Case Report

Use of Mefloquine in Multidrug-Resistant *Mycobacterium avium* Complex Pulmonary Disease in an HIV-Negative Patient

Juan Ramirez, MD; Carol Mason, MD, FCCP; and Juzar Ali, MD, FRCP(C), FCCP
Division of Pulmonary, Critical Care Medicine, Louisiana State University Health Sciences Center, New Orleans, Louisiana

ABSTRACT

Introduction: *Mycobacterium avium* complex (MAC) is a leading cause of pulmonary disease (PD), even in those with intact immunity, representing about 30% of the cases of pleuropulmonary mycobacterial infection. Based on previous studies, macrolides are the only agents used in the treatment of MAC disease for which there is a correlation between in vitro susceptibility and in vivo (clinical) response. However, resistance develops rapidly if single-agent treatment is used. Data regarding treatment of macrolide-resistant MAC (MRMAC) and multidrug-resistant MAC (MDRMAC) are sparse.

Case summary: A 50-year-old, HIV-negative white man, weighing 53.6 kg, with severe chronic obstructive pulmonary disease and bronchiectasis was initially on treatment for MAC-PD and MRMAC. The patient was followed between 1999 and 2006. His treatment history revealed that in addition to the multiple drugs administered during the course of his illness, thalidomide, interferon-γ, and mefloquine were also administered. The patient died ~7 years later due to respiratory failure and overwhelming infection.


Key words: bronchiectasis, mycobacteria, nontuberculous mycobacteria, *Mycobacterium avium* complex, *Mycobacterium avium* complex pulmonary disease, macrolide-resistant *Mycobacterium avium* complex, multidrug-resistant, mefloquine, acid-fast bacillus.
INTRODUCTION

*Mycobacterium avium* complex (MAC) is recognized as one of the most common nontuberculous mycobacterial pathogens found in humans and accounts for ~30% of all mycobacterial infections. It has been known to cause disseminated disease in those who suffer from HIV infection, where it typically presents as disseminated disease. It has also been found to be a cause of pulmonary disease (PD) in non-HIV patients and those with apparently intact immunity. Although *M avium-intracellulare* (MAI) complex can be isolated from the sputum of apparently healthy individuals, it might cause lung disease and progression of underlying lung disease leading to respiratory failure and even death. HIV-negative patients with underlying lung disease may acquire MAC infection. However, it has been suggested that MAC might cause progressive lung disease in patients without underlying lung disease, particularly in middle-aged and elderly women. It has also been suggested that deficient interferon-γ (INF-γ) pathways or an abnormal α1-antiprotease gene might play a predisposing role in some patients. Patients with chest wall deformities such as kyphoscoliosis and pectus excavatum are also at greater risk for acquiring MAC infection.

The clinical presentation of MAC-PD infection in an HIV-negative host varies and depends on the population studied. Table I illustrates the clinical classification based on its presentation in an HIV-negative patient. In this classification, complex MAC includes cases in which earlier treatment has failed or the disease process is recurring and progressing. Because of the prevalence of *M avium* and MAI in the environment, it is not surprising that some patients might be infected by more than a single strain. However, a single strain of *M avium* tends to persist in patients with advanced fibrocavitary disease. Patients with fibronodular bronchiectasis might develop different strains over time, sug-

<table>
<thead>
<tr>
<th>Clinical Categories</th>
<th>Suggested Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot tub lung</td>
<td>Avoidance, steroids, or 2 drugs such as ethambutol and macrolide</td>
</tr>
<tr>
<td>“Simple colonization”</td>
<td>Bronchial toilet/nebulized treatment with aminoglycoside</td>
</tr>
<tr>
<td>Simple persisters and/or</td>
<td>Clarithromycin or azithromycin with ethambutol</td>
</tr>
<tr>
<td>disease</td>
<td></td>
</tr>
<tr>
<td>Complex disease</td>
<td>Clarithromycin, ethambutol, and rifabutin or azithromycin, ethambutol, and rifabutin</td>
</tr>
<tr>
<td>Complicated disease</td>
<td>Customized regimen based on drug sensitivity and/or surgery</td>
</tr>
</tbody>
</table>

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gesting a susceptibility to the organism that allows reinfection after it has been eradicated. Reasons for treatment failure in these chronic cases include drug resistance, poor drug penetration into the damaged lung, patient intolerance to treatment, or erratic compliance. The relative resistance to penetration of antimycobacteria into lung tissue is presumably due to the lipophilicity of the cell wall. Moreover, 50% of all cases of treatment failure might be attributed to MAC isolates that are resistant to macrolides. Studies of clarithromycin-resistant MAC strains isolated from mice and patients with confirmed diagnoses of MAIs by exposing mycobacteria to mefloquine, in vitro susceptibility testing, and human macrophage data, have demonstrated activity of mefloquine on MAC. Mefloquine, moxifloxacin, and ethambutol, combined, were evaluated against both clarithromycin-resistant (CLR-R) and CLR-susceptible (CLR-S) MAC. Mefloquine (40 mg/kg/day), moxifloxacin (100 mg/kg/day), or ethambutol (100 mg/kg/day) was administered to mice for 4 weeks. Mefloquine was bactericidal, whereas moxifloxacin and ethambutol were bacteriostatic against both MAC strain 101 CLR-R and CLR-S. The combination of mefloquine and ethambutol reduced \((P < 0.05, \text{for comparison with controls})\), and the combination of mefloquine and moxifloxacin significantly reduced, the load of CLR-R in both the liver and the spleen. Treatment with all 3 drugs was associated with \(-1\) log reduction of CLR-R after 1 week, \(2.1\) log reductions of CLR-R after 4 weeks, and \(2.17\) log reductions in MAC/mL blood. Treatment of MAC 101 CLR-S strain had comparable results.

In this case report, we describe the first HIV-negative patient with multidrug-resistant MAC (MDRMAC) and MAC-PD, failing standard treatment, to whose regimen mefloquine was added. A search of the literature using the PubMed database and searching from 1999 to 2007 with key words mefloquine, MAC, and HIV, did not identify any other case report on the use of mefloquine in an HIV-negative host with resistant MAC-PD.

**CASE REPORT**

A 50-year-old, HIV-negative, white man, weighing 53.6 kg, was admitted to the Louisiana State University Hospital Sciences Center affiliate Hospital at the Kenner Regional Campus with increasing dyspnea, cough, intermittent fever, and progressive fatigue. His medical history revealed tuberculosis, chronic obstructive pulmonary disease (COPD), bronchiectasis, and MAC-PD. Current diagnosis was based on underlying lung disease, persistent sputum cultures exhibiting MAC infection, and the absence of other bacterial growth on respiratory specimens. The patient's medical report also revealed a 30 pack-year smoking history and no known occupational exposure or substance abuse. A review of the patient's previous laboratory findings revealed a normal immunoglobulin panel and a normal CD4/CD8 ratio. His HIV test was negative, and during the course of his illness, his CD4 and CD8 INF-\(\gamma\) levels in peripheral whole blood-by-flow cytometry were normal. He had initially received empiric
treatment for MAC-PD and later for macrolide-resistant MAC (MRMAC) based on serial culture data from 1999 to 2006 (Table II). During the course of his follow-up, culture and sensitivity testing were performed at various intervals by the Medical Center of Louisiana New Orleans Hospital Laboratory, New Orleans, Louisiana; the University of Texas Health Center, Tyler, Texas; and the National Jewish Medical and Research Center, Denver, Colorado. The patient received intermittent broad-spectrum antibiotics and nebulization for the treatment of acute exacerbation of bronchiectasis. The patient eventually developed MDRMAC confirmed by serial culture results. Because of extensive bilateral disease and poor respiratory reserve, surgery was not an option. The patient had also previously been enrolled in a randomized, double-blind, placebo-controlled trial in which he received inhaled INF-γ as part of a thrice weekly standard triple-drug treatment with a macrolide, ethambutol, and rifampin with and without inhaled INF-γ. An interim analysis of the trial data did not reveal any difference in outcomes between the 2 groups, and the trial was terminated after 52 weeks. The patient was later treated with thalidomide for ~1 month but discontinued due to extreme drowsiness (Table II). Because of the patient's multidrug-resistant profile, he was also treated with mefloquine 1000 mg/d for 3 months. No adverse events (AEs) related to treatment were noted. However, potential AEs were monitored by telephone inquiries and evaluation at the follow-up visits to the Medical Center of Louisiana New Orleans Hospital clinic. At his 3-month follow-up visit, the results of his sputum culture again revealed MDRMAC, suggesting colonization.

On admission, physical examination revealed a cachectic man exhibiting accessory respiratory muscle use with an oxygen saturation of 82% on room air. The patient had temporal wasting, pale conjunctiva, and mucosa; his trachea was deviated to the right, and there was mild jugular venous distension. Lung examination revealed significant egophony and whispered pectoriloquy on the right side with decreased breath sounds in the base. Coarse crackles were heard in the left lung. Other aspects of his physical examination were noncontributory. A computed tomography scan of the chest revealed severe bilateral disease with right lung destruction and multiple pulmonary nodules and cavities. The patient was treated with intravenous piperacillin-tazobactam 3.375 g every 6 hours and intravenous ciprofloxacin 400 mg every 8 hours for 7 days along with daily nebulized tobramycin and albuterol 2.5 mg/3 cc every 4 hours for exacerbation of bronchiectasis. His cultures for MAC remained positive throughout the admission. At discharge, he was again placed on oral mefloquine 1 g QD along with ethambutol oral 800 mg QD. Throughout his clinical course, he was reported as being compliant (ie, having administered ≥80% of drug) with mefloquine treatment with no reports of AEs. The patient was closely monitored and questioned by telephone regarding potential gastrointestinal and neuropsychiatric AEs. However, no AEs were reported. After ~1 month, the patient was readmitted for respiratory failure and died 10 days after hospital admission. An autopsy was not performed.
Table II. Bacteriologic profile and treatment course of *Mycobacterium avium* complex (MAC) and multidrug-resistant MAC in an HIV-negative patient with MDRMAC pulmonary disease.

<table>
<thead>
<tr>
<th>Date</th>
<th>Sputum Smear</th>
<th>Sputum Culture</th>
<th>In Vitro Resistance</th>
<th>Treatment Regimen</th>
<th>Other Treatment Modalities Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>Numerous</td>
<td>Positive</td>
<td>Cl, E, Rb</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>Numerous</td>
<td>Positive</td>
<td>Rb, R, K, Cy, E, Sm, Cl</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>Moderate</td>
<td>Positive</td>
<td>All except high-dose Rb and Sm</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Numerous</td>
<td>Positive</td>
<td>Cl, E, Rb, C, Cf, A</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Moderate</td>
<td>Positive</td>
<td>Cl, E, Rb, C, Cf, A</td>
<td>None</td>
<td>INF-γ</td>
</tr>
<tr>
<td>2002</td>
<td>Numerous</td>
<td>Positive</td>
<td>All except high-dose Rb</td>
<td>E, Rb, Cf, L</td>
<td>None</td>
</tr>
<tr>
<td>July 2003</td>
<td>Moderate</td>
<td>Positive</td>
<td>All except K</td>
<td>Az, M, Mf, Rb, L, C</td>
<td>Inhaled A/G</td>
</tr>
<tr>
<td>October 2003</td>
<td>Numerous</td>
<td>Positive</td>
<td>All except high-dose Rb</td>
<td>Az, M, Mf, Rb, L, C</td>
<td>Inhaled A/G</td>
</tr>
<tr>
<td>December 2003</td>
<td>Numerous</td>
<td>Positive</td>
<td>All except high-dose Rb</td>
<td>Az, M, Mf, Rb, L, C</td>
<td>Thalidomide × 1 month</td>
</tr>
<tr>
<td>June 2004</td>
<td>Numerous</td>
<td>Positive</td>
<td>All except Rb</td>
<td>Az, M, Rb, L, C</td>
<td>Inhaled tobramycin</td>
</tr>
<tr>
<td>2005</td>
<td>None</td>
<td>None</td>
<td>Lost to follow-up</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>June 2006</td>
<td>Numerous</td>
<td>Positive</td>
<td>All</td>
<td>Mf, M, E</td>
<td>Inhaled tobramycin</td>
</tr>
<tr>
<td>August 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cl = clarithromycin; E = ethambutol; Rb = rifabutin; R = rifampin; K = kanamycin; Cy = cycloserine; Sm = streptomycin; C = ciprofloxacin; Cf = clofazime; A = amikacin; INF-γ = interferon-γ; L = linezolid; Az = azithromycin; M = moxifloxacin; Mf = melfloquine; A/G = aminoglycoside.
DISCUSSION
Clinical trials\textsuperscript{13,14} have not found susceptibility testing to medications used for MAC to be uniformly useful. The American Thoracic Society (ATS) and the Infectious Diseases Society of America's (IDSA)\textsuperscript{13} \textit{2007 statement on non-tuberculous mycobacterial diseases recommends against testing of agents other than clarithromycin}. With the exception of clarithromycin, the role and the predictability of in vitro susceptibility testing of MAC are controversial. However, the National Committee for Clinical Laboratory Standards (NCCLS)\textsuperscript{14} \textit{2000 guidelines for susceptibility testing of mycobacteria, Nocardia, and other aerobic actinomycetes}, recommend that clarithromycin susceptibility testing be done for respiratory MAC isolates in patients with PD. The NCCLS guidelines also recommend that clarithromycin susceptibility testing be done on respiratory isolates in patients who received prior macrolide treatment and on those who relapse while receiving macrolide treatment. In a randomized, double-blind, dose-ranging study\textsuperscript{15} in patients with AIDS, clarithromycin was found to be the only medication to have an association between clinical response and the results of in vitro susceptibility testing. In this report, adjusting treatment to sensitivity testing results improved sputum culture conversion in MAC lung disease, but studies\textsuperscript{16} do not reveal similar benefits having been found with drugs such as ethambutol and rifampin. Relative resistance to individual medications notwithstanding, a possible synergistic effect of combined treatment on MAC, might explain the lack of an association between sensitivity testing and clinical outcomes.\textsuperscript{17} The sputum conversion rates, however, have been found to be significantly lower in patients who are infected with CLR-R strains, have had prior treatment, or were acid-fast bacillus smear positive at entry irrespective of type and extent of disease.\textsuperscript{18}

According to the ATS/IDSA 2007 recommended guidelines,\textsuperscript{13} patients with nodular/bronchiectatic disease should receive a thrice weekly regimen of clarithromycin (1000 mg) or azithromycin (500 mg), rifampin (600 mg), and ethambutol (25 mg/kg). Patients with fibrocavitary MAC lung disease or severe nodular/bronchiectatic disease should receive a daily regimen of clarithromycin (500–1000 mg) or azithromycin (250 mg), rifampin (600 mg) or rifabutin (150–300 mg), and ethambutol (15 mg/kg) along with the consideration of the administration of a 3 × weekly amikacin or streptomycin (10–15 mg/kg) early treatment. Typically, treatment should be continued until the patient is culture negative for ~1 year.

Data regarding treatment of MRMAC and MDRMAC are sparse. Risk factors that might contribute to the development of macrolide resistance include extended macrolide monotherapy or macrolide with fluoroquinolone adjunct treatment.\textsuperscript{19} Mefloquine (a derivative of 4-quinolinemethanol), used for the prophylaxis of chloroquine-resistant \textit{Plasmodium falciparum} malaria, might be useful adjunct treatment for MDRMAC, although human studies are lacking. The mechanism of action is not clear, and it has been suggested that, based on its effect on \textit{P falciparum}, mefloquine might have
some effect on the membranes of MAC organisms. Experimental and in vitro studies found that mefloquine is bactericidal against both CLR-R and CLR-S strains. The advantage of mefloquine is its long $t_{1/2}$ (6.5–33 days) and synergy with ethambutol. It is active against MAC strains in vitro and can achieve 60 to 80 x greater intracellular concentrations than extracellular concentrations. The Bermudez et al experimental study tested MAC strains resistant to clarithromycin, isoniazid, streptomycin, pyrazinamide, and rifampin, and found these to be susceptible to mefloquine. Ethambutol and mefloquine together were also active in the blood to a greater extent than ethambutol alone. Limited human postmortem data indicate that mefloquine (in a prophylactic dosing regimen) achieves a high level of 190 mg/kg in the lung.

In our case, we added mefloquine 2 times to our patient’s regimen (20 mg/kg QD) due to severe and progressive disease and the failing of all other treatment. A literature search from 1999 to 2007 using the PubMed database and key words mefloquine, MAC, and HIV, did not identify any other case report on the use of mefloquine in a patient with resistant MAC-PD in an HIV-negative host. However, Nannini et al reported its successful use along with linezolid, moxifloxacin, and granulocyte colony-stimulating factor in disseminated MAC infection in an HIV-negative patient with chronic lymphocytic leukemia. In our case, no AEs were observed or reported during the course of treatment. No obvious benefit was noted, however, perhaps due to the relatively short treatment period or other factors of comorbidity (ie, COPD and bronchiectasis) in this patient. Further human studies are needed to establish potential efficacy and long-term tolerability with mefloquine treatment for severe MDRMAC.

CONCLUSION
This report describes the use of mefloquine as adjunct treatment in an HIV-negative patient with MDRMAC-PD. Mefloquine appeared to be well tolerated by the patient.

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REFERENCES


