due to nontuberculous mycobacterium appears to be increasing [1,2]. Lung disease due to MAC typically presents as an upper lobe cavitary infection in patients with chronic obstructive pulmonary disease (COPD) or as multiple small nodules in patients with multifocal bronchiectasis [3-5]. The latter presentation is becoming increasingly more common and often manifests as a chronic pulmonary disease in thin, middle-aged to elderly female hosts often accompanied by systemic symptoms [6].

Eradication of MAC, which is the goal of antimicrobial drug therapy, requires a combination of antimicrobial agents for a period of at least one year after conversion of sputum cultures from positive to negative [5]. The duration of antimicrobial therapy commonly exceeds 18 months or more. Success, defined as sustained eradication of the organism is only achieved in 55% of patients treated with a macrolide based regimen [4]. The duration of therapy, the suboptimal sustained benefit, and morbidity of drug toxicity often leads to reluctance to pursue treatment or premature discontinuation of therapy. In a meta-
analysis of studies examining the efficacy of a macrolide containing antibiotic regimen, the patient dropout rate ranged from 11-31%. Kim reported only 14/33 (42%) patients who became culture negative with therapy completed the full treatment course. Furthermore, even after completion of recommended therapy, many patients will grow MAC organisms again and require repeated prolonged courses of therapy. In a study of 34 patients treated for 18 months with combination drug therapy, 11/34 (32%) grew MAC in sputum one year following discontinuation of therapy [6].

The difficulties of permanent eradication of MAC in patients with pulmonary infections in association with multifocal bronchiectasis and the indolent, chronic nature of the disease coupled with a paucity of rigorous trials demonstrating improvements in patient centered outcomes with successful and sustained organism eradication encourages the exploration of treatment strategies focused on MAC suppression rather than eradication in this population. We have observed sustained clinical benefit, radiographic improvement, and persistently negative sputum cultures in some patients whose MAC treatment had to be prematurely aborted due to drug intolerance.

However, recurrent MAC infection following treatment with a macrolide containing regimen has been associated with subsequent macrolide resistant MAC [7]. Thus, there is concern that suppressive strategies may lead to the development of macrolide resistance.

We designed this prospective observational pilot study as a preliminary step to examine the effects of a 3 month course of triple antimicrobial therapy in patients with MAC pulmonary infection in the setting of bronchiectasis. The primary goal was to investigate the development of macrolide resistance. Secondary goals were to assess the impact of this approach on patient tolerability of therapy, radiographic and spirometric changes, and QOL.

Methods

Subjects

The study design was approved the Institutional Review Board at Mayo Clinic in Florida and was funded solely by the Mayo Foundation. Symptomatic adult patients, at least 18 years of age, who met diagnostic criteria for macrolide sensitive MAC pulmonary disease, associated with multifocal bronchiectasis and multiple small nodules on HRCT and who were felt to require antimicrobial therapy by their treating physician were identified [5]. Patients with a history of cystic fibrosis or HIV/AIDS, fibrocavitary disease due to MAC infection, a known allergy or intolerance to any of the study medications, ophthalmological conditions which would preclude the use of ethambutol, treatment for MAC within the two years prior to study enrollment, other non tuberculosis mycobacterial (NTM) infections, or those who were pregnant were excluded.

Study design

After establishing study eligibility and providing informed consent, participants underwent baseline testing including history and physical examination, body mass index (BMI) determination, PFTs, HRCT of the chest, sputum culture for acid-fast bacilli (AFB) and other organisms, macrolide sensitivity testing of MAC, laboratory data including complete blood count, general chemistries including hepatic transaminases, erythrocyte sedimentation rate (ESR), C-reactive protein, and, pregnancy testing for women with child bearing potential.

All participants underwent baseline ophthalmological examination including visual field and Ishihara color plates testing and completed a SGRQ and short form-12 (SF-12) QOL assessment.

After baseline testing, enrolled participants were treated with an oral, three drug antimicrobial combination consisting of clarithromycin 1000 mg/daily, ethambutol 25 mg per kg, and rifampin 600 mg administered three times per week. Study drugs were initiated sequentially; ethambutol followed by rifampin, and then clarithromycin, at one week intervals to enhance tolerance. Participants exhibiting intolerance to the clarithromycin during the first week of drug administration were permitted to be switched to azithromycin for the remainder of the treatment period.

Study visits occurred at baseline, at the conclusion of the three month drug treatment period and at six months. At each of these three time points subjects underwent a history and physical examination, subjective assessment of drug tolerability, laboratory and sputum testing, QOL assessments, and PFTs. Overall disease stability and PFT findings at baseline were compared with patients prior findings at the time of clinical evaluations. The change in disease severity at study baseline incorporated both objective and subjective assessments and was jointly established by the clinician and patient. At the three month visit, subjects underwent a second ophthalmological evaluation to confirm absence of ethambutol induced ophthalmic toxicity. At the six month visit subjects also underwent a HRCT of the chest which was compared with baseline exam. The HRCT was interpreted by a radiologist who was blinded to subjects’ participation in this trial.

The sputum specimen was produced by spontaneous or induced expectoration and digested using MycoPrep (N-acetyl-L-cysteine sodium hydroxide) to remove any bacteria that would compete with the mycobacteria to improve recovery. Once digestion was completed, AFB smears were prepared using Phenolic Acridine Orange Stain and reviewed by a technologist. The specimen was inoculated onto each side of a Middlebrook 7H11/7H11 selective biplate and Middlebrook 7H9 liquid media (MGIT) tube, incubated at 37°C with 8% CO2, and held for 56 days. The MGIT cultures were incubated in the BACTEC 960 and held for 42 days. Cultures were read once weekly for duration of incubation.

It was established a priori that a subjects’ participation in the study would be terminated in the event that any of the following occur: an elevation of transaminases equal to or greater than three times baseline, evidence of ethambutol ophthalmic toxicity, an allergic reaction to any of the drugs, severe intolerance to any of the drugs including but not limited to persistent adverse gastrointestinal effects, diffuse joint aches, profound fatigue or patient request.

Statistical analysis

This is a single-arm, proof of concept study; thus, baseline, 3-month and 6-month data is provided in descriptive terms using median and interquartile range (IQR). The Wilcoxon signed rank test was used to compare three-month and six-month QOL measurements with baseline values.

Results

Enrollment began December 1, 2008 and the final patient completed the study December 25, 2010. The duration of the study period for each patient was 6 months. Fourteen participants were consented for this study. One was determined to be moribund and withdrawn prior to drug initiation; he subsequently died. One participant was not compliant with study medication and did not complete the course of treatment. The remaining 12 participants were included in the analysis. Six months data was unavailable for one of these 12 subjects due to hospitalization for cardiac problems that were determined to be

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unrelated to the study. Of note, subsequent sputum cultures from this subject after the conclusion of the study period demonstrated growth of MAC but no macrolide resistance.

Baseline characteristics of the twelve study participants are shown in Table 1. The study cohort was predominantly female with a median age of 69 years. All were Caucasian. Seven participants were never smokers; four participants had a BMI <20. Airflow obstruction, defined as an FEV1/FVC ratio <70 % was present in 7/12 (58%). CT scans demonstrated non-cavitary nodular bronchiectasis on the CT scan. Additionally, one patient had an area of cavity formation on CT scan of the chest.

To be eligible for treatment, patients had to be experiencing symptoms attributable to NTM. At enrollment, all patients had cough, mostly productive, several had intermittent hemoptysis, and most had fatigue and dyspnea on exertion. One demonstrated the inability to maintain optimal body weight. These symptoms were not quantitatively assessed but were queried as part of HRQOL tools.

As per protocol, no patient had been treated for NTM within the two years prior to enrollment. Three of the patients had been treated in the past ending therapy between nine and three years prior to this study.

A composite list of symptoms experienced by enrolled subjects after study enrollment included: flu-like symptoms, headache, nausea, loss of balance, weakness, hemoptysis, dry skin, chills, muscle aches, fever, dry heaves, confusion, cold, heart burn, shortness of breath, cough, dizziness, sweats, alcohol sensitivity and dark colored urine. No subject needed to discontinue therapy due to side effects. There was no biochemical evidence of hepatotoxicity or ocular toxicity (Table 2). There were no clinically meaningful changes in measures of inflammation including ESR, C-reactive protein, or white blood cell count.

HRCT findings were stable compared with prior clinical evaluations in the majority of patients. At 6 months follow-up, HRCT findings were stable or improved in 9/11 (Table 3).

| Variable | Baseline (n=12) | 3 months (n=12) | 6 months (n=11) |
|----------|----------------|----------------|----------------|
| WBC (×10^3/μL) | 6.7 (5.8, 7.6) | 5.9 (5.2, 6.6) | 8.3 (5.2, 6.8) |
| Hemoglobin (g/dL) | 13.1 (12.5, 13.8) | 13.5 (12.6, 13.9) | 12.7 (12.1, 13.6) |
| Sedimentation rate (mm/h) | 15.5 (9.5, 25.0) | 14.5 (9.0, 28.0) | 18.0 (8.0, 25.0) |
| C-reactive protein (mg/L) | 5.2 (2.7, 16.4) | 6.3 (2.2, 10.5) | 11.8 (2.0, 21.3) |
| AST (units/L) | 24.5 (24.0, 26.5) | 24.5 (22.0, 27.5) | 23.0 (21.0, 26.0) |
| Creatinine (mg/dL) | 0.7 (0.7, 1.0) | 0.8 (0.7, 0.9) | 0.8 (0.7, 1.0) |
| Blood glucose (mg/dL) | 89.5 (86.0, 94.5) | 92.5 (91.0, 95.0) | 92.0 (96.0, 95.0) |
| Macrolides sensitivity | 11/11 d (100%) | 1/1 (100%) | 6/6 (100%) |

| Variable | Summary* (N=12) |
|----------|----------------|
| Completed 3 month treatment of 3 drugs in study | 12 (100%) |
| Completed 6 month follow-up | 11 (92%) |
| Age at consent date | 69 (62-76) |
| Sex-Female | 9 (75%) |
| Race-Caucasian | 12 (100%) |
| Change in disease severity prior to enrollment | 6 (50%) |
| Stable | 1 (8%) |
| Worse | 5 (42%) |
| Never smoked b | 7 (58%) |
| History of hemoptysis in last 6 months | 2 (17%) |
| Hemoptysis while on treatment | 0 (0%) |
| BMI (kg/m^2) | 23.2 (18.6, 23.9) |
| FEV1 (L) | 1.8 (1.3, 2.0) |
| pp FEV1 (%) | 64 (47, 70) |
| FEV1/FVC (%) | 63 (59, 74) |
| DLCO | 14.0 (11.7, 17.2) |
| ppDLCO (%) | 66 (60, 74) |

| Variable | Baseline (n=12) | 3 months–baseline (n=11) | 6 months–baseline (n=11) |
|----------|----------------|--------------------------|--------------------------|
| SGRQb | Summary | P | Summary | P |
| Symptoms | 52.4 (41.9, 79.2) | -22 (-26.3, -9.3) | 0.016 | -6.5 (-27.6, -1.7) | 0.12 |
| Activity | 62.8 (27.8, 70.8) | 0.0 (-16.7, 11.6) | 0.49 | -9.9 (-19.6, 4.9) | 0.43 |
| Impacts | 29.3 (20.7, 39.9) | -2.5 (-4.8, 9.5) | 0.79 | -4.2 (-14.0, 9.3) | 0.46 |
| Total | 42.2 (29.2, 55.3) | -5.1 (-10.9, 6.5) | 0.47 | -7.4 (-16.2, 11.8) | 0.37 |
| SF-12b | Physical subscale | 38.3 (25.3, 50.3) | 1.7 (-7.6, 7.1) | 0.58 | 2.3 (-4.1, 7.3) | 0.63 |
| Mental subscale | 51.1 (41.2, 56.1) | 3.0 (-3.3, 10.8) | 0.24 | 3.0 (1.0, 7.6) | 0.049 |

| Variable | Baseline (n=12) | 3 months (n=12) | 6 months (n=11) |
|----------|----------------|----------------|----------------|
| No. of patients treated in hospital | 12 | 11 | 11 |
| No. of patients with positive MAC culture | 12 | 11 | 11 |
| No. of patients with negative MAC culture | 0 | 0 | 0 |
| No. of patients with positive MAC culture before study | 12 | 11 | 11 |
| No. of patients with negative MAC culture before study | 0 | 0 | 0 |
| No. of patients with positive MAC culture after study | 12 | 11 | 11 |
| No. of patients with negative MAC culture after study | 0 | 0 | 0 |
| No. of patients with positive MAC culture at baseline | 12 | 11 | 11 |
| No. of patients with negative MAC culture at baseline | 0 | 0 | 0 |
| No. of patients with positive MAC culture at 3 months | 11 | 10 | 9 |
| No. of patients with negative MAC culture at 3 months | 1 | 1 | 1 |
| No. of patients with positive MAC culture at 6 months | 10 | 9 | 8 |
| No. of patients with negative MAC culture at 6 months | 2 | 2 | 3 |

| Variable | trt | 3 months | 6 months |
|----------|-----|----------|----------|
| pp DLCO (%) | 66 (60, 74) | 66 (60, 74) | 66 (60, 74) |

Table 1: Baseline patient characteristics.
Discussion

Pulmonary infections due to NTM, are most commonly attributable to MAC [5]. Historically, MAC pulmonary infection presented as upper lobe fibrocavitary disease in males with COPD. However, it is increasingly recognized as a pathogen in patients with underlying multifocal nodular bronchiectasis [9,10].

The currently recommended treatment approach consists of the concomitant administration of multiple antimicrobials for a prolonged period of time. However, this approach is costly, poorly tolerated, and often associated with disease recurrence once therapy is completed [6,11]. Drug tolerability, especially in patients with nodular bronchiectasis who tend to be elderly females often with characteristic phenotypes including low BMI, is especially problematic [12]. Furthermore, there is little data demonstrating improvement in patient centered outcomes including QOL measures with antimicrobial therapy.

As demonstrated in our cohort, these patients have a reduced health related quality of life compared to normal age matched controls. Mehta et al., previously showed a reduction in both SF-36 and SGRQ scores compared with Canadian population-based normals in 51 patients with NTM pulmonary infections [13]. We found similar reductions in HRQOL in patients with bronchiectasis with and without NTM infections. (Moss, JE, Johnson MM. unpublished data). In this cohort of 126 subjects with an average age of 72 years, the mean SGRQ symptom score was 48 ± 24. This was significantly worse than both normals and patients with COPD as compared with a normal population [14].

The expectorated sputum samples of patients with nodular bronchiectasis characteristically demonstrate polymicrobial bacterial growth [15]. The structural airway changes of bronchiectasis typically preclude complete eradication of these organisms. Thus, treatment is focused on bronchial hygiene with intermittent antimicrobial therapy for clinical manifestations of disease exacerbations.

It is well established that MAC with the original strain or a new strain, may reoccur in those who have completed therapy and have achieved culture negativity [13]. This phenomenon suggests that complete and permanent eradication of these organisms may not be uniformly possible. Thus, we hypothesize that suppression rather than eradication of MAC may be a more appropriate therapeutic paradigm in patients with nodular bronchiectasis. This pilot study demonstrates that a three month triple antibiotic program incorporating a macrolide for patients with MAC pulmonary infection in association with bronchiectasis is well tolerated, associated with stability or improvement in PFT, HRCT findings, and QOL measures, and does not induce macrolide resistance.

There are notable limitations with our study that warrant attention. As a pilot study, it is, by design, very small. Replication of our findings in larger studies would be required for adoption of this strategy. This study was designed to assure that resistance was not induced by this treatment strategy prior to commencing larger scale efficacy studies. The absence of detectable MAC to assess for resistance in 92% and 45% of subjects at 3 and 6 months, respectively, is also a potential limitation. However, the absence of detectable MAC does support our hypothesis that short course therapy decreases the burden of infection. More vigorous attempts to culture MAC and assess resistance with bronchoscopy may have yielded helpful information, however bronchoscopic recovery of sputum would not be reflective of clinical practice. Additionally, the duration of follow-up was relatively short. Because enrollment was only offered to a patient when the clinician felt bronchoscopic recovery of sputum would not be reflective of clinical practice. Additionally, the duration of follow-up was relatively short. Because enrollment was only offered to a patient when the clinician felt active treatment for MAC was needed, it is plausible selection bias influenced our findings. However, initiation of antimicrobial therapy when deemed clinically indicated reflects standard management.

Taken together, our data suggests that a three month triple antibiotic program including a macrolide antibiotic for patients with MAC pulmonary infection in association with nodular bronchiectasis is safe, well tolerated, and is not associated with the development of macrolide resistance. This study does not demonstrate short course...
therapy is equivalent to standard therapy. This pilot study was designed to address tolerance of short course therapy and its impact on the development of resistance in future NTM cultures. Given the high rate of recurrence of NTM in patients successfully treated with standard prolonged therapy, we believe that a philosophical change in therapeutic goals from organism eradication to suppression merits strong consideration. Periodic short course therapy may allow appropriate organism suppression in the absence of the development of resistance and may offer better tolerability and less morbidity than currently recommended treatment approaches. It is conceivable that periodic three month courses of therapy may improve quality of life in patients. Larger, prospective comparative investigations of longer duration comparing this approach with standard prolonged triple drug therapy on patient centered outcomes, including HRQOL, are warranted.

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