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Treatment Outcome of Combination Therapy Including Clarithromycin for *Mycobacterium avium* Complex Pulmonary Disease

Eun Young Kim, Su Young Chi, In Jae Oh, Kyu Sik Kim, Yu Il Kim, Sung Chul Lim, Young Chul Kim, and Yong Soo Kwon

Department of Internal Medicine, Chonnam National University Hospital, Gwangju, Korea

Background/Aims: The frequency of nontuberculous mycobacteria pulmonary disease in HIV-negative patients is increasing; the most common pathogen in Korea is the *Mycobacterium avium* complex (MAC). However, few studies have evaluated the treatment outcome of MAC pulmonary disease in Korea.
Methods: The efficacy of a clarithromycin-containing regimen for MAC pulmonary disease was studied in 42 patients treated for more than 6 months between January 2005 and December 2008. All patients were treated with a regimen consisting of clarithromycin, rifampin, and ethambutol. Streptomycin was added in 10 patients.
Results: Among the 42 patients, a negative culture conversion was achieved in 33 (78.6%), and the median duration of treatment in these patients was 19 months (interquartile range [IQR], 16 to 22). Of the 33 patients with a negative culture conversion, 14 completed treatment. During the follow-up period (median, 10 months; IQR, 4 to 20) for the 14 patients, one relapsed at 24 months after treatment completion. The culture conversion rate was significantly higher in patients who were treated with more than 500 mg/day clarithromycin (87.1% vs. 54.5%, $p = 0.038$).
Conclusions: The combined regimen including clarithromycin was effective against MAC pulmonary disease. High-dose clarithromycin of more than 500 mg/day may improve the outcome of patients with MAC pulmonary disease. **(Korean J Intern Med 2011;26:54-59)**

Keywords: *Mycobacterium avium* complex; Treatment outcome; Clarithromycin

INTRODUCTION

Mycobacterium avium complex (MAC) is the most common pathogen of nontuberculous mycobacterial pulmonary diseases in Korea [1-4]. Recently, the frequency of this infection has been increasing [1,2,5]. The American Thoracic Society (ATS)/Infectious Disease Society of America (IDSA) has recommended a combination drug regimen including clarithromycin or azithromycin, rifampin or rifabutin, and ethambutol for treating MAC pulmonary disease in human immunodeficiency virus (HIV)-negative patients [6]. Streptomycin has been recommended for patients with severe and advanced, especially fibrocavitary, disease or previously treated disease [6]. The Korean Academy of Tuberculosis and Respiratory Diseases has recommended a similar regimen in their 2005 guidelines of tuberculosis management [7]. However, few studies have been conducted on the treatment outcomes from a combined antibiotic therapy for MAC pulmonary disease in Korea [8]. Therefore, the efficacy of a clarithromycin-containing regimen for MAC pulmonary disease was investigated in this study.

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Correspondence to Yong Soo Kwon, M.D.
Department of Internal Medicine, Chonnam National University Hospital, Hak-dong, Dong-gu, Gwangju 501-757, Korea
Tel: 82-62-220-6573, Fax: 82-62-225-8578, E-mail: yskwon@chonnam.ac.kr

METHODS

Patients

A retrospective review of the medical records of 123 patients with MAC pulmonary disease, diagnosed using the 2007 criteria of the ATS, from January 2005 to December 2008 at Chonnam National University Hospital in Gwangju, South Korea, was performed. Permission was obtained from the institutional review board to review and publish patient records retrospectively. Among the 123 patients, 52 patients who did not receive treatment, 14 who were transferred to their referring institutions after diagnosis of MAC pulmonary disease, and two who died due to causes not attributed to MAC pulmonary disease were excluded. Thirteen patients who were treated for less than 6 months were also excluded. Among these patients, seven were lost to follow-up, five received combination drug treatment for less than 6 months at the end of the study period, and one refused treatment. Finally, 42 patients who received combination drug treatment for more than 6 months were included in this study. No patient had been previously treated for MAC pulmonary disease before presenting to this hospital.

Treatment protocol

All patients were managed according to the 1997 (1) and 2007 (2) guidelines recommended by the ATS. The initial daily doses were clarithromycin (500-1,000 mg/day), rifampin (450 mg for body weight ≤ 50 kg or 600 mg for body weight > 50 kg), and ethambutol (25 mg/kg per day for 2 months followed by 15 mg/kg per day). Streptomycin was given intramuscularly to patients with severe or fibrocavitary disease at 10-15 mg/kg, three times per week for the first 3 to 6 months as tolerated.

Microbiological and radiological evaluation

Sputum smears and mycobacterial cultures were collected using standard methods [9]. *M. avium* and *M. intracellulare* were identified by multiplex polymerase chain reaction (PCR) assay, as described previously [10]. Amplification for all multiplex PCR reactions was performed in a DNA thermal cycler (GeneAmp PCR 9600, Perkin-Elmer, Waltham, MA, USA).

Computed tomography (CT) scans were obtained from all patients at the start of treatment to evaluate lesions including cavities and bronchiectasis and underlying pulmonary conditions. Chest radiographs were obtained initially and at least every 3 months thereafter. Chest radiography and CT scan findings were classified as upper lobe cavitary or nodular bronchiectatic forms.

Assessment of efficacy

Efficacy was evaluated based on culture conversion rate, improvement of radiological findings, and clinical symptoms. Culture conversion was defined as three consecutive negative sputum cultures during the treatment period, with the time of conversion defined as the date of the first negative culture. Conversion to a negative culture was assumed if the patient could not expectorate sputum. A sputum relapse was defined as two consecutive positive cultures after culture conversion. The clinical symptoms and radiological findings were compared at the initiation of treatment and the end of treatment to determine clinical and radiological efficacy; the findings were divided into three categories including "improvement," "no change," and "aggravation."

Statistical analyses

All results were presented as the median and interquartile range (IQR) or number and percent because the majority of the data did not follow a normal distribution. Categorical variables were analyzed with the Pearson's chi-square test or Fisher's exact test, as appropriate. Continuous variables were analyzed with the Mann-Whitney *U* test. Statistical significance was established at a $p < 0.05$.

RESULTS

Patient characteristics

Forty-two patients with MAC pulmonary disease who had received combination antibiotic therapy for more than 6 months were included in this study. Among the 42 patients, 25 (60%) were male and 17 (40%) were female. The median age of the patients was 65 years (range, 55 to 74) (Table 1). Most patients had respiratory symptoms such as cough (71%), sputum (71%), hemoptysis (24%), and dyspnea (14%). Fourteen patients had a positive sputum acid-fast bacilli (AFB) smear at the time of the initial antibiotic treatment. The radiologic classifications included 17 (40%) and 25 (60%) patients with upper lobe cavitary and nodular bronchiectatic disease, respectively. Of the 42 patients, 22 (52%) had a history of antituberculosis treatment.

Table 1. Baseline characteristics of the 42 patients with MAC pulmonary disease

Characteristics	Total (n = 42)
Age, yr	65 (55 - 74)
Gender, male	25 (60)
Body mass index, kg/m^2	18.8 (17.7 - 22.1)
Smoking history	
Non-smoker	22
Ex-smoker	14
Current smoker	6
Respiratory symptoms	
Cough	30 (71)
Sputum	30 (71)
Hemoptysis	10 (24)
Dyspnea	6 (14)
Positive sputum AFB smear	14 (33)
Type of disease	
Upper lobe cavitary form	17 (40)
Nodular bronchiectatic form	25 (60)
Etiology	
M. avium	10 (24)
M. intracellulare	32 (76)

Values are presented as number (%) or median (interquartile range).
MAC, *Mycobacterium avium* complex; AFB, acid-fast bacilli.

Antibiotic treatment

The median duration of treatment was 18 months (IQR, 13 to 22). The dose of CAM (clarithromycin) dose was 1,000 mg/day for 30 patients, 750 mg/day for one patient, 500 mg/day for 10 patients, and 250 mg/day for one patient. Streptomycin was given to six (14%) patients for a median of 3 months (IQR, 2 to 8).

Of the 42 patients, 21 (50%) completed the combined treatment. Among the 21 patients who did not complete the treatment course, three were transferred to another hospital at 13, 15, and 22 months of combined treatment, and one patient was lost to follow-up after 16 months of combined treatment. The remaining 17 patients continued to be treated until the end of the study period.

Treatment outcome

The overall culture conversion rate was 78.6% (33/42), and the median time to culture conversion was 49 days (IQR, 28 to 77). Of the 42 patients, 21 (50%) completed the combined treatment. Among the 21 patients who completed treatment, 14 (67%) achieved culture conversion and continued to have a negative conversion for a median of 10 months (IQR, 4 to 20) during follow-up. One patient relapsed at 24 months after treatment completion. No significant difference was observed between patients with and without treatment completion with regard to clinical characteristics such as age (p = 0.970), body mass index (BMI; p = 0.755), positive sputum AFB smear at the start of treatment (p = 0.197), or type of disease (p = 0.753). However, treatment duration was significantly longer in patients that completed treatment (median, 20 months; IQR, 19 to 24 months) compared with patients that did not complete treatment (median, 16 months; IQR, 15 to 20 months) (p = 0.006).

Twenty-two (52%) patients showed improvement on radiologic findings, 15 (36%) were unchanged, and five (12%) had aggravated disease. Symptoms were evaluated among 33 patients by medical chart review; 12 (36%) were improved, 18 (55%) were unchanged, and three (9%) had aggravated symptoms.

Patients with upper lobe cavitary disease had significantly lower culture conversion rates compared with patients with nodular bronchiectatic disease (30% vs. 70%, p = 0.019). Radiologic and symptomatic responses were significantly better in the patients who underwent culture conversion. No significant differences in age, gender, BMI, sputum AFB smear, or duration of treatment were observed between patients who did and did not undergo culture conversion (Table 2).

The culture conversion rate was significantly higher in patients who received more than 500 mg/day of clarithromycin (87.1%) than in patients who received less than 500 mg/day of clarithromycin (54.5%, p = 0.038). The radiologic findings showed also significantly higher rates of improvement in patients who received more than 500 mg/day of clarithromycin than in patients who received less than 500 mg/day of clarithromycin (61% vs. 27%, p = 0.016). Symptomatic improvement tended to be better in patients who received more than 500 mg/day of clarithromycin than in patients who received less than 500 mg/day, although the difference was not statistically significant (46% vs. 11%, p = 0.129). No significant differences in age, gender, BMI, sputum AFB smear, duration of treatment, or use of streptomycin were observed between patients who received more than 500 mg/day of clarithromycin and those who received less than 500 mg/day (data not shown).

Adverse effects

Gastrointestinal symptoms (e.g., anorexia, nausea, dyspepsia, and diarrhea) associated with the combined

Table 2. Characteristics of the 42 patients with or without culture conversion to negative

	Culture negative conversion (n = 33)	Persistent positive (n = 9)	*p* value
Age, yr	65 (55 - 74)	68 (55 - 74)	0.471
Gender, male	18 (55)	7 (78)	0.271
Body mass index, kg/m^2	18.8 (18.0 - 22.1)	18.0 (16.2 - 23.3)	0.457
Positive sputum AFB smear	11 (33)	3 (38)	1.000
Type of disease			
Upper lobe cavitary form	10 (30)	7 (78)	0.019
Nodular bronchiectatic form	23 (70)	2 (22)	
Duration of treatment, mon	18.0 (13.0 - 20.0)	19.0 (12.5 - 24.5)	0.414
Dose of clarithromycin, mg/day			
≤ 500	6 (18)	5 (56)	0.038
> 500	27 (82)	4 (44)	
Use of streptomycin	3 (9)	3 (33)	0.101
Radiographic response			
Improvement	22 (67)	0 (0)	< 0.001
No change	11 (33)	4 (44)	
Aggravation	0 (0)	5 (56)	
Symptomatic response			
Improvement	12 (46)	0 (0)	0.018
No change	13 (50)	5 (71)	
Aggravation	1 (4)	2 (29)	

Values are presented as number (%) or median (interquartile range).
Fisher's exact test or Mann-Whitney *U* test was performed as appropriate.
AFB, acid-fast bacilli.

antibiotic treatment developed in four (9.5%) patients. In these four patients, three continued clarithromycin without a dose reduction due to mild symptoms. One patient had to reduce the dose of clarithromycin from 1,000 mg/day to 500 mg/day. Two (5%) patients discontinued ethambutol because of optic neuritis.

DISCUSSION

The treatment outcome of MAC pulmonary disease was disappointing before the use of newer macrolide antibiotics such as clarithromycin and azithromycin [6]. Since 1990, the introduction of newer macrolide antibiotics, treatment of pulmonary MAC disease has improved patient outcome [11,12]. Wallace et al. [12] reported on clinical trials using a clarithromycin-containing regimen including clarithromycin, ethambutol, rifabutin or rifampin, and initial treatment with streptomycin; the regimen achieved a greater than 90% culture conversion rate. However, the culture conversion rate was 64% when the patients who dropped out of the treatment trial and those who relapsed were included. Most other studies using the macrolide-containing regimen showed a similar culture conversion rate [13].

In the present study, the combined therapy including clarithromycin achieved a 79% culture conversion rate after excluding patients who received the treatment for less than 6 months. This is a relatively high treatment response compared to other studies; however, if the patients who were lost to follow up (n = 7) and those who refused treatment (n = 1) were included, the culture conversion rate was 66% (33/50). Therefore, the treatment outcome in this study was consistent with previous studies. In a Korean study [8], culture conversion rates with a clarithromycin-containing regimen were only 60% (9/15). If the patients who dropped out and relapsed were included, the culture conversion rate was lower than 60%, relatively lower than that in our study. Higher sputum smear positive rates at the start of treatment in their study compared with those in our study (87% vs. 33%) suggest that patients in their study had more severe disease than those in our study. However, that study may not be generalizable, because only 15 patients enrolled

and 33% (5/15) of all patients received treatment for less than 12 months.

The side effects of clarithromycin such as gastrointestinal irritation and hepatotoxicity could limit the long-term use of this drug, especially in elderly patients [14]. Recent ATS/IDSA guidelines suggest reducing the dose of clarithromycin (500 mg/day or 250 mg twice) in patients with advanced age or a small body mass [6]. However, the efficacy of different doses of clarithromycin has not been well studied. Clarithromycin had an inhibitory effect on bacterial growth at a sub-inhibitory concentration in an *in vitro* study [15] and higher doses of clarithromycin showed higher concentrations in the bronchial epithelial lining fluid in a human study [16]. Two clinical trials with a limited number of enrolled patients showed similar results. Kobashi and Matsushima [17] reported that higher doses of clarithromycin (600 mg/day vs. 400 mg/day) resulted in a higher sputum conversion rate in patients with MAC pulmonary disease. Hasegawa et al. [18] also demonstrated that a higher dose of clarithromycin (800 mg/day vs. 400 mg/day) was better for obtaining culture conversion. In the present study, more than 500 mg/day of clarithromycin resulted in significantly higher culture conversion rates. The previous two studies showed that the higher dose of clarithromycin did not have significantly different rates of adverse events compared to lower doses [17,18]. In the present study, adverse effects were not significantly different in the patients who received less than 500 mg (27%) compared with those who received more than 500 mg (13%) of clarithromycin (p = 0.353).

Another factor related to the treatment outcome in this study was a different type of MAC pulmonary disease. Upper lobe cavitary disease was associated with a significantly lower culture conversion rate compared with the nodular bronchiectatic form. Although some studies showed no difference in treatment outcome between cavitary disease and non-cavitary disease [19,20], a large prospective study showed that patients with non-cavitary disease had a four-times higher (95% confidence interval, 1.74 to 9.19; p = 0.001) culture response rate than patients with cavitary disease [21]. Therefore, more aggressive treatment is recommended in patients with cavitary MAC pulmonary disease than the non-cavitary form [6].

The major limitation of the present study was the retrospective study design. The information obtained was limited to what was available in the medical records. Furthermore, clarithromycin susceptibility testing was not performed. Although the ATS/IDSA guidelines recommend that previously untreated MAC isolates should be tested by clarithromycin susceptibility testing [6], untreated MAC isolates are usually susceptible to clarithromycin [6,22], which might have influenced the treatment outcome data. Moreover, the long-term treatment outcome could not be evaluated in this study. Half of all patients did not complete the treatment, and the median follow-up duration after treatment completion in the remaining half was only 10 months. Therefore, longer follow-up studies are needed to fully evaluate the long-term outcome of MAC pulmonary disease.

In conclusion, a combined treatment consisting of clarithromycin, rifampin, and ethambutol with or without the initial use of streptomycin was effective for previously untreated MAC pulmonary disease. High dose claithromycin, more than 500 mg/day, may improve the treatment outcome of MAC pulmonary disease.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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