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Clinical Significance of the Differentiation Between *Mycobacterium avium* and *Mycobacterium intracellulare* in *M avium* Complex Lung Disease

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Background: **_Mycobacterium avium_ and _Mycobacterium intracellulare_ are grouped together as the _M avium_ complex; however, little is known about the clinical impact of this species differentiation. This study compared the clinical features and prognoses of patients with _M avium_ and _M intracellulare_ lung disease.**

Methods: **From 2000 to 2009, 590 patients were given a new diagnosis of _M avium_ complex lung disease; 323 (55%) had _M avium_ lung disease, and 267 (45%) had _M intracellulare_ lung disease.**

Results: **Compared with the patients with _M avium_ lung disease, the patients with _M intracellulare_ lung disease were more likely to have the following characteristics: older age (64 vs 59 years, $P = .002$), a lower BMI (19.5 kg/m² vs 20.6 kg/m², $P < .001$), respiratory symptoms such as cough (84% vs 74%, $P = .005$), a history of previous treatment for TB (51% vs 31%, $P < .001$), the fibrocavitary form of the disease (26% vs 13%, $P < .001$), smear-positive sputum (56% vs 38%, $P < .001$), antibiotic therapy during the 24 months of follow-up (58% vs 42%, $P < .001$), and an unfavorable microbiologic response after combination antibiotic treatment (56% vs 74%, $P = .001$).**

Conclusions: **Patients with _M intracellulare_ lung disease exhibited a more severe presentation and had a worse prognosis than patients with _M avium_ lung disease in terms of disease progression and treatment response. Therefore, species differentiation between _M avium_ and _M intracellulare_ may have prognostic and therapeutic implications.** ***CHEST 2012; 142(6):1482–1488***

Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HR = hazard ratio; MAC = *Mycobacterium avium* complex; NTM = nontuberculous mycobacteria

Mycobacterium avium complex (MAC) predominantly consists of *M avium* and *Mycobacterium intracellulare* and is the most frequent etiology of pulmonary disease caused by nontuberculous mycobacteria (NTM).[1,2] *M avium* and *M intracellulare* cannot be differentiated through traditional physical and biochemical tests.[1] Most laboratories and studies report these species as *M avium-intracellulare* or MAC because they are considered to be highly similar, and the clinical features of patients who are infected with these two species are considered indistinguishable.[3-6]

MAC lung disease does not always require antibiotic therapy, and the decision to initiate therapy is

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based on the potential risks and benefits for individual patients.[1,7] Immediate treatment usually is recommended for the fibrocavitary form of MAC lung disease because of progressive lung destruction, whereas the nodular bronchiectatic form of MAC lung disease demonstrates variable disease progression.[1,7] A substantial proportion of patients with the nodular bronchiectatic form of MAC lung disease do not have progressive or severe disease; therefore, they can be closely monitored without long-term antibiotic therapy.[8]

Currently, *M avium* and *M intracellulare* are grouped together as MAC, and the advantage of species differentiation is unclear.[1,2] Limited and conflicting data are available regarding the value of species differentiation between *M avium* and *M intracellulare*.[9-11] Therefore, little is known about the differences in the clinical features, disease progression, and responses to treatment between *M avium* and *M intracellulare* lung disease. MAC lung disease is becoming more common in Korea.[12-14] In this study, we compared the clinical features and prognoses of patients with *M avium* and *M intracellulare* lung disease who had been given this diagnosis within the past 10 years.

Materials and Methods

Study Population

Consecutive patients with MAC lung disease who were given the diagnosis between January 2000 and December 2009 were identified using the database of the NTM Registry of Samsung Medical Center (a 1,950-bed referral hospital in Seoul, South Korea).[12,15] The data from January 2008 to December 2009 are being used in an ongoing prospective observational cohort study to investigate NTM lung disease.[16] This study protocol was approved by the institutional review board of the Samsung Medical Center (IRB approval 2011-10-076).

During this 10-year period, 683 patients were given a diagnosis of MAC lung disease. All met the diagnostic criteria for NTM lung disease according to the guidelines of the American Thoracic Society.[1] After 93 patients with a history of previous NTM lung disease were excluded, 590 patients without a history of prior treatment of NTM lung disease were enrolled in this study.

Microbiologic Examination Data Analysis

Medical records included sputum smears and mycobacterial cultures, which had been performed using standard methods.[12,15] Records described NTM species that were identified using a polymerase chain reaction-restriction fragment length polymorphism method based on the β-subunit of RNA polymerase gene *rpoB*.[17] This genotypic method could accurately discriminate *M avium* and *M intracellulare*. At our institution, this method was used for the entire study period.

The sputum samples were obtained on two or more occasions after the initial presentation. When NTM other than *M avium* and *M intracellulare* were recovered more than twice during the follow-up period, the patients were reclassified as having mixed infection and excluded from the study.

Radiologic Examination Data Analysis

We classified chest radiography and high-resolution CT scan findings obtained at the time of diagnosis as showing either fibrocavitary disease or nodular bronchiectatic disease. When the disease did not belong to either the fibrocavitary form or the nodular bronchiectatic form, it was deemed unclassifiable.[18,19]

Patient Management Data Analysis

MAC lung disease may progress slowly. Furthermore, patients may not require treatment or may require combination antibiotic therapy. After this information was discussed with the patients, an observation period of at least 6 to 12 months without antibiotic treatment usually was implemented. When the disease was clearly recognized as progressive, the patients received combination antibiotic therapy. In patients with serious symptoms and advanced or progressive radiographic abnormalities, antibiotic therapy was initiated immediately.[15] Disease progression was determined by observing patients with MAC lung disease until combination antibiotic therapy was initiated.[20] All the patients who began antibiotic therapy received standardized combination antibiotic therapy, which consisted of oral clarithromycin, rifampin, and ethambutol.[1,2] Streptomycin IM was administered in patients with severe disease.[15]

Sputum conversion was defined as three consecutive negative cultures within 6 months, and the time of conversion was defined as the date of the first negative culture.[15] A favorable microbiologic response was defined as a treatment duration of >12 months and sputum conversion within 12 months. Therefore, patients who received antibiotic therapy for <12 months were excluded from treatment outcome analysis.

Statistical Analysis

All data are presented as medians and interquartile ranges for the continuous variables and as numbers (percentages) for the categorical variables. The data were compared using Student *t* test for the continuous variables and χ^2 test or Fisher exact test for the categorical variables.

The Kaplan-Meier method was used to estimate the cumulative rate for initiating antibiotic therapy. The log-rank test was used to test for a significant difference between the curves. To determine whether *M avium* or *M intracellulare* was associated with disease progression, we performed univariable and multivariable Cox proportional hazard regression analyses. In the multivariable Cox regression model, a priori age, sex, BMI, sputum smear status, and disease type were controlled to compare the adjusted hazard rates between *M avium* and *M intracellulare*.

A multiple logistic regression analysis was used to identify the independent prognostic factors associated with unfavorable outcomes to antibiotic therapy. The variables, including species, dose reduction of clarithromycin, combined use of streptomycin for ≥ 8 weeks, surgical resection, and the a priori potential confounding factors, were added to a multiple logistic regression model in which an unfavorable microbiologic response was the outcome variable. All statistical analyses were performed using SAS, version 9.1 software (SAS Institute Inc); a two-sided $P<.05$ was considered significant.

Results

Clinical Features of MAC Lung Disease

During the 10-year period, 590 patients with MAC lung disease were identified. The etiologic organisms included *M avium* in 323 patients (55%) and

M intracellulare in 267 (45%). Other MAC member species, such as *Mycobacterium colombiense*, were not found during the study period. All patients were HIV negative.

As shown in Table 1, patients with *M intracellulare* lung disease typically were older than patients with *M avium* lung disease (64 years vs 59 years, $P = .002$) and more likely to have a history of TB treatment (51% vs 31%, $P < .001$) and idiopathic pulmonary fibrosis (6% vs 1%, $P < .001$). Respiratory symptoms such as cough (84% vs 74%, $P = .005$), sputum (81% vs 73%, $P = .023$), and weight loss (6% vs 3%, $P = .035$) were more common in patients with *M intracellulare* lung disease than in those with *M avium* lung disease.

The erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) level at the time of diagnosis were significantly higher in patients with *M intracellulare* lung disease than in those with *M avium* lung disease (ESR, 33 mm/h vs 25 mm/h [$P = .001$]; CRP, 0.29 mg/dL vs 0.14 mg/dL [$P < .001$]). Patients with *M intracellulare* lung disease typically had a higher percentage of sputum smear results that were positive for acid-fast bacilli (56% vs 38%, $P < .001$). The fibrocavitary form was more common (26% vs 13%) than the nodular bronchiectatic form (64% vs 74%) in patients with *M intracellulare* lung disease ($P < .001$) (Table 1).

Progression to the Initiation of Antibiotic Treatment

The median follow-up duration did not differ between the patients with *M avium* lung disease (39 months) and those with *M intracellulare* lung disease (38 months, $P = .910$). During the follow-up period, the proportion of patients who required combination antibiotic therapy was higher among those with *M intracellulare* lung disease ($P < .001$) (Fig 1). The cumulative rate for initiating antibiotic therapy at 24 months in patients with *M intracellulare* lung disease was 58% (95% CI, 52%-64%) vs 42% (95% CI, 36%-47%) in patients with *M avium* lung disease ($P < .001$).

These differences remained significant after an adjustment using Cox regression for differences in age, sex, BMI, sputum smear status, and radiologic type. *M intracellulare* infection was an independent prognostic factor in the progression to the initiation of antibiotic treatment (adjusted hazard ratio [HR], 1.36; 95% CI, 1.09-1.70; $P = .007$) (Table 2). In addition, patients with positive sputum smears (adjusted HR, 1.43; 95% CI, 1.13-1.81; $P = .003$) and those

Table 1—*Baseline Characteristics of the Patients With* Mycobacterium avium *and* Mycobacterium intracellulare *Lung Disease*

Characteristic	*M avium* (n = 323)	*M intracellulare* (n = 267)	*P* Value
Male sex	142 (44)	132 (49)	.184
Age, y	59 (50-67)	64 (53-71)	.002
BMI, kg/m^2	20.6 (19.2-22.5)	19.5 (17.4-21.1)	< .001
Nonsmoker	234 (72)	177 (67)	.120
Associated diseases			
Previous TB	99 (31)	137 (51)	< .001
Bronchiectasis	251 (78)	185 (69)	.020
COPD	24 (7)	29 (11)	.147
IPF	2 (1)	16 (6)	< .001
Malignancy	62 (19)	46 (17)	.539
Chronic heart disease	53 (16)	41 (15)	.728
Diabetes mellitus	36 (11)	24 (9)	.388
Chronic liver disease	17 (5)	17 (6)	.567
Symptoms			
Cough	240 (74)	224 (84)	.005
Sputum	237 (73)	217 (81)	.023
Hemoptysis	76 (24)	59 (22)	.680
Weight loss	9 (3)	17 (6)	.035
Fever	5 (2)	5 (2)	.761
Laboratory findings			
Positive AFB smear	124 (38)	149 (56)	< .001
ESR, mm/h	25 (14-45)	33 (18-64)	.001
CRP, mg/dL	0.14 (0.04-0.55)	0.29 (0.07-1.45)	< .001
Type of disease			< .001
Fibrocavitary	42 (13)	70 (26)	
Nodular bronchiectatic	239 (74)	170 (64)	
Unclassifiable	42 (13)	27 (10)	

Data are presented as median (interquartile range) or No. (%). AFB = acid-fast bacilli; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IPF = idiopathic pulmonary fibrosis.

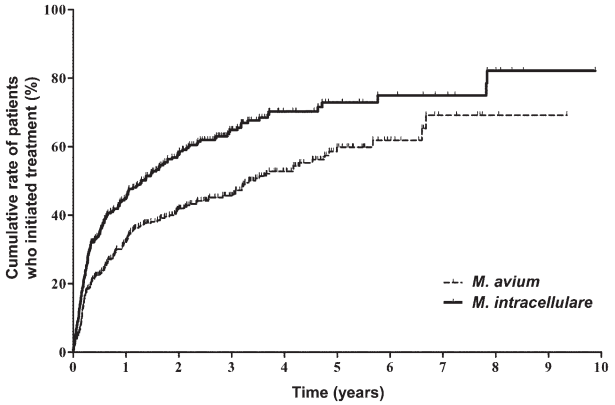

FIGURE 1. Kaplan-Meier curves of the probability of initiating antibiotic treatment in patients with *Mycobacterium avium* complex lung disease. The proportion of patients who received antibiotic treatment was higher in those with *Mycobacterium intracellulare* disease than in those with *M avium* disease ($P < .001$). *M* = *Mycobacterium.*

with the fibrocavitary form (adjusted HR, 2.84; 95% CI, 2.14-3.78; $P < .001$) were more likely to receive antibiotic treatment. Conversely, older patients were less likely to receive antibiotic treatment during the follow-up period (adjusted HR, 0.76; 95% CI, 0.61-0.95; $P = .018$).

Treatment Outcomes

Combination antibiotic therapy was initiated in 330 patients by the end of August 2011. Of these patients, 35 who received antibiotic therapy for < 12 months and who were still being treated were excluded from further analysis. Of the remaining 295 patients (158 with *M intracellulare* lung disease, 137 with *M avium* lung disease), the overall favorable microbiologic response was significantly lower in patients with *M intracellulare* lung disease (88 of 158 [56%]) than in those with *M avium* lung disease (102 of 137 [74%], $P = .001$).

After adjusting for potential confounding factors, the final multiple logistic regression model revealed that *M intracellulare* infection (adjusted OR, 1.91; 95% CI, 1.09-3.34; $P = .024$), age > 60 years (adjusted OR, 1.87; 95% CI, 1.06-3.32; $P = .031$), and the fibrocavitary form (adjusted OR, 2.00; 95% CI, 1.05-3.82; $P = .035$) were independently associated with an unfavorable microbiologic response (Table 3).

DISCUSSION

This study examined > 500 patients with MAC lung disease and focused primarily on the clinical relevance of species differentiation between *M avium* and *M intracellulare*. In the present cohort of patients with MAC without HIV infection, *M avium* and *M intracellulare* differed in the clinical features, disease progression, and treatment response to antibiotic therapy. Patients with *M intracellulare* lung disease exhibited a more severe and advanced clinical presentation at the time of diagnosis, were more likely to receive antibiotic treatment during the follow-up period, and had lower treatment response rates than those with *M avium* lung disease.

The epidemiologic data suggest that the incidence and prevalence of MAC infections are increasing in many countries.[21-26] *M avium* and *M intracellulare* are infrequently differentiated in clinical practice and the medical literature; however, these mycobacteria exhibit a significantly different pathogenicity and biology.[11] The majority of AIDS-related MAC infections are due to *M avium*, and disseminated *M avium* infections typically occur only after the $CD4^+$ T-lymphocyte count is < 50/μL, which suggests that cellular immunodeficiency is a risk factor for *M avium* (but not for *M intracellulare*) infection.[27] A previous study using an animal model suggested that *M intracellulare* was more virulent than *M avium*.[28]

We found that patients with *M intracellulare* lung disease are more likely to have had fibrocavitary disease; therefore, more patients have smear-positive sputum specimens. The ESR and serum CRP level were

Table 2—*Predictors of the Progression to the Initiation of Antibiotic Therapy in Patients With* M avium *Complex Lung Disease*

	Univariable Cox Regression		Multivariable Cox Regression	
Predictor	HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Male sex	1.39 (1.12-1.72)	.003	1.07 (0.83-1.36)	.609
Age > 60 y	0.90 (0.72-1.11)	.322	0.76 (0.61-0.95)	.018
BMI < 18.5 kg/m²	1.43 (1.13-1.82)	.003	1.15 (0.89-1.48)	.292
M intracellulare	1.56 (1.26-1.94)	< .001	1.36 (1.09-1.70)	.007
Sputum AFB smear (+)	1.91 (1.53-2.37)	< .001	1.43 (1.13-1.81)	.003
Type of disease				
Nodular bronchiectatic	1.00	Reference	1.00	Reference
Fibrocavitary	3.53 (2.75-4.52)	< .001	2.84 (2.14-3.78)	< .001
Unclassifiable	1.10 (0.75-1.60)	.625	1.23 (0.83-1.81)	.304

HR = hazard ratio. See Table 1 legend for expansion of other abbreviations.

Table 3—*Predictors of Unfavorable Treatment Responses in Patients With* M avium *Complex Lung Disease*

Patient Characteristic	Favorable Response (n = 190)	Unfavorable Response (n = 105)	Univariable Analysis *P* Value	Multivariable Logistic Regression	
				Adjusted OR (95% CI)	*P* Value
Male sex	83 (44)	69 (66)	< .001	1.67 (0.93-2.98)	.087
Age > 60 y	87 (46)	68 (65)	.002	1.87 (1.06-3.32)	.031
BMI < 18.5 kg/m^2	46 (24)	44 (42)	.002	1.70 (0.95-3.06)	.076
M intracellulare	88 (46)	70 (67)	.001	1.91 (1.09-3.34)	.024
Type of disease					
Nodular bronchiectatic	132 (69)	45 (43)	Reference	1.00	Reference
Fibrocavitary	41 (22)	48 (46)	< .001	2.00 (1.05-3.82)	.035
Unclassifiable	17 (9)	12 (11)	.079	2.08 (0.84-5.13)	.114
Sputum AFB smear (+)	107 (56)	77 (73)	.004	1.57 (0.84-2.93)	.163
Dose reduction of clarithromycin	20 (11)	9 (9)	.589	0.53 (0.21-1.36)	.185
Combined use of streptomycin ≥ 8 wk	112 (59)	58 (55)	.537	0.61 (0.34-1.10)	.099
Surgical resection	6 (3)	6 (6)	.358	2.34 (0.66-8.35)	.190

Data are presented as No. (%), unless otherwise indicated. See Table 1 legend for expansion of abbreviations.

significantly increased in patients with *M intracellulare* lung disease compared with those with *M avium* lung disease. Chronic inflammation may have contributed to a more severe and advanced clinical presentation at the time of diagnosis in patients with *M intracellulare* lung disease.

MAC lung disease does not always require antibiotic therapy.[1,7] However, treatment of MAC lung disease may require long-term antibiotic treatment. Patients may meet the diagnostic criteria but not have progressive or severe disease; therefore, these patients are closely monitored with regular sputum collection.[1] In a recent study, long-term antibiotic therapy was administered to < 20% of patients in the United States and about 50% of patients in Canada and South Korea after being given a diagnosis of MAC lung disease.[15,24,29] Even after disease recognition, physicians may opt for a wait-and-see approach before prescribing antibiotics because of the reported low treatment efficacy and high drug toxicity.[24] This approach is the treatment practice at our hospital. During the study, antibiotic treatment typically was started after a diagnosis in patients with the fibrocavitary form of MAC lung disease; however, antibiotic treatment was frequently initiated in patients with the nodular bronchiectatic form of MAC lung disease after the recognition of disease progression during follow-up.

Patients may remain in a stable condition for years or may progress rapidly.[1,2] However, there are few studies in which patients with well-defined characteristics exhibit disease progression.[8] Currently, there is no consensus regarding the treatment of patients with MAC lung disease. A study in Japan found that 60% of patients with nodular bronchiectatic MAC lung disease demonstrated disease progression, whereas 40% of patients were stable during a mean observation period of 28 months.[8] Several studies suggest that bacterial virulence plays an important role in the development and progression of invasive MAC infection; however, a direct comparison of virulence between *M avium* and *M intracellulare* was not available.[30,31] In the present study, *M intracellulare* infection was newly identified as an important predictor of progression to the initiation of treatment among patients with MAC lung disease.

To our knowledge, this analysis is the first to demonstrate that the treatment response rate is lower in *M intracellulare* lung disease than in *M avium* lung disease in patients who received the same standardized combination antibiotic therapy. Previous clinical studies that evaluated the treatment efficacy of macrolide-based antibiotic regimens or assessed the prognostic factors for MAC lung disease did not distinguish between *M avium* and *M intracellulare* lung disease.[2,3,32,33] Our previous small-scale study suggested that the treatment response rate was slightly lower in patients with *M intracellulare* than in those with *M avium* lung disease, but this was not statistically significant.[15] The current study included approximately 300 patients with MAC lung disease who received combination antibiotics for > 12 months. We demonstrated that *M intracellulare* infection was independently associated with an unfavorable microbiologic response. Interestingly, a previous study of 51 patients with macrolide-resistant MAC lung disease revealed that the majority (77%) of isolates were *M intracellulare* rather than *M avium*, and *M intracellulare* strains were more common among the isolates from fibrocavitary disease than among those from nodular bronchiectatic disease.[5]

The present study has several limitations. First, it was conducted at a single center; therefore, it was not representative of Korea because of referral bias. Second, the decision to initiate long-term combination antibiotic therapy did not depend on firmly

established objective criteria. However, we believe that the probability of referral to our hospital and the decision to initiate antibiotic therapy were distributed equally among patients with *M avium* vs *M intracellulare* lung disease.

In summary, patients with *M intracellulare* lung disease exhibited a more severe and advanced clinical presentation at the time of diagnosis and had a worse prognosis than patients with *M avium* lung disease in terms of disease progression and treatment response. Therefore, species differentiation between *M avium* and *M intracellulare* may have prognostic and therapeutic implications. Additional studies are warranted to verify these findings.

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Dr Koh: contributed to the study design, data acquisition and interpretation, study supervision, and writing of the manuscript.
Dr Jeong: contributed to the study design, data acquisition and interpretation, and writing of the manuscript.
Dr Jeon: contributed to the data acquisition and interpretation and critical revision and final approval of the manuscript.
Dr N. Y. Lee: contributed to the data acquisition and interpretation and critical revision and final approval of the manuscript.
Dr K. S. Lee: contributed to the data acquisition and interpretation and critical revision and final approval of the manuscript.
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