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CLINICAL THERAPEUTICS

Clinical Characteristics and Treatment Outcomes of Patients with Macrolide-Resistant *Mycobacterium massiliense* Lung Disease

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ABSTRACT Macrolide antibiotics are cornerstones in the treatment of *Mycobacterium massiliense* lung disease. Despite the emergence of resistance, limited data on macrolide-resistant *M. massiliense* lung disease are available. This study evaluated the clinical features and treatment outcomes of patients and the molecular characteristics of macrolide-resistant *M. massiliense* isolates. We performed a retrospective review of medical records and genetic analyses of clinical isolates from 15 patients who had macrolide-resistant *M. massiliense* lung disease between September 2005 and February 2015. Nine patients (60%) had the nodular bronchiectatic form of the disease, and six (40%) had the fibrocavitary form. Before the detection of macrolide resistance, three patients (20%) were treated with macrolide monotherapy, four (27%) with therapy for presumed *Mycobacterium avium* complex infections, and eight (53%) with combination antibiotic therapy for *M. massiliense* lung disease. The median treatment duration after the detection of resistance was 18.7 months (interquartile range, 11.2 to 39.8 months). Treatment outcomes were poor, with a favorable outcome being achieved for only one patient (7%), who underwent surgery in addition to antibiotic therapy. The 1-, 3-, and 5-year mortality rates were 7, 13, and 33%, respectively. Of the 15 clinical isolates, 14 (93%) had point mutations at position 2058 ($n = 9$) or 2059 ($n = 5$) of the 23S rRNA gene, resulting in macrolide resistance. Our study indicates that treatment outcomes are poor and mortality rates are high after the development of macrolide resistance in patients with *M. massiliense* lung disease. Thus, preventing the development of macrolide resistance should be a key consideration during treatment.

KEYWORDS nontuberculous mycobacteria, *Mycobacterium massiliense*, macrolides, drug resistance

Pulmonary disease caused by nontuberculous mycobacteria (NTM) is increasing worldwide (1, 2); for patients with chronic lung diseases, such as bronchiectasis or cystic fibrosis, the *Mycobacterium abscessus* complex (MABC) is the most important cause of pulmonary infections due to rapidly growing mycobacteria (3, 4). Currently, the MABC can be divided into three subspecies, i.e., *M. abscessus* subsp. *abscessus* (hereafter *M. abscessus*), *M. abscessus* subsp. *massiliense* (hereafter *M. massiliense*), and *M. abscessus* subsp. *bolletii* (hereafter *M. bolletii*) (5, 6). Of the three subspecies, *M.*

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TABLE 1 Clinical characteristics at the time of diagnosis of macrolide-resistant *Mycobacterium massiliense* lung disease

Characteristic[a]	Total	Nodular bronchiectatic form	Fibrocavitary form	*P*
No. (%) of patients	15 (100)	9 (60)	6 (40)	
Female (no. [%])	10 (67)	7 (78)	3 (50)	0.329
Age (median [IQR]) (yr)	57 (48–67)	57 (46–65)	61 (51–72)	0.388
BMI (median [IQR]) (kg/m^2)	21.1 (18.6–22.3)	21.5 (19.9–23.1)	18.4 (16.5–22.0)	0.088
Nonsmoker (no. [%])	11 (73)	8 (89)	3 (50)	0.235
Previous treatment for pulmonary TB (no. [%])	9 (60)	3 (33)	6 (100)	0.028
Previous treatment for NTM lung disease (no. [%])	1 (7)	0	1 (17)	0.4
Comorbidities (no. [%])				
COPD	5 (33)	2 (22)	3 (50)	0.329
Bronchiectasis	11 (73)	9 (100)	2 (33)	0.011
Chronic pulmonary aspergillosis	2 (13)	0	2 (33)	0.143
Chronic heart disease	1 (7)	1 (11)	0	1.0
Laboratory findings				
Positive sputum AFB smear (no. [%])	13 (87)	7 (78)	6 (100)	0.486
ESR (median [IQR]) (mm/h)	56 (45–75)	48 (19–66)	78 (56–86)	0.018
CRP level (median [IQR]) (mg/dl)	1.03 (0.25–4.85)	0.56 (0.10–1.50)	5.65 (2.09–9.33)	0.026
Cavitary lesions on HRCT scans (no. [%])	10 (67)	4 (44)	6 (100)	0.044
Pulmonary function test results				
FVC (median [IQR]) (liters)	2.81 (2.08–3.44)	2.81 (2.53–3.46)	2.43 (1.72–3.49)	0.529
FVC (median [IQR]) (% of predicted)	81 (67–93)	84.0 (80.5–97.5)	68.0 (47.0–96.5)	0.224
FEV_1 (median [IQR]) (liters)	1.97 (1.40–2.55)	1.97 (1.65–2.65)	1.74 (0.87–2.44)	0.456
FEV_1 (median [IQR]) (% of predicted)	75 (49–88)	81.0 (71.0–91.5)	61.5 (39.5–87.3)	0.224

[a]BMI, body mass index; TB, tuberculosis; NTM, nontuberculous mycobacteria; COPD, chronic obstructive pulmonary disease; AFB, acid-fast bacilli; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; HRCT, high-resolution computed tomography; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s.

abscessus is the most common pathogen (45 to 65%), followed by *M. massiliense* (20 to 55%) and *M. bolletii* (1 to 18%) (7).

The response rates for macrolide-based antibiotic therapy are much higher among patients with *M. massiliense* lung disease than among those with *M. abscessus* lung disease (8–10). This is likely due to the presence of a functional ribosomal methyl transferase *erm*(41) gene in *M. abscessus*, which results in inducible macrolide resistance, observed as susceptibility to macrolides at day 3 but resistance at day 14 of drug susceptibility testing (DST). In contrast, the *erm*(41) gene is nonfunctional in *M. massiliense*, and inducible resistance does not occur (11–14). Therefore, macrolide antibiotics, such as clarithromycin and azithromycin, are cornerstones in the antibiotic treatment of *M. massiliense* lung disease (15–18).

Acquired macrolide resistance (observed as resistance at day 3 of DST) can develop during macrolide antibiotic treatment of *M. massiliense* lung disease, however, and is conferred by mutations in the drug-binding pocket of the 23S rRNA gene (*rrl*), at nucleotide positions 2058 and 2059 (19–22). Although previous laboratory studies observed this acquired macrolide resistance in some *M. massiliense* clinical isolates, no published data are available regarding the risk factors or clinical characteristics of macrolide-resistant *M. massiliense* lung disease or the treatment outcomes of affected patients. Our aims in this study were to evaluate the clinical features and treatment outcomes of patients with macrolide-resistant *M. massiliense* lung disease, as well as to examine the molecular characteristics of the pathogen.

RESULTS

Patient characteristics. A total of 15 patients were diagnosed with macrolide-resistant *M. massiliense* lung disease during the study period. The clinical characteristics of the patients are summarized in Table 1. Some of the clinical data for two of the patients were included in a recently published article (18); data for the remaining patients have not been reported previously. There were 10 female patients (67%), and the median age of all patients was 57 years (interquartile range [IQR], 48 to 67 years).

TABLE 2 Treatment regimens before the detection of macrolide-resistant *Mycobacterium massiliense* lung disease

Treatment regimen[a]	No. (%)	Duration of exposure (median [IQR])		
		Macrolide (mo)	Macrolide without IV antibiotics (mo)	IV antibiotics (wk)
Macrolide monotherapy	3 (20)	3.0 (NA)	3.0 (NA)	0
Combined antibiotic therapy for presumed MAC lung disease	4 (27)	11.0 (5.4–20.3)	11.0 (5.4–20.3)	0
Macrolide + RIF + EMB	3			
Macrolide + RIF + EMB + FQ	1			
Combined antibiotic therapy for *M. massiliense* lung disease	8 (53)	12.5 (10.0–18.5)	12.0 (9.6–18.0)	2.0 (2.0–3.5)
Macrolide + IV antibiotics	2			
Macrolide + IV antibiotics + RIF + EMB + FQ[b]	2			
Macrolide + IV antibiotics + FQ ± DOX	4			
Total	15 (100)	10.0 (4.0–17.0)	10.0 (4.0–16.5)	1.4 (0–2.0)

[a]Intravenous antibiotics included amikacin and cefoxitin (or imipenem). MAC, *M. avium* complex; IV, intravenous; RIF, rifampin; EMB, ethambutol; FQ, fluoroquinolone; DOX, doxycycline; NA, not available.
[b]Two patients had mixed infections with *M. massiliense* and *M. avium* complex.

Nine patients (60%) had a history of previous treatment for pulmonary tuberculosis. One patient (7%) had a history of previous treatment for NTM lung disease caused by a mixed infection with *M. intracellulare* and *M. massiliense*.

Sputum smears were positive for acid-fast bacilli (AFB) for 13 patients (87%) at the time macrolide resistance was detected. Chest radiography and high-resolution computed tomography (HRCT) findings were available for all patients. Nine patients (60%) had the nodular bronchiectatic form of the disease, and six (40%) had the fibrocavitary form. Cavitary lesions were found on HRCT scans for all patients with the fibrocavitary form and for four patients (44%) with the nodular bronchiectatic form. The patients with the fibrocavitary form had a higher rate of previous tuberculosis history (100% versus 33%; $P = 0.028$) and higher values for serum inflammatory markers, such as the erythrocyte sedimentation rate (78 versus 48 mm/h; $P = 0.018$) and C-reactive protein levels (5.65 versus 0.56 mg/dl; $P = 0.026$).

Antibiotic therapy before the detection of macrolide-resistant *M. massiliense*. For nine patients (60%), macrolide resistance was detected when they were transferred to our hospital after long-term antibiotic treatment at other hospitals; for six patients (40%), macrolide resistance developed during antibiotic treatment at our institution. All patients received macrolide treatment, and the median duration of macrolide exposure before the detection of macrolide resistance was 10.0 months (IQR, 4.0 to 17.0 months).

Macrolide monotherapy had been prescribed for three patients (20%), i.e., one who refused hospitalization for combination intravenous antibiotic therapy for *M. massiliense* lung disease, one for treatment of multidrug-resistant tuberculosis, and one for an MABC infection without subspecies differentiation. Combined anti-NTM antibiotic therapy, consisting of a macrolide, rifampin, and ethambutol, had been prescribed for four patients (27%) for presumed *M. avium* complex (MAC) infections without precise identification of the etiological organism for the NTM lung disease. Combined antibiotic therapy for *M. massiliense* lung disease, consisting of a macrolide, amikacin, and cefoxitin (or imipenem), had been prescribed for eight patients (53%), two of whom also received rifampin and ethambutol because they had mixed infections with *M. massiliense* and MAC. The median duration of intravenous antibiotic exposure for these eight patients was 2.0 weeks (IQR, 2.0 to 3.5 weeks) (Table 2).

Treatment and outcomes after the detection of macrolide-resistant *M. massiliense*. The treatment regimens after the detection of macrolide resistance and the subsequent treatment outcomes are summarized in Table 3. After the detection of macrolide resistance, macrolides continued to be prescribed for all patients. Amikacin ($n = 10$ [67%]), cefoxitin or imipenem ($n = 10$ [67%]), fluoroquinolone ($n = 5$ [33%]), doxycycline ($n = 3$ [20%]), linezolid ($n = 1$ [7%]), trimethoprim-sulfamethoxazole ($n =$

TABLE 3 Treatment modalities and outcomes after the detection of macrolide-resistant *Mycobacterium massiliense* lung disease

Parameter[a]	Total (n = 15)	Nodular bronchiectatic form (n = 9)	Fibrocavitary form (n = 6)
Antibiotic therapy (no. [%])			
Amikacin	10 (67)	7 (78)	3 (50)
Cefoxitin or imipenem	10 (67)	7 (78)	3 (50)
Macrolide	15 (100)	9 (100)	6 (100)
Fluoroquinolone	5 (33)	4 (44)	1 (17)
Doxycycline	3 (20)	2 (22)	1 (17)
Linezolid	1 (7)	0	1 (17)
Trimethoprim-sulfamethoxazole	2 (13)	1 (11)	1 (17)
Clofazimine	7 (47)	5 (56)	2 (33)
Amikacin inhalation	5 (33)	4 (44)	1 (17)
Surgical resection (no. [%])	3 (20)	1 (11)	2 (33)
Total treatment duration (median [IQR]) (mo)	18.7 (11.2–39.8)	19.6 (15.0–62.7)	14.7 (7.7–30.4)
Treatment outcome (no. [%])			
Sputum culture conversion within 12 mo	1 (7)	0	1 (17)
Sputum culture conversion at end of treatment	2 (13)	1 (11)	1 (17)
Deaths			
Time from detection of resistance to death (median [IQR]) (mo)	38.7 (11.4–41.9)	41.9	19.3
1-yr deaths (no. [%])	1 (7)	0	1 (17)
3-yr deaths (no. [%])	2 (13)	0	2 (33)
5-yr deaths (no. [%])	5 (33)	2 (22)	3 (50)
Death due to NTM lung disease (no. [%])	4 (27)	1 (11)	3 (50)
Death due to all causes (no. [%])	5 (33)	2 (22)	3 (50)

[a]NTM, nontuberculous mycobacteria.

2 [13%]), clofazimine (n = 7 [47%]), and amikacin inhalation (n = 5 [33%]) were used at the discretion of the attending physicians. The median duration of antibiotic therapy after the detection of macrolide resistance was 18.7 months (IQR, 11.2 to 39.8 months). Ten patients (67%) received amikacin and cefoxitin (or imipenem), and the median duration of intravenous antibiotic treatment was 3.5 weeks (IQR, 1.9 to 13.1 weeks). Three patients (20%) underwent surgical resection; two with the fibrocavitary form underwent lobectomy at 6.4 or 1.0 months after the detection of macrolide resistance, and one with the nodular bronchiectatic form underwent segmentectomy 8.4 months after the detection of macrolide resistance.

Based on the occurrence and timing of sputum culture conversion (see Materials and Methods), only one patient (7%) achieved a favorable outcome. That patient, who showed negative sputum culture results within 12 months of treatment after the detection of macrolide resistance, had undergone lobectomy, with the negative sputum cultures occurring 2 months after surgery. Although surgical resection was performed for three patients, the other two patients failed to achieve sputum culture conversion even after surgery. One patient who had not undergone surgery eventually achieved sputum culture conversion 25 months after the detection of macrolide resistance. During the median follow-up period of 38.7 months (IQR, 11.4 to 41.9 months) after the detection of macrolide resistance, the all-cause mortality rate was 33% (5/15 patients). The overall cumulative mortality rates at 1, 3, and 5 years were 7% (n = 1), 13% (n = 2), and 33% (n = 5), respectively.

Genetic analysis of macrolide-resistant *M. massiliense* isolates. Macrolide-resistant *M. massiliense* isolates were available from all patients for genetic analysis. We found point mutations at position 2058 (n = 9) or 2059 (n = 5) of the 23S rRNA gene in all but one of the isolates. The most common mutation was a nucleotide change from adenine to guanine (9/15 patients [60%]), followed by cytosine (3/15 patients [20%]) and thymine (2/15 patients [13%]) (Table 4).

DISCUSSION

In this study, we investigated the clinical characteristics and treatment outcomes of 15 patients with macrolide-resistant *M. massiliense* lung disease, as well as the molec-

TABLE 4 Analysis of mutations in the 23S rRNA (*rrl*) gene of macrolide-resistant *Mycobacterium massiliense* clinical isolates ($n = 15$)

Point mutation at position 2058 or 2059[a]	No. (%)
Presence of mutation	14 (93)
Adenine → guanine	9 (60)
A2058G	4
A2059G	5
Adenine → cytosine	3 (20)
A2058C	3
A2059C	0
Adenine → thymine	2 (13)
A2058T	2
A2059T	0
Absence of mutation	1 (7)

[a]*E. coli rrl* numbering was used.

ular characteristics of the disease isolates. Overall, the treatment outcomes were very poor, with limited effective treatment options. Among the 15 patients, a median of 18.7 months of antibiotic treatment after the detection of macrolide resistance generated a favorable outcome for only one patient (7%), and the 5-year mortality rate after the development of macrolide resistance was high (33%).

Among MABC lung disease variants, *M. massiliense* lung disease has demonstrated higher treatment success rates (88 to 96%) than has *M. abscessus* lung disease (25 to 42%) (8, 9) because inducible resistance is not found in *M. massiliense*, which has a partially deleted, nonfunctional *erm*(41) gene (19). However, the treatment success rate was only 7% in this study of macrolide-resistant *M. massiliense* lung disease. In addition to our study results, a previous report suggested that susceptibility to clarithromycin was the only significant independent predictor of a favorable microbiological response in MABC lung disease, including *M. massiliense* lung disease (23, 24).

Despite the clinical implications of such a report, little research on the risk factors that contribute to the development of macrolide resistance in *M. massiliense* lung disease has been published. We found macrolide monotherapy to be an important such risk factor. Overall, seven patients (7/15 patients [47%]) had received a macrolide without other effective antibiotics for *M. massiliense* before the emergence of macrolide resistance. In particular, before transferring to our hospital, four patients (4/15 patients [27%]) received treatment at other hospitals for presumed MAC infections, based on multiple positive NTM cultures, but without precise identification of the etiological organism for the NTM lung disease. Rifampin and ethambutol, which are routinely used to treat MAC, show poor activity in both *M. abscessus* and *M. massiliense* infections (25). Hence, the patients receiving presumed anti-MAC treatment could be regarded as receiving macrolide monotherapy for *M. massiliense* lung disease.

We found eight patients (8/15 patients [53%]) who developed macrolide resistance after receiving a macrolide with other antibiotics effective against *M. massiliense*. That finding suggests that macrolide resistance could develop during the weak antibiotic regimens used during the continuation phase, after completion of an initiation phase that includes multiple intravenous antibiotics. In our previous study, we found that macrolide resistance developed infrequently among patients with *M. massiliense* lung disease (5% [2/43 patients]), even those receiving macrolide monotherapy, if the monotherapy followed 2 weeks of combination antibiotic therapy (18). Therefore, in our present study, the higher rate of macrolide resistance might be specifically associated with greater bacterial burdens in those eight patients. All eight patients had positive AFB smears, and five patients had cavitary disease at the time macrolide-resistant *M. massiliense* lung disease was diagnosed. Three patients had noncavitary nodular bronchiectatic *M. massiliense* lung disease, however, which suggests that the weak antibiotic regimens used during the continuation phase could contribute to the

development of macrolide resistance in *M. massiliense* lung disease. Therefore, the consequences of developing macrolide resistance are too important to allow recommendation of macrolide monotherapy for treatment of *M. massiliense* lung disease during the continuation phase, even though most patients were effectively treated in our previous study (18).

In this study, various antibiotics were administered after the diagnosis of macrolide-resistant *M. massiliense* lung disease; however, none of the treatment regimens was successful. Newer agents, such as inhaled amikacin and clofazimine, have shown some encouraging preliminary results in the treatment of refractory MABC lung disease (26, 27), but optimal antibiotic regimens for *M. massiliense* lung disease have not been established. Recently, the U.S. Cystic Fibrosis Foundation and the European Cystic Fibrosis Society recommended that the continuation phase of *M. abscessus* lung disease treatment include a daily oral macrolide, inhaled amikacin, and two or three additional oral antibiotics, such as clofazimine, minocycline, or moxifloxacin (4). Further research is needed to establish optimal treatment regimens for *M. massiliense* lung disease, especially macrolide-resistant disease, and to prevent the development of macrolide resistance during treatment.

In our study, all macrolide-resistant *M. massiliense* isolates except one had point mutations at position 2058 or 2059 of the 23S rRNA. Of these point mutations, the most common was the transition from adenine to guanine at position 2058, consistent with the findings of previous studies (20, 22, 28, 29). In previous studies, all clarithromycin-resistant *M. massiliense* isolates had *rrl* mutations (19, 20, 22, 28–30). If macrolide treatment pressure continues, NTM are likely to develop a stable resistant lineage (31). However, the acquisition of an *rrl* mutation obviously confers a biofitness disadvantage to NTM in the absence of macrolide antibiotics; mutational macrolide resistance thus appears to occur infrequently in spite of prolonged macrolide monotherapy (18). In the present study, the one *M. massiliense* isolate without an *rrl* mutation had low-level clarithromycin resistance (MIC, 8 μg/ml) (18). Low-level drug resistance can initially be mediated by activation of an efflux pump early in the treatment period. An inactive efflux pump is thought to be the first step in acquiring mutational resistance, which is associated with high-level clarithromycin resistance (32).

Our study had several limitations. First, it was conducted at a single referral center and included a small number of patients. Second, treatment regimens, including the addition of intravenous antibiotics, were chosen by the attending physicians, without an established institutional protocol. Further studies with larger numbers of patients are needed to evaluate the efficacy of antibiotic therapy in the treatment of macrolide-resistant *M. massiliense* lung disease.

In conclusion, we found that macrolide resistance could develop in patients with *M. massiliense* lung disease, especially those with large mycobacterial burdens, after macrolide monotherapy or during weak antibiotic regimens in the continuation phase after an initiation phase that included multiple intravenous antibiotics. Treatment outcomes are poor and mortality rates are high after the development of macrolide resistance. Therefore, preventing the development of macrolide resistance during the treatment of *M. massiliense* lung disease is of major concern, and the appearance of resistance in our patient population underscores the need for more effective therapies for this disease.

MATERIALS AND METHODS

Study population. We reviewed the medical records for all patients who had macrolide-resistant *M. massiliense* lung disease between September 2005 and February 2015, as identified from the NTM Registry of Samsung Medical Center (a 1,979-bed referral hospital in Seoul, South Korea). All patients fulfilled the diagnostic criteria for NTM lung disease (3). This retrospective study was approved by the institutional review board (IRB) of Samsung Medical Center (IRB application no. 2016-07-016). The patient information was anonymized and deidentified prior to analysis; therefore, requirements for informed consent were waived.

Radiographic and microbiological examinations. The fibrocavitary form of the disease (previously called the upper lobe cavitary form) was defined by the presence of cavitary opacities, mainly in the upper lobes. The nodular bronchiectatic form was defined by the presence of bronchiectasis and

multiple nodules on chest HRCT scans, irrespective of the presence of small cavities (diameters of <3 cm) in the lungs (33, 34).

Sputum smears and cultures of AFB were obtained using standard methods (33). During the study period, NTM species were identified by a PCR and restriction fragment length polymorphism method based on the *rpoB* gene or by reverse blot hybridization assay of the *rpoB* gene (35–38), followed by multilocus sequencing analysis of *rrs*, *hsp65*, and *rpoB* (39). DST was performed at the Korean Institute of Tuberculosis, using the broth microdilution method (40). Isolates with MICs of ≥8 μg/ml were considered clarithromycin resistant (40). MICs for azithromycin were not determined, as clarithromycin is the class drug for macrolides (40).

M. massiliense isolates were stored at −80°C, for further analysis, at the time of detection of macrolide resistance. The *erm*(41) gene was detected by PCR sequencing, as described previously (19). For detection of point mutations at position 2058 or 2059 (*Escherichia coli* numbering) in the 23S rRNA gene, we performed PCR to amplify the region corresponding to domain V of the 23S rRNA gene, according to the method described previously (41). The primers 23SF1 and 23SRIII were used for PCR and sequencing (41).

Antibiotic therapy and treatment outcomes. Although the initial treatment regimens for macrolide-susceptible *M. massiliense* lung disease were standardized (8, 18), treatment regimens for macrolide-resistant *M. massiliense* lung disease were not standardized in our institution during the study period. Patients with mild symptoms when macrolide resistance was detected received oral antibiotics at the outpatient clinic. Patients with severe symptoms were hospitalized and received intravenous amikacin (15 mg/kg/day, in two divided doses) and cefoxitin (200 mg/kg/day [maximum of 12 g/day], in three divided doses) for 2 to 4 weeks. If an adverse reaction associated with cefoxitin occurred, then imipenem (750 mg, three times per day) was substituted for cefoxitin (8, 18), along with oral antibiotics. For the oral antibiotics, treatment with a macrolide (clarithromycin at 1,000 mg/day or azithromycin at 250 mg/day) was continued for all patients and additional drugs, such as a fluoroquinolone (ciprofloxacin at 1,000 mg/day or moxifloxacin at 400 mg/day), doxycycline (200 mg/day), linezolid (600 mg/day), trimethoprim-sulfamethoxazole (320 and 1,600 mg/day), clofazimine (100 mg/day), or inhaled amikacin (250 to 500 mg/day), were used at the discretion of the attending physicians.

Treatment outcomes were assessed by sputum culture conversion after the detection of macrolide-resistant *M. massiliense* lung disease; conversion was defined as three consecutive negative cultures, with the time of conversion defined as the date of the first negative culture (8, 18). A favorable outcome was defined as sputum culture conversion within 12 months after the initiation of treatment and maintenance for ≥12 months with treatment. Sputum culture conversion was also tested at the end of treatment.

Statistical analysis. Data are presented as the median and IQR for continuous variables and as the frequency and percentage for categorical variables. Data were compared with the Mann-Whitney *U* test for continuous variables, because of nonnormality, and with Pearson's chi-square test or Fisher's exact test for categorical variables. All tests were two-sided, and *P* values of <0.05 were considered significant. Data were analyzed using IBM SPSS Statistics for Windows (version 23.0; IBM, Armonk, NY, USA).

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