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Risk Factors for Recurrence after Successful Treatment of *Mycobacterium avium* Complex Lung Disease

Bo Young Lee,[a] Sunyoung Kim,[b] YoonKi Hong,[c] Sang-Do Lee,[a] Woo Sung Kim,[a] Dong Soon Kim,[a] Tae Sun Shim,[a] Kyung-Wook Jo[a]

Division of Pulmonary and Critical Care Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea[a]; Department of Internal Medicine, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, South Korea[b]; Department of Internal Medicine, Kangwon National University Hospital, Chuncheon, South Korea[c]

This study analyzed the recurrence rate and risk factors for recurrence of *Mycobacterium avium* complex (MAC) lung disease in patients successfully treated for this disease. The medical records of 158 patients successfully treated for MAC lung disease at a tertiary referral center in South Korea between March 2000 and December 2009 were retrospectively analyzed. Recurrence was recorded, and factors associated with recurrence were analyzed. The mean age of the 158 patients was 60.7 ± 11.1 years. The etiologic agent was *Mycobacterium avium* in 77 patients (48.7%) and *Mycobacterium intracellulare* in 81 patients (51.3%). Radiographic features included nodular bronchiectatic disease in 95 (60.1%), fibrocavitary disease in 49 (31.0%), and an unclassifiable form in 14 (8.9%) patients. Almost all (98.7%, 156/158) patients had been previously treated with a macrolide-containing regimen, and 68 (43.0%) patients had received treatment with an aminoglycoside. During a median follow-up of 43.8 months after completion of therapy, 50 patients (31.6%) experienced recurrence, at a median of 11.9 months after treatment completion. Multivariate analysis showed that only the nodular bronchiectatic form of the disease (hazard ratio, 2.39; 95% confidence interval, 1.19 to 4.81) was independently associated with an increased risk of recurrence. Recurrence after successful treatment is frequent in patients with MAC lung disease. The recurrence rate was significantly higher in patients with the nodular bronchiectatic form than in those with the fibrocavitary form or an unclassifiable form of the disease.

The incidence of lung disease caused by nontuberculous mycobacteria (NTM) has been increasing worldwide, including in South Korea, making NTM disease an emerging public health threat (1, 2). Chronic lung infection is the most common form of NTM infection (3). Etiologically, NTM lung disease in South Korea is most frequently caused by *Mycobacterium avium* complex (MAC), consisting of *Mycobacterium avium* and *Mycobacterium intracellulare* (4).

The treatment success rate for MAC lung disease is unsatisfactory. Macrolide-containing regimens have been found to successfully eradicate MAC lung disease in only 60 to 80% of patients, with 20 to 40% failing to respond to treatment (4–6). In addition, a significant proportion of successfully treated patients experience disease recurrence (1). To date, however, limited information is available regarding the optimal regimen and treatment outcomes for patients with recurrent MAC lung disease (7). Moreover, patient characteristics associated with recurrence after successful treatment have not been determined.

This study was therefore designed to determine the recurrence rate and risk factors for recurrence in patients successfully treated for MAC lung disease.

MATERIALS AND METHODS

Study subjects. A retrospective review of the medical records of Asan Medical Center, a 2,700-bed referral hospital in Seoul, South Korea, revealed the growth, at least once, of MAC strains in sputum mycobacterial cultures from 1,520 patients between March 2000 and December 2009. Of these 1,520 patients, 483 fulfilled the 2007 American Thoracic Society (ATS) diagnostic criteria (7) for MAC lung disease. The most common reason for excluding the remaining patients on the basis of ATS criteria was that only one sputum sample from these patients was positive. In addition, some patients did not meet the clinical criteria because they either did not exhibit symptoms or failed to show radiological changes. In our cohort, a cure was defined as no positive culture after at least 12 months of continuous treatment after sputum conversion. Treatment completion was defined as the termination of treatment by the attending physician in the absence of a positive sputum sample, even when the treatment duration was <12 months after achieving sputum conversion. Treatment success was defined as either cure or treatment completion. Of 483 patients fulfilling ATS criteria, 293 were treated, 158 successfully, for MAC lung disease; these 158 patients constituted the study cohort (Fig. 1). Male gender, current or past smoking, a positive AFB smear at treatment initiation, and the fibrocavitary form of the disease were factors that were significantly more prominent in patients without treatment success than in those with treatment success. The medical records of 158 patients with treatment success were analyzed retrospectively in April 2014. The following variables were evaluated for association with recurrence: (i) demographic characteristics, (ii) medical history, (iii) etiologic agents, and (iv) severity and radiological findings.

The study protocol was approved by the Institutional Review Board of the Asan Medical Center, which waived the requirement for informed consent because of the retrospective nature of the analysis.

Antibiotic treatment and assessment of treatment outcomes. All patients with MAC lung disease who began antibiotic therapy received combinations of oral antibiotics. Most received a macrolide (generally clarithromycin), ethambutol, and rifampin as recommended by the ATS (7).

Received 18 October 2014 **Returned for modification** 16 January 2015
Accepted 26 February 2015

Accepted manuscript posted online 9 March 2015

Citation Lee BY, Kim S, Hong Y, Lee S-D, Kim WS, Kim DS, Shim TS, Jo K-W. 2015. Risk factors for recurrence after successful treatment of *Mycobacterium avium* complex lung disease. Antimicrob Agents Chemother 59:2972–2977. doi:10.1128/AAC.04577-14.

Address correspondence to Kyung-Wook Jo, heathcliff6800@hanmail.net.

doi:10.1128/AAC.04577-14

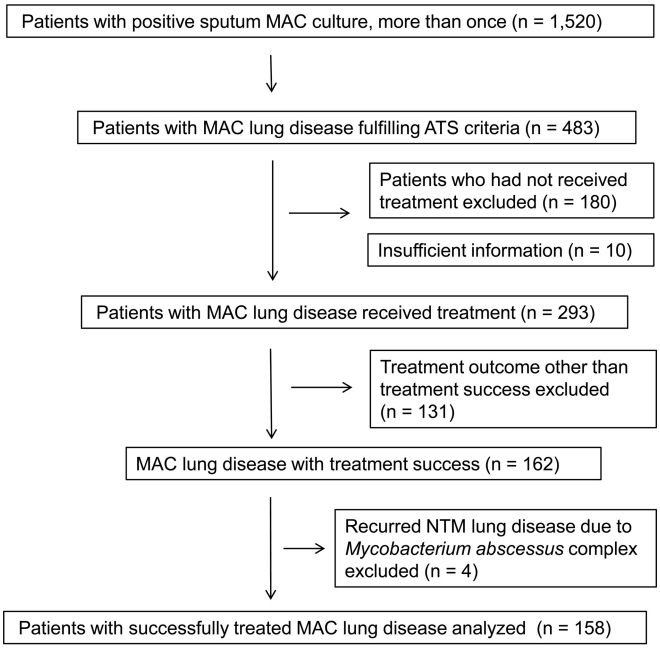

FIG 1 Subject selection. MAC, *Mycobacterium avium* complex; ATS, American Thoracic Society.

Because intermittent therapy is not common in South Korea, many patients with nodular bronchiectasis received daily therapy. Although the administration of an aminoglycoside (generally streptomycin) was at the discretion of the attending physician, it was prescribed for most patients with the fibrocavitary form of the disease.

Sputum conversion was defined as three consecutive negative cultures within 6 months, with the time conversion defined as the date of the first negative culture (6). Patients who could not expectorate sputum during treatment were regarded as having converted to negative. Recurrence was defined as two consecutive positive MAC cultures after sputum conversion (6).

Radiological evaluation. Radiographic abnormalities were classified according to distinct disease patterns on chest computed tomography (CT) as (i) fibrocavitary, (ii) nodular bronchiectatic, and (iii) unclassifiable forms (8). Patients were diagnosed with the fibrocavitary form if CT showed the presence of apical fibrocavitary lesions, and they were diagnosed with the nodular bronchiectatic form if CT showed multiple nodules with bronchiectasis. Patients were diagnosed with the unclassifiable form if CT did not discern any specific pattern because of underlying pulmonary disease or if there were severe nodules with consolidation.

Drug susceptibility tests. The MIC of clarithromycin was determined using the broth microdilution method as described previously (9). Drugs ranged in concentration from 0.5 to 64 μg/ml. MAC isolates with an MIC of ≤8 μg/ml were considered susceptible, whereas those with an MIC of ≥32 μg/ml were considered resistant (9).

Statistical analysis. All analyses were performed using SPSS software (version 12.0; SPSS, Chicago, IL). Continuous variables in the two groups were compared using Student *t* tests or Mann-Whitney U tests, whereas categorical variables were compared using the χ^2 or Fisher's exact test. Hazard ratio (HR) and Cox regression analysis were used to calculate the adjusted risk. Independent variables were selected on the basis of (i) their statistical significance in univariate analysis and (ii) clinical significance revealed in previous studies (4, 8, 10). All tests of significance were two-sided; *P* values of <0.05 were considered statistically significant.

RESULTS

Characteristics of the study subjects. The 158 patients included 75 males (47.5%) and 83 females (52.5%); their mean age was 60.7 ± 11.1 years. The etiologic agent was *M. avium* in 77 patients (48.7%) and *M. intracellulare* in 81 patients (51.3%). Radiographic features included nodular bronchiectatic disease in 95 (60.1%), fibrocavitary disease in 49 (31.0%), and an unclassifiable form in 14 (8.9%) patients. All 79 patients (50.0%) tested for HIV were negative. Clarithromycin susceptibility results were available for 100 patients: the MAC isolates recovered from 96 patients (96%) were susceptible to clarithromycin, and the isolate from 1 patient (1%) was intermediate in resistance, while the isolates from 3 patients (3%) were resistant.

Cure was achieved in 101 patients (63.9%) and treatment completion in 57 patients (36.1%). The patients with cure had a significantly longer period of total treatment than those with treatment completion (mean durations of total treatment, 478 days and 428 days, respectively; $P < 0.001$). The treatment duration after achieving sputum conversion was also longer in patients with cure than in those with treatment completion (mean durations, 428 and 284 days, respectively; $P < 0.001$). The baseline characteristics and follow-up durations after completion of therapy were comparable for the two groups.

Recurrence of MAC lung disease. During a median follow-up of 43.8 months (interquartile range [IQR], 24.1 to 61.5 months) after completion of therapy, 50 patients (31.6%) successfully treated for MAC lung disease experienced disease recurrence, at a median of 11.9 months (IQR, 6.1 to 30.1 months) after completion of therapy. Disease recurrence was observed in 5 of 49 (10.2%) patients with cavitary disease and in 39 of 95 (41.1%) patients with nodular bronchiectasis. A clarithromycin susceptibility test was performed for 40 of 50 patients (80%) with disease recurrence. Among the 40 patients, MAC isolates from 38 patients (95%) were susceptible to clarithromycin, while isolates from 2 patients (5%) were resistant.

The baseline characteristics of the 50 patients with disease recurrence were comparable to those of the 108 without disease recurrence, except that the radiological type of disease differed significantly between these two groups (Table 1). The rate of recurrence was similar for patients with cure and for those with treatment completion (33.6% and 28.1%, respectively; $P = 0.593$).

Recurrent isolates were of the same species as the original isolates in most cases, i.e., among the 26 patients who had been originally infected with *M. avium*, the etiologic agent of recurrence was *M. avium* in 21 patients (80.8%) and *M. intracellulare* in 5 patients (19.2%). Among 24 patients whose original isolate was *M. intracellulare*, the recurrent isolate was *M. intracellulare* in 20 patients (83.3%) and *M. avium* in 4 patients (16.7%).

Previous antibiotic treatment modalities. Of the 158 patients, 156 (98.7%) had previously been treated with a macrolide (generally clarithromycin)-containing regimen. The most frequently prescribed regimen was a combination of clarithromycin, ethambutol, and rifamycin (90.5%, 143/158). In addition, 68 patients (43.0%) had received an aminoglycoside (generally streptomycin).

The detailed previous treatment history of the 158 patients is shown in Table 2. The overall treatment duration, the regimen prescribed, the number of patients treated with aminoglycosides, and the number who underwent surgical resection were similar regardless of recurrence status.

Risk factors for recurrence. Recurrence was significantly more frequent in patients aged ≤65 years than in those >65 years and in

TABLE 1 Demographic and clinical characteristics of the 158 patients successfully treated for MAC lung disease[a]

Characteristic (unit)	Total ($n = 158$)	With recurrence ($n = 50$)	Without recurrence ($n = 108$)	*P* value
Age (yr)	60.7 ± 11.1	59.4 ± 10.4	61.3 ± 11.4	0.297
Male gender	75 (47.5)	20 (40.0)	55 (50.9)	0.201
BMI at initiation of first treatment (kg/m^2)	20.3 ± 2.7	19.9 ± 2.3	20.5 ± 2.9	0.170
BMI at completion of first treatment (kg/m^2)	20.3 ± 2.6	19.9 ± 2.1	21.5 ± 2.7	0.299
Current or past smoker	63 (39.9)	15 (30.0)	48 (44.4)	0.085
Previous history of TB treatment	76 (48.1)	27 (54.0)	49 (45.4)	0.313
Underlying diseases				0.129
Chronic lung disease	25 (15.8)	3 (6.0)	22 (20.4)	
Diabetes mellitus	10 (6.3)	3 (6.0)	7 (6.5)	
Malignancy	31 (19.6)	11 (22.0)	20 (18.5)	
Etiology				0.576
Mycobacterium avium	77 (48.7)	26 (52.0)	51 (47.2)	
Mycobacterium intracellulare	81 (51.3)	24 (48.0)	57 (52.7)	
Positive AFB smear at treatment initiation	85 (53.8)	28 (56.0)	57 (52.8)	0.706
Type of disease				0.001
Fibrocavitary	49 (31.0)	5 (10.0)	44 (40.7)	
Nodular bronchiectatic	95 (60.1)	39 (78.0)	56 (51.9)	
Unclassifiable form	14 (8.9)	6 (12.0)	8 (7.4)	
No. of involved lobes[b]	3 (1–6)	3 (1–6)	3 (1–6)	0.810

[a] Data are mean value ± standard deviation, mean (range), or number (%). Abbreviations: MAC, *Mycobacterium avium* complex; BMI, body mass index; TB, tuberculosis; AFB, acid-fast bacillus.
[b] Six lobes were assessed in each patient's lungs (the lingular segment was considered a separate lobe).

patients with nodular bronchiectatic disease than in those with other forms of the disease. The final Cox regression model showed that the nodular bronchiectatic form of the disease (HR, 2.39; 95% confidence interval [CI], 1.19 to 4.81) was the only independent predictor of recurrence (Table 3). Age was an insignificant predictor of recurrence in multivariate analysis. Figure 2 shows the Kaplan-Meier curves of the probability of recurrence.

Treatment of patients with recurrent MAC lung disease. Of the 50 patients with recurrence, 27 (54.0%) received retreatment. The remaining 23 patients did not receive retreatment because the radiologic changes were small ($n = 9$), because the patients had minimal symptoms ($n = 7$), because the patients refused retreatment ($n = 6$), or for other reasons ($n = 2$). Of the 27 retreated patients, 21 (77.8%) had nodular bronchiectasis. All 27 received macrolide-containing regimens; in addition, 12 patients received streptomycin and 5 received rifabutin. Retreatment was successful in 21 of the 27 (77.8%) patients. Of the 21 patients who attained treatment success after retreatment, no patient experienced recurrence during the median 10.6 months (IQR, 6.2 to 28.4 months) of follow-up.

DISCUSSION

Treatment outcomes in patients with MAC lung disease have been unsatisfactory, even after the introduction of newer macrolide-containing regimens, with success rates ranging from 60% to 80% (4–6). In addition, some successfully treated patients can experience disease recurrence (1). To date, however, risk factors for recurrence in these patients have not been determined. To our

TABLE 2 Initial treatment modalities in the 158 patients successfully treated for MAC lung disease[a]

Characteristic (unit)	Total ($n = 158$)	With recurrence ($n = 50$)	Without recurrence ($n = 108$)	*P* value
Total treatment duration (mo)	15.2 ± 3.2	15.3 ± 2.0	15.2 ± 3.6	0.791
Patients treated with macrolide-containing regimen	156 (98.7)	50 (100.0)	106 (98.1)	1.000
Patients treated with ethambutol	151 (95.6)	49 (98.0)	102 (94.4)	0.433
Duration of ethambutol treatment (mo)	14.2 ± 4.2	14.8 ± 2.8	14.0 ± 4.7	0.236
Patients treated with aminoglycoside	68 (43.0)	19 (38.0)	49 (45.4)	0.384
Duration of aminoglycoside treatment (wk)	5.1 ± 2.8	5.3 ± 2.9	5.1 ± 2.8	0.743
Total dose of aminoglycoside (g)	70.5 ± 39.1	72.3 ± 49.4	69.8 ± 35.0	0.818
Patients undergoing surgical resection	4 (2.5)	1 (2.0)	3 (2.8)	1.000

[a] Data are mean value ± standard deviation or number (%). MAC, *Mycobacterium avium* complex.

TABLE 3 Predictors of recurrence in 158 patients successfully treated for MAC lung disease[a]

Characteristic	No. (%) of patients: With recurrence ($n = 50$)	No. (%) of patients: Without recurrence ($n = 108$)	Univariate analysis *P* value	Multivariate analysis: Adjusted HR (95% CI)	Multivariate analysis: *P* value
Age ≤65 years	39 (78.0)	65 (60.2)	0.028	1.43 (0.85–2.32)	0.212
Body mass index <18.5 kg/m^2	16 (32.0)	29 (26.9)	0.505	0.97 (0.52–1.79)	0.915
Positive sputum AFB smear	28 (56.0)	57 (52.8)	0.734	1.27 (0.76–2.29)	0.425
Nodular bronchiectatic form of disease	39 (78.0)	56 (51.9)	0.002	2.39 (1.19–4.81)	0.014
Mycobacterium intracellulare	24 (48.0)	57 (52.8)	0.576	1.02 (0.58–1.80)	0.949

[a] MAC, *Mycobacterium avium* complex; HR, hazard ratio; AFB, acid-fast bacillus.

knowledge, this is the first study to analyze factors associated with recurrence in patients successfully treated for MAC lung disease. The most important finding of this study was that the recurrence rate was significantly higher in patients with the nodular bronchiectatic form of the disease than in those with the fibrocavitary or an unclassifiable form.

In patients with pulmonary tuberculosis, the most consistent risk factors for recurrence within 2 years of treatment success were a positive acid-fast bacillus (AFB) culture after 2 months of treatment and cavitation on the initial chest X ray, probably because these two parameters are associated with a higher initial mycobacterial load (11–13). Despite our finding that approximately two-thirds of recurrences of MAC lung disease occurred within 2 years, factors related to mycobacterial burden, including a positive AFB smear at treatment initiation and the fibrocavitary form of the disease, were not associated with disease recurrence. This suggested that the mechanism of disease recurrence following successful treatment differs between patients with MAC and those with pulmonary tuberculosis. In other words, unlike pulmonary tuberculosis, which can recur 1 to 2 years after completion of therapy due to the persistence of tuberculosis bacilli despite an apparent cure (14), MAC lung disease may be more likely to recur in patients with a factor predisposing to the acquisition of new bacterial strains. A subset of patients with NTM lung disease were shown to possess a novel predisposing feature, characterized by lower levels of whole-blood interferon gamma after *ex vivo* stimulation and altered adipokine levels in serum (3). Genetic factors contributing to host susceptibility to NTM infection among patients with nodular bronchiectatic disease have also been suggested (15). In addition, many patients with nodular bronchiectasis have multiple MAC strains, suggesting polyclonal or recurrent infection with distinct strains (16). Moreover, most infections after completing treatment were found to result from new strains, primarily in patients with nodular bronchiectasis (17). In addition, Wallace et al. recently reported that microbiological recurrence occurred in 74 of 155 patients (48%) with nodular bronchiectasis after completion of therapy: 75% were reinfection isolates and 25% were true relapse isolates (18). All of these findings indicated that a substantial portion of patients with a distinct phenotype may be repeatedly infected with new MAC isolates after successful treatment, a finding supported by the results presented here.

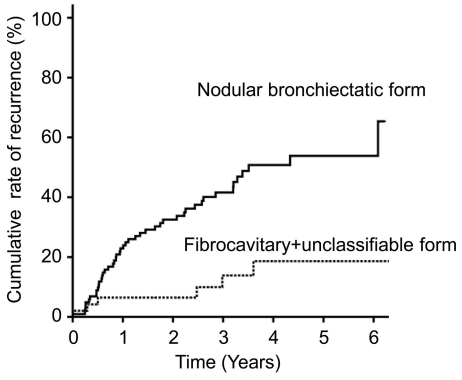

FIG 2 Kaplan-Meier curves of the probability of recurrence in patients successfully treated for *Mycobacterium avium* complex lung disease. The proportion of patients with recurrence was higher for those with the nodular bronchiectatic form than in those with the fibrocavitary form or the unclassifiable form of the disease ($P < 0.001$).

Recurrence rates of MAC lung disease following successful treatment with macrolide-containing regimens (6, 18–23) have been found to range from 8.3% (21) to 48% (18). This study showed a relatively high recurrence rate (31.6%). Discrepancies in recurrence rates may be due to differences in the drug combinations used to treat patients, in the doses or durations of aminoglycoside treatment, in the type of disease, and, most importantly, in the duration of the follow-up period after completion of therapy. Approximately one-third of our patients with recurrent MAC lung disease were diagnosed more than 2 years after completion of therapy. Thus, the relatively long follow-up period (median, 43.8 months after completion of therapy) of the patients in the present study resulted in more patients with disease recurrence.

Although several studies have analyzed treatment options for patients with refractory MAC lung disease (24–26), little is known about optimal treatment options for patients with recurrent MAC lung disease. Although ATS guidelines recommend treatment of previously treated patients with rifabutin rather than rifampin and the inclusion of an aminoglycoside (7), the outcomes of this regimen in patients with recurrent MAC lung disease have not been reported yet. All of our patients with recurrent disease were treated with a macrolide-containing regimen, with fewer than one-half being prescribed streptomycin and rifabutin. Retreatment was successful in 78% of these patients, suggesting that, despite a considerable proportion of patients with the nodular bronchiectasis type of MAC lung disease experiencing recurrence after successful treatment, the overall retreatment outcomes were favorable.

The treatment of MAC with antituberculosis drugs was initially disappointing, but the introduction of newer macrolides has resulted in improved treatment outcomes (18). Current treatment recommendations include a macrolide, ethambutol, and rifamycin (7). Although the overall success rate remains unsatisfactory,

patients with the nodular bronchiectatic form of the disease experienced significantly higher culture conversion rates than patients with the fibrocavitary form of the disease (10, 27, 28). The findings presented here suggest that, although patients with fibrocavitary disease had generally unfavorable outcomes, recurrence after treatment completion is unusual once it has been successfully treated. In contrast, the recurrence rate of nodular bronchiectatic disease is relatively high, despite treatment outcomes being usually successful. Of our 50 patients with recurrent MAC lung disease, 19 (38%) had been treated with an aminoglycoside-containing regimen, although only 5 had the fibrocavitary form of the disease. The reason for prescribing aminoglycosides to some patients with the nonfibrocavitary type of disease is unclear because there is no established protocol and the choices of drugs and regimens are at the discretion of the attending physician. However, it may have been because of disease severity, because aminoglycosides have been recommended in the first 2 or 3 months of treatment for patients with severe and extensive disease, as well as those with fibrocavitary disease (7).

This study had several limitations, the most significant of which were its performance at a single referral center, its retrospective design, and its inclusion of a small number of patients. Prospective, multicenter studies with larger numbers of patients are required to confirm our findings. In addition, because we did not perform molecular analysis, we were unable to distinguish between relapse (infection with the original strain) and reinfection (infection with a new strain). However, recurrent MAC lung disease is reported to result usually from infection with new strains.

In conclusion, a large proportion of patients successfully treated for MAC lung disease can experience later recurrence. The recurrence rate was significantly higher in patients with the nodular bronchiectatic form of the disease than in those without, suggesting that patients successfully treated for the nodular bronchiectatic form of MAC lung disease be followed up for a sufficient period of time to assess and, if necessary, be treated for disease recurrence.

ACKNOWLEDGMENT

We declare that we have no conflicts of interest.

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