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A shorter treatment duration may be sufficient for patients with *Mycobacterium massiliense* lung disease than with *Mycobacterium abscessus* lung disease☆

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Summary
Background: *Mycobacterium abscessus* complex is the second most common organism isolated from patients with nontuberculous mycobacterial (NTM) lung disease in South Korea. This study aimed to compare clinical features and treatment outcomes of *M. abscessus* and *Mycobacterium massiliense* lung disease.
Methods: We retrospectively identified stored clinical isolates of *M. abscessus* complex as either *M. abscessus* or *M. massiliense* and reviewed medical records to compare clinical characteristics and treatment responses. All patients were treated empirically over several months with multidrug regimens, including a macrolide and one or more parenteral agents.
Results: Of the 249 patient isolates tested, 128 (59 with *M. abscessus* and 69 with *M. massiliense*) met the American Thoracic Society diagnostic criteria for NTM pulmonary disease, and treatment outcomes were analyzed in 48 patients (26 with *M. abscessus* and

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22 with *M. massiliense*). The clinical and radiologic findings were similar between the two groups. Although the durations of parenteral and total treatment were significantly shorter in patients with *M. massiliense* than in those with *M. abscessus* (4.7 months vs 7.4 months, $P = .006$, and 12.1 months vs 16.3 months, $P = .043$), the treatment success rate was significantly higher in patients with *M. massiliense* (95.5%) than in *M. abscessus* cases (42.3%, $P < .001$).

Conclusion: Patients with *M. massiliense* pulmonary infection responded better to this antibiotic strategy than those with *M. abscessus* infection. A shortened duration of treatment may be sufficient for *M. massiliense* pulmonary infection.

Introduction

Nontuberculous mycobacteria (NTM), which includes rapidly growing mycobacteria (RGM), are ubiquitous organisms increasingly emerging as important human pathogens [1,2]. In Korea, *Mycobacterium abscessus* complex is the most frequent RGM causing chronic lung disease [3]. *M. abscessus* complex is also notable for its resistance to first-line anti-tuberculosis drug and treatment difficulty with poor clinical outcomes [4]. In 2007, the American Thoracic Society (ATS) recommended periodic administration of multidrug therapy for affected cases, including a macrolide and one or more parenteral agents (amikacin, cefoxitin, or imipenem), or a combination of parenteral agents, over several (2–4) months [1]. However, these treatments are quite difficult and there are no established optimal treatment regimens showing good long-term outcomes [5]. *M. abscessus* complex is the second most commonly isolated NTM in Korea. In addition, the prevalence of chronic lung disease due to *M. abscessus* complex is increasing in South Korea [3].

For a long time, *M. abscessus*, *Mycobacterium massiliense*, and *Mycobacterium bolletii* had been thought to represent subgroups of a single species because of an overlap in biochemical and genetic properties. However, in 2006, two of these RGM species, *M. massiliense* and *M. bolletii*, have been separated from *M. abscessus* based on <97% *rpoB* gene sequence homology [6]. Recently, in 2011, *M. massiliense* and *M. bolletii* were united and reclassified as a single subspecies within *M. abscessus*: *M. abscessus* subsp. *bolletii* comb. nov [7]. However, the placement of *M. massiliense* within the boundary of *M. abscessus* subsp. *bolletii* remains highly controversial with regard to clinical aspects. Therefore, we used the old taxonomy instead of new one. In Korea, *M. abscessus* and *M. massiliense* infections present in almost equal numbers, whereas *M. bolletii* is very rare. Two recent studies have reported that patients with *M. massiliense* infections had significantly better treatment responses to combination antibiotic therapy than those with *M. abscessus* infections [8,9]. The aim of the present study was to evaluate the differences in the clinical characteristics and treatment outcomes between *M. massiliense* and *M. abscessus* pulmonary infections in a Korean population.

Materials and methods

Study population

Patients who were diagnosed with *M. abscessus* complex lung disease and who were treated based on 2007 ATS guidelines from January 2006 to June 2012 at the Asan Medical Center (Seoul, South Korea) were retrospectively evaluated. Clinical, radiological, and microbiological characteristics, management, and treatment outcome data were retrospectively collected from medical records. Initial standard posteroanterior and lateral chest radiographs (CXRs) and computed tomography (CT) results were reanalyzed based on seven categories: bronchiectasis, bronchiolitis, cavities, consolidation, bilateral involvement, multilobar involvement (≥3 lobes with abnormalities), and type of disease (nodular bronchiectatic form, upper lobe cavitary form, and unclassifiable form). This study was approved by the Institutional Review Board of the Asan Medical Center. Informed consent was waived because of the retrospective nature of the study.

Microbiological examination

Acid-fast bacilli (AFB) were cultured in both solid Ogawa medium (Korean Institute of Tuberculosis, Osong, Korea) and a liquid MGIT system (Becton Dickinson, Sparks, MD). Cultured isolates were identified as *Mycobacterium tuberculosis* or NTM using the Duplex PCR test (Seegene Inc., Seoul, Korea). NTM species were identified using a polymerase chain reaction-restriction fragment length polymorphism method, based on the *rpoB* gene [10]. Further differentiation among *M. abscessus* complex members was performed at the Department of Microbiology, Seoul National University College of Medicine (Seoul, Korea) using sequence analysis targeting the *rpoB* and *hsp65* genes [8]. The *in vitro* antimicrobial susceptibility of *M. abscessus* was tested using a commercial kit (Sensititre; TREK Diagnostic Systems, Cleveland, OH) and interpreted according to the Clinical and Laboratory Standards Institute (CLSI) document M24-A of 2003 [11].

We defined "persistent culture conversion" as the first negative sputum culture with at least one subsequent negative culture and no subsequent positive results during

treatment, and "initial sputum culture conversion" as the first negative sputum culture with at least one subsequent negative culture regardless of reversion thereafter. Microbiological relapse was defined as two consecutive positive cultures after sputum conversion [12].

Patient management

As described in a previous report [13], all of our study patients were treated according to ATS guidelines. The treatment regimen comprised a multidrug therapy, including a macrolide and one or more parenteral agents over 2—4 months. At treatment initiation, information on the differentiation between *M. abscessus* and *M. massiliense* was unavailable and only became so in 2011. The expected durations of cefoxitin/imipenem treatment, amikacin treatment, and total treatment were 2—4 months, 6 months, and more than 12 months (1 year after culture conversion), respectively. However, the decision on the actual treatment duration was made by the attending physicians, considering the timing of culture conversion, drug adverse reactions, concomitant diseases, and so on. In the case of localized disease, surgical treatment was also considered.

Assessment of treatment outcomes

Treatment outcomes were evaluated until December 31st, 2013. Treatment outcomes were classified as treatment success, failure, or default. "Treatment success" was defined to satisfy all of the following criteria: (1) culture conversion; (2) clinical improvement; (3) minimum duration of medication at least 6 months; and (4) treatment completion to the satisfaction of the attending physician. The time of conversion was defined as the date of the first negative culture. If the patient could not expectorate sputum, it was considered that the sputum had converted to negative. Clinical improvement was defined as an improvement in clinical symptoms and a decrease or at least no change in abnormal shadows on chest radiography or CT scanning. "Failure" was defined as failure to convert to negative sputum culture after treatment for 6 months or more and an absence of clinical improvement. "Default" was defined as interruption of treatment for more than 2 consecutive months. "Relapse" was defined as more than two consecutive positive cultures after treatment completion. Patients were examined every 2 weeks for 1 month and then every 1—2 months for the whole duration of treatment. Sputum AFB smear/culture and chest radiography were requested at each visit. After completion of treatment, patients were followed up clinically and radiologically, and bacteriologically if necessary, every 3—6 months [13].

Data analysis

Results are presented as the mean ± standard deviation (SDs). Differences between categorical variables were assessed using the chi-squared test or Fisher's exact test, as appropriate, and differences between continuous variables were explored using the unpaired *t*-test. A *P* value $<.05$ was considered statistically significant. Multivariate analysis was not performed because of the small sample size. All statistical analyses were performed using SPSS Version 13 for Windows (SPSS Inc., Chicago, IL) and Microsoft Excel 7.0 (Microsoft Corporation, Redmond, WA).

Results

Baseline clinical characteristics

From January 2006 to June 2012, *M. abscessus* complex clinical isolates from 249 patients were kept in storage, allowing sequence analysis. Sequence analysis of the *rpoB* and *hsp65* genes of these 249 clinical isolates of *M. abscessus* complex resulted in the identification of 113 *M. abscessus* isolates (45.4%) and 136 *M. massiliense* isolates (54.6%). There were no *M. bolletii* isolates. Of the isolates from 249 patients, 128 patients (59 with *M. abscessus* and 69 with *M. massiliense*) met the diagnostic criteria for NTM pulmonary disease according to ATS guidelines (Fig. 1). Of

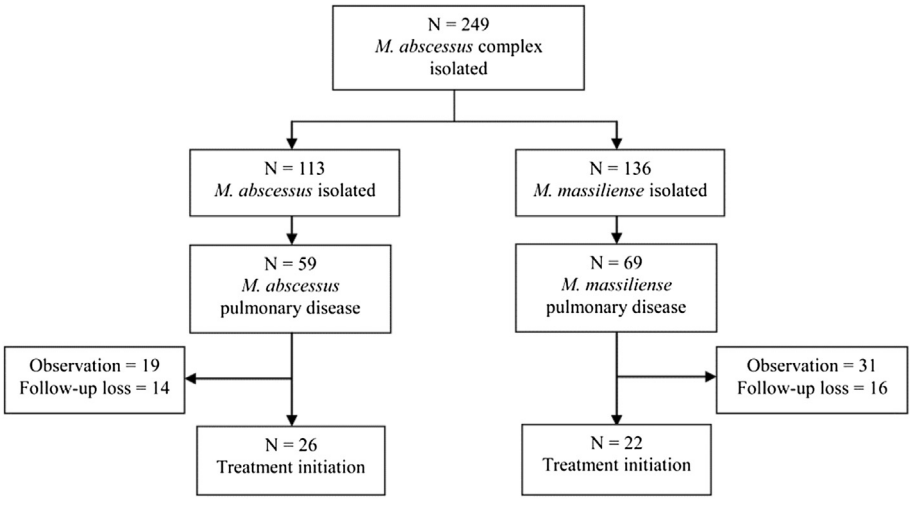

Figure 1 Flow diagram of progress through the phases of this study.

Table 1 Baseline clinical characteristics of the 48 patients with *Mycobacterium abscessus* complex pulmonary disease.

Patient characteristics	*M. abscessus* $n = 26$ (%)	*M. massiliense* $n = 22$ (%)	Total $n = 48$ (%)	*P* value
Age, years, mean ± SD	56.8 ± 11.1	58.8 ± 12.4	57.7 ± 11.6	.558
Gender, female	17 (65.4)	18 (81.8)	35 (72.9)	.202
BMI, kg/m^2, mean ± SD	20.4 ± 2.7	20.0 ± 3.0	20.2 ± 2.8	.641
Previous pulmonary tuberculosis	12 (46.2)	9 (40.9)	21 (43.8)	.715
Never smoker	21 (80.8)	20 (90.9)	41 (85.4)	.429
FVC, % predicted, mean ± SD	75.5 ± 16.3	79.9 ± 16.5	77.3 ± 16.3	.424
FEV_1, % predicted, mean ± SD	73.6 ± 19.3	83.6 ± 18.4	77.7 ± 19.3	.125
AFB smear positive	22 (84.6)	17 (77.3)	39 (81.3)	.713
Symptoms				
Cough	17 (65.4)	18 (81.8)	35 (72.9)	.202
Sputum	22 (84.6)	17 (77.3)	39 (81.3)	.713
Hemoptysis	10 (38.5)	13 (59.1)	23 (47.9)	.154
Dyspnea	8 (30.8)	11 (50.0)	19 (39.6)	.175
Easy fatigability	11 (42.3)	5 (22.7)	16 (33.3)	.152

Abbreviations: SD, standard deviation; BMI, body mass index; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; AFB, acid-fast bacilli.

the 128 patients who met our study criteria, 26 with *M. abscessus* and 22 with *M. massiliense* infections received parenteral antimicrobial treatment. We compared clinical characteristics and treatment outcomes between the 26 patients with *M. abscessus* and 22 patients with *M. massiliense* infections. Table 1 summarizes the baseline characteristics of the patients. No significant differences were found between the *M. abscessus* and *M. massiliense* groups in any of the baseline characteristics, including demographic data and respiratory symptoms. The radiographic findings were generally similar in both groups. Patients with *M. abscessus* had nearly twice the frequency of cavitation but the difference was not statistically significant (Table 2).

Drug susceptibility tests (DSTs) were performed on 38 isolates of *M. abscessus* complex recovered from 48 patients (Table 3). *M. abscessus* was susceptible to amikacin (100%), cefoxitin (95.5%), and clarithromycin (95.5%), and *M. massiliense* was susceptible to amikacin (100%), cefoxitin (81.3%), and clarithromycin (100%) without statistical significance.

Antimicrobial treatment

As described in a previous report [13], all patients were treated according to ATS guidelines [1], and the treatment regimen was individualized based on patient tolerance (Table 4). The multidrug therapy consisted of a macrolide and one or more parenteral agents (amikacin and/or cefoxitin/imipenem) over 2–4 months. In all patients, clarithromycin (1000 mg/day) was selected as the first choice; in six patients, clarithromycin was replaced by azithromycin (250 mg/day) because of adverse reactions, mainly gastrointestinal problems. The durations of parenteral and total treatment were significantly shorter in the patients with *M. massiliense* than in those with *M. abscessus* (4.7 months and 7.4 months, $P = .006$, and 12.1 months and 16.3 months, $P = .043$, respectively).

Surgical treatment

Nine of our patients (18.8%), eight with *M. abscessus* infection and one with *M. massiliense* infection, underwent

Table 2 Baseline chest CT findings of the 48 study patients with *Mycobacterium abscessus* complex pulmonary disease.

Chest CT findings	*M. abscessus* $n = 26$ (%)	*M. massiliense* $n = 22$ (%)	Total $n = 48$ (%)	*P* value
Bronchiectasis	25 (96.2)	18 (81.8)	43 (89.6)	.165
Bronchiolitis	25 (96.2)	20 (90.9)	45 (93.8)	.587
Cavities	9 (34.6)	4 (18.2)	13 (27.1)	.202
Consolidation	16 (61.5)	11 (50.0)	27 (56.3)	.422
Bilateral involvement	20 (76.9)	16 (72.7)	36 (75.0)	.738
Multilobar (≥3 lobes)	21 (80.8)	17 (77.3)	38 (79.2)	.766
Type of disease				
Nodular bronchiectatic form	17 (65.4)	18 (81.8)	35 (72.9)	
Upper lobe cavitary form	8 (30.8)	3 (13.6)	11 (22.9)	.371
Unclassifiable form	1 (3.8)	1 (4.5)	2 (4.2)	

Abbreviations: CT, computed tomography.

Table 3 *In Vitro* susceptibility test results of 22 *Mycobacterium abscessus* and 16 *Mycobacterium massiliense* isolates from the study cohort.

Drug	Species	No. (%) of isolates			*P* value
		Susceptible	Intermediate	Resistant	
Clarithromycin	*M. abscessus*	21 (95.5)	0	1 (4.5)	1.00
	M. massiliense	16 (100.0)	0	0	
Amikacin	*M. abscessus*	20 (90.9)	2 (9.1)	0	1.00
	M. massiliense	14 (87.5)	2 (12.5)	0	
Cefoxitin	*M. abscessus*	2 (9.1)	19 (86.4)	1 (4.5)	.326
	M. massiliense	2 (12.5)	11 (68.8)	3 (18.8)	
Ciprofloxacin	*M. abscessus*	2 (9.1)	4 (18.2)	16 (72.7)	.387
	M. massiliense	0 (0.0)	2 (12.5)	14 (87.5)	
Linezolid	*M. abscessus*	15 (68.2)	3 (13.6)	4 (18.2)	.438
	M. massiliense	11 (68.8)	4 (25.0)	1 (6.3)	

Drugs and breakpoints are listed according to the recommendations contained in the NCCLS document M24-A2.

adjunctive surgical resection during medical treatment, and seven of these nine patients (77.8%) successfully completed treatment. The most common indication for surgery was culture conversion failure (8 patients, 88.9%). Two patients had two surgical procedures, and a total of seven lobectomies, two pneumonectomies, one segmentectomy, and one wedge resection were performed. Postoperative complications occurred in two patients (22.2%), including postoperative pneumonia in one and bronchopleural fistula and wound dehiscence in the other. All patients continued antibiotic therapy postoperatively.

Treatment outcomes

Among our 128 included patients, 50 had been observed without treatment and 30 were lost to follow-up (Fig. 1). A final cohort of 48 patients was therefore included in our treatment outcome analysis (Table 5). Both symptomatic and radiographic improvement rates were lower for patients with *M. abscessus* infection than for those with *M. massiliense* infection (50.0% vs 81.8%, $P = .022$, and 34.6% vs 72.7%, $P = .008$, respectively). Cultures persistently converted to negative in 32 patients (66.7%) at a mean duration of 114 ± 185 days. The persistent culture conversion rate was lower in patients with *M. abscessus* infection than in those with *M. massiliense* infection (42.3% and 95.5%, respectively; $P = .029$) and the time to negative culture conversion was shorter in the *M. massiliense* group (42 ± 13 days) than in the *M. abscessus* group (239 ± 78 days) ($P = .030$). Initial culture conversion and then reversion was observed in 8 (30.8%) and 1 (4.5%) patients, respectively.

The treatment success, failure, and default rates were 42.3% (11/26), 42.3% (11/26), and 15.4% (4/26), in *M. abscessus* group, and 95.5% (21/22), 4.5% (1/22), and 0% (0/22), in *M. massiliense* group, respectively. The treatment success rate was higher in patients with *M. massiliense* infection than in those with *M. abscessus* infection (95.5% [21/22] vs 42.3% [11/26], $P < .001$). The rate of successful treatment completion without relapse was also higher in patients with *M. massiliense* disease than in patients with *M. abscessus* disease (77.3% [17/22] vs 30.8% [8/26], $P < .05$) during the follow-up period (mean 1087 ± 848 days, range 52—2756 days).

Discussion

Since *M. massiliense* was distinguished as a separate organism from *M. abscessus*, only two studies have compared

Table 4 Treatment modalities for *Mycobacterium abscessus* and *Mycobacterium massiliense* lung disease.

Treatment modality	*M.abscessus* $n = 26$ (%)	*M.massiliense* $n = 22$ (%)	Total $n = 48$ (%)	*P* value
Surgical treatment	8 (30.8)	1 (4.5)	9 (18.8)	.024
Medical treatment				
Macrolide/amikacin/cefoxitin	10 (38.5)	9 (40.9)	19 (39.6)	
Macrolide/amikacin/imipenem	8 (30.8)	4 (18.2)	12 (25.0)	
Macrolide/amikacin	4 (15.4)	7 (31.8)	11 (22.9)	
Macrolide/cefoxitin	2 (7.7)	2 (9.1)	4 (8.3)	
Macrolide/imipenem	2 (7.7)	0	2 (4.2)	
Clarithromycin/azithromycin	23/3	19/3	42/6	
Duration of parenteral treatment, month, mean ± SD	7.4 ± 3.9	4.7 ± 2.5	6.0 ± 3.6	.006
Total duration of treatment, month, mean ± SD	16.3 ± 11.6	12.1 ± 4.4	14.3 ± 9.4	.043

Abbreviations: SD, standard deviation.

Table 5 Treatment responses of the study patients with *Mycobacterium abscessus* and *Mycobacterium massiliense* lung disease.

Treatment response	*M.abscessus* $n = 26$ (%)	*M.massiliense* $n = 22$ (%)	Total $n = 48$ (%)	*P* value
Symptomatic response				.022
Improved	13 (50.0)	18 (81.8)	31 (64.6)	
Unchanged	13 (50.0)	4 (18.2)	17 (35.4)	
Radiographic response				.008
Improved	9 (34.6)	16 (72.7)	25 (52.1)	
Unchanged	9 (34.6)	6 (27.3)	15 (31.3)	
Worsened	8 (30.8)	0 (0.0)	8 (16.6)	
Microbiologic response				.029
Persistent culture conversion	11 (42.3)	21 (95.5)	32 (66.7)	
Initial culture conversion and reversion	8 (30.8)	1 (4.5)	9 (18.8)	
Failure of culture conversion	7 (26.9)	0 (0.0)	7 (14.6)	
Time to culture conversion, day, mean ± SD	239 ± 78	42 ± 13	114 ± 185	.030
Successful treatment completion	11 (42.3)	21 (95.5)	32 (66.7)	.000
Relapse	3/11 (27.3)	4/21 (19.0)	7/32 (21.9)	.667
Time to relapse, day, mean ± SD	131 ± 94	491 ± 259	336 ± 271	.074

Abbreviations: SD, standard deviation.

the clinical characteristics and treatment responses of *M. abscessus* and *M. massiliense* infections [8,9]. Our present data reconfirmed that patients with *M. massiliense* infections showed more a favorable response to the same combination antibiotic therapy than those with *M. abscessus* infections. However, the previous report did not present information that would support shorter treatment duration for *M. massiliense* lung disease than for *M. abscessus* lung disease. Moreover, our present study demonstrated a significantly shorter duration of treatment and time to negative culture conversion in patients with *M. massiliense* than in cases with *M. abscessus*. From a clinical point of view, these data suggest that the treatment guidelines for infected patients may be differentially developed based on the causative organisms: *M. massiliense* vs *M. abscessus*. To the best of our knowledge, this is the first study to focus primarily on the treatment duration of the species differentiation between *M. abscessus* and *M. massiliense*.

Traditionally, *M. abscessus* lung disease has been associated with substantial morbidity and mortality. Hence, it has been regarded as a chronic incurable infection with current combination antibiotic treatments [1,2]. Moreover, the ATS guidelines comment that the goal of 12 months of negative sputum cultures while on therapy may be reasonable. However, after completion of intravenous drug therapy, oral therapy is extremely limited, and could include a macrolide, linezolid, or possibly other agents. Nevertheless, the effectiveness of macrolide is limited because of inducible resistance, and it is unclear if there is any reliable effective oral drug [1]. Therefore, the optimal regimen and duration of treatment for *M. abscessus* complex lung diseases after completion of intravenous drug remain unclear.

Our present study findings reconfirmed that the favorable microbiological response rate is higher in patients with *M. massiliense* infection than in *M. abscessus* cases. Our current data have demonstrated a significantly shorter treatment duration and time to negative culture conversion in patients with *M. massiliense* than in those with *M. abscessus*. Moreover, in more than half of our *M. massiliense* patients ($n = 13$), negative culture conversion occurred within 1 month of treatment initiation. This indicates that treatment of *M. massiliense* lung disease may be easier and can be of shorter duration than that of *M. abscessus*. In our hospital, the differentiation of these two bacterial subtypes was not part of routine practice until 2011. Accordingly, we treated the affected patients until 2012 without knowing the subtype of *M. abscessus* complex. Hence, the significantly shorter duration of treatment in patients with *M. massiliense* disease could be because the clinicians decided to complete the treatment earlier based on a favorable treatment response and rapid culture conversion. From a clinical stand point, our present data may suggest the possibility of shortening the treatment duration for *M. massiliense* infection. Additional studies are needed to access the effectiveness of a shortened treatment duration for *M. massiliense* lung disease.

Inducible resistance to clarithromycin may explain the poor treatment outcomes seen in patients with *M. abscessus* lung disease. Koh et al. [8] reported that all *M. abscessus* isolates showed inducible resistance to clarithromycin, unlike *M. massiliense* isolates. These authors found that the induction of the erythromycin ribosome methyltransferase gene (erm [41]) led to macrolide resistance in *M. abscessus* infection but not in *M. massiliense* infection. Such a difference in inducible resistance could explain the better treatment outcomes of *M. massiliense* lung disease cases. In our present study, we did not test for inducible resistance to clarithromycin and further investigations are needed to address this issue.

Azithromycin may be a better option for treating *M. abscessus* infection than clarithromycin, whereas both macrolides appear to be reasonable options for treating *M. massiliense* infection. A recent report compared the activity of clarithromycin and azithromycin in experimental models, and found that the azithromycin treatment showed

greater efficacy than clarithromycin against *M. abscessus* infection because clarithromycin is a more potent inducer of erm (41) expression than azithromycin in *M. abscessus* [14]. In our present study, clarithromycin was initially selected as the first treatment choice, and only six patients received azithromycin instead of clarithromycin because of an adverse reaction. Therefore, it was impossible to compare the treatment responses of the clarithromycin-treated and azithromycin-treated groups in this study. Prospective controlled trials are needed to assess the effectiveness of azithromycin instead of clarithromycin in patients with *M. abscessus* infection.

Our present report has several limitations inherent to its retrospective and single-center study design. The number of enrolled patients was small and the definition of treatment outcomes were arbitrarily chosen because no standardized definitions are yet available. Moreover, the follow-up duration after treatment completion was insufficient to determine relapse rate. We could however reconfirm from our present data that patients in Korea with a *M. massiliense* infection showed more successful treatment outcomes than those with *M. abscessus* infections. The treatment duration was also significantly shorter in patients with *M. massiliense* infection than in those with *M. abscessus* infection. Future studies focusing on optimal treatment durations are needed for patients infected with these bacteria.

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Conflicts of interest

All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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