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CLINICAL THERAPEUTICS

Intermittent Antibiotic Therapy for Recurrent Nodular Bronchiectatic *Mycobacterium avium* Complex Lung Disease

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ABSTRACT Intermittent, three-times-weekly oral antibiotic therapy is recommended for the initial treatment of noncavitary nodular bronchiectatic (NB) *Mycobacterium avium* complex (MAC) lung disease. However, intermittent therapy is not recommended for patients who have been previously treated. We evaluated 53 patients with recurrent noncavitary NB MAC lung disease who underwent antibiotic treatment for ≥12 months with daily therapy ($n = 26$) or intermittent therapy ($n = 27$) between January 2008 and December 2015. Baseline characteristics were comparable between daily therapy and intermittent therapy groups. Sputum culture conversion rates did not differ between daily therapy (21/26, 81%) and intermittent therapy (22/27, 82%) groups. Compared to the etiologic organism at the time of previous treatment, recurrent MAC lung disease was caused by the same MAC species in 38 patients (72%) and by a different MAC species in 15 patients (28%). Genotype analysis in patients with sequenced paired isolates revealed that 86% (12/14) of cases with same species recurrence were due to reinfection with a new MAC genotype. In conclusion, most recurrent noncavitary NB MAC lung disease cases were caused by reinfection rather than relapse. Intermittent antibiotic therapy is a reasonable treatment strategy for recurrent noncavitary NB MAC lung disease.

KEYWORDS *Mycobacterium avium* complex, *Mycobacterium avium*, *Mycobacterium intracellulare*, recurrence, treatment outcome

Mycobacterium avium complex (MAC) lung disease is the most common form of lung disease caused by nontuberculous mycobacteria (NTM), and its incidence and prevalence are increasing worldwide (1–3). MAC lung disease usually has two major clinical phenotypes: fibrocavitary and nodular bronchiectatic (NB) (4–7). The fibrocavitary form is characterized by cavitary lesions that occur predominantly in the upper lobes and usually develops in older males with underlying lung disease, such as previous pulmonary tuberculosis and/or chronic obstructive pulmonary disease (4–7). The NB form occurs predominantly in postmenopausal, nonsmoking females (4–7) and can present as bilateral bronchiectasis with multiple nodules and tree-in-bud opacities on high-resolution computed tomography (HRCT) (8, 9).

Macrolide-based combination antibiotic therapy is recommended as the initial therapy for MAC lung disease, and the current guidelines published by the American

Received 30 August 2017 **Returned for modification** 17 October 2017 **Accepted** 27 November 2017

Accepted manuscript posted online 4 December 2017

Citation Jhun BW, Moon SM, Kim S-Y, Park HY, Jeon K, Kwon OJ, Huh HJ, Ki C-S, Lee NY, Chung MJ, Lee KS, Shin SJ, Daley CL, Koh W-J. 2018. Intermittent antibiotic therapy for recurrent nodular bronchiectatic *Mycobacterium avium* complex lung disease. Antimicrob Agents Chemother 62:e01812-17. https://doi.org/10.1128/AAC.01812-17.

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Thoracic Society and Infectious Diseases Society of America in 2007 recommend different antibiotic regimens according to clinical phenotype: intermittent, three-times-weekly oral administration of three drugs (macrolide, ethambutol [EMB], and rifamycin) for noncavitary NB MAC lung disease versus daily oral drugs with or without administration of parenteral drugs, such as streptomycin or amikacin, for cavitary MAC lung disease (4). For previously treated disease, however, the guidelines recommend more aggressive therapy with three oral drugs daily plus parenteral drug administration regardless of clinical phenotype (4). Intermittent therapy is not recommended for patients who have been previously treated (4).

Recurrence of MAC lung disease is not uncommon after successful treatment completion, especially in patients with NB MAC lung disease (10–15). In addition, evidence is mounting that the majority of recurrences are due to reinfection by new MAC genotypes rather than true relapse with the same MAC genotypes (10, 14–17). These data suggest that an aggressive strategy with daily oral drugs plus parenteral drugs for all patients with recurrent MAC lung disease might not be necessary and that intermittent oral antibiotic therapy might be more appropriate in patients with recurrent NB MAC lung disease.

However, no published data are available regarding the treatment outcomes of intermittent antibiotic therapy for patients with recurrent NB MAC lung disease. We hypothesized that the treatment outcomes would not be different between the daily therapy group and the intermittent therapy in recurrent NB MAC lung disease. The purpose of the present study was to compare the clinical efficacy of intermittent antibiotic therapy with daily therapy in patients with recurrent noncavitary NB MAC lung disease.

RESULTS

Baseline characteristics. The characteristics of the 53 study patients are shown in Table 1. None of the patients tested positive for human immunodeficiency virus. The median age was 63 years (interquartile range [IQR], 54 to 71 years), and most patients (76%) were female. There were no significant differences in age, sex, body mass index, smoking history, underlying conditions, or etiologic organism between the daily therapy and intermittent therapy groups. Positivity of the sputum AFB smear at treatment initiation (31% versus 30%) and the time interval between the initial treatment completion and diagnosis of recurrent MAC lung disease (12.3 months; IQR, 6.0 to 29.8 months versus 21.3 months; IQR, 12.3 to 29.5 months) did not differ between the daily therapy and intermittent therapy groups (Table 1). The most common etiological organism of recurrent MAC lung disease was *M. intracellulare* ($n = 29$, 55%), followed by *M. avium* ($n = 23$, 43%), and mixed infection with *M. avium* and *M. intracellulare* ($n = 1$, 2%). Compared to the etiologic organism at the time of previous treatment, recurrent MAC lung disease was caused by the same MAC species in 38 patients (72%) and by a different MAC species in 15 patients (28%) (Table 2).

Antibiotic treatment. All patients were treated with a combination of antibiotics consisting of a macrolide, EMB, and rifampin (RIF) (Table 3). Azithromycin (AZM) was the macrolide initially used in more than half of the daily therapy group (14/26, 54%) and in all patients in the intermittent therapy group (27/27, 100%). Clarithromycin (CLR) was replaced with AZM in five (5/26, 19%) patients in the daily therapy group, while AZM was replaced with CLR in one (1/27, 4%) patient in the intermittent therapy group during the treatment period. In the daily therapy group, streptomycin or kanamycin was used in six patients (23%) for a median of 3.0 months (IQR, 2.3 to 3.5 months). The median of total treatment duration was longer in the daily therapy group (23.2 months; IQR, 8.5 to 26.5 months) than in the intermittent therapy group (19.3 months; IQR, 16.5 to 23.0 months; $P = 0.023$).

Antibiotic treatment was modified in six patients during the study period. EMB was discontinued in one patient in the daily therapy group due to visual disturbances after 1 month of EMB treatment, and RIF was discontinued in five patients in the intermittent therapy group due to gastrointestinal intolerance after a median of 5.5 months (IQR, 1.9

TABLE 1 Baseline characteristics of study patients

Characteristics[a]	No. (%) or median (IQR)[b]			P
	Total (n = 53)	Daily therapy (n = 26)	Intermittent therapy (n = 27)	
Age (yrs)	63 (54–71)	64 (54–71)	63 (53–71)	0.727
Sex, female	40 (76)	21 (81)	19 (70)	0.526
Body mass index, kg/m^2	19.6 (18.3–21.0)	20.2 (18.4–21.2)	19.3 (18.0–20.9)	0.333
Never smoker	45 (85)	24 (92)	21 (78)	0.250
Underlying condition				
Bronchiectasis	53 (100)	26 (100)	27 (100)	NA
Previous tuberculosis	18 (34)	9 (35)	9 (33)	0.999
Chronic obstructive lung disease	3 (6)	0 (0)	3 (11)	0.236
Diabetes mellitus	4 (8)	1 (4)	3 (11)	0.610
Chronic heart disease	3 (6)	1 (4)	2 (7)	0.999
Etiologic organism				0.999
M. avium	23 (43)	11 (42)	12 (44)	
M. intracellulare	29 (55)	14 (54)	15 (56)	
M. avium and *M. intracellulare*	1 (2)	1 (4)	0 (0)	
Positive sputum AFB smear	16 (30)	8 (31)	8 (30)	0.999
ESR (mm/h)	31 (16–57)	42 (9–58)	25 (17–57)	0.801
CRP (mg/dl)	0.10 (0.04–0.52)	0.11 (0.04–1.40)	0.09 (0.04–0.24)	0.442
Pulmonary function test				
FEV_1 (%)	83 (66–90)	86 (71–94)	79 (63–89)	0.181
FVC (%)	83 (71–91)	88 (69–97)	82 (69–90)	0.239
Time interval between initial treatment completion and recurrence (mos)	16.8 (8.2–29.6)	12.3 (6.0–29.8)	21.3 (12.3–29.5)	0.188

[a]Abbreviations: AFB, acid-fast bacilli; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.
[b]Data are presented as numbers (%) or as medians (interquartile ranges). NA, not applicable.

to 12.1 months) of RIF treatment, but there were no significant differences in antibiotic treatment modifications between the two groups.

Treatment outcomes. After 12 months of antibiotic treatment, there were no differences in symptom improvement (92 versus 85%; $P = 0.416$) or HRCT improvement (69 versus 70%; $P = 0.608$) between the daily therapy and intermittent therapy groups (Table 4).

Forty-three (81%) patients achieved sputum culture conversion and maintained negative cultures for more than 12 months. The culture conversion rates were not different between the daily therapy (81%) and intermittent therapy groups (82%, $P = 0.999$), and it showed similar clinical efficacy of both treatment strategies (Table 4). Further analysis demonstrated that the crude and adjusted proportions of culture conversion also did not differ between the daily therapy and intermittent therapy groups (Table 5).

In addition, there was no difference in median time to culture conversion between the daily therapy group (1.6 months; IQR, 1.1 to 5.0 months) and intermittent therapy group (1.3 months; IQR, 1.0 to 10.1 months; $P = 0.920$) (Table 4). Among 10 patients

TABLE 2 Etiologic organism

Etiology at previous treatment	Etiology at recurrence (no. of patients)			
	M. avium	*M. intracellulare*	*M. avium* and *M. intracellulare*	Total
M. avium	18	9	1	28
M. intracellulare	3	20	0	23
M. avium and *M. intracellulare*	2	0	0	2
Total	23	29	1	53

TABLE 3 Antibiotic treatment regimen

Regimen[a]	No. (%) or median (IQR)[b]			
	Total (n = 53)	Daily therapy (n = 26)	Intermittent therapy (n = 27)	P
Macrolide	53 (100)	26 (100)	27 (100)	NA
CLR	7	7	0	
AZM	40	14	26	
CLR, followed by AZM	5	5	0	
AZM, followed by CLR	1	0	1	
EMB	53 (100)	26 (100)	27 (100)	NA
RIF	53 (100)	26 (100)	27 (100)	NA
Aminoglycoside	6 (11)	6 (23)	0	0.010
Streptomycin	4	4	0	
Kanamycin	2	2	0	
Total treatment duration (mos)	20.1 (17.3–25.9)	23.2 (18.5–26.5)	19.3 (16.5–23.0)	0.023

[a]Abbreviations: AZM, azithromycin; CLR, clarithromycin; EMB, ethambutol; RIF, rifampin.
[b]Data are presented as numbers (%) or as medians (interquartile ranges). NA, not applicable.

who had persistent positive sputum cultures after 12 months of antibiotic therapy, macrolide resistance developed in two patients who received daily therapy, whereas the other eight patients remained susceptible to CLR.

Of the 43 patients who completed treatment for recurrent MAC lung disease (21 patients in the daily therapy group and 22 patients in the intermittent therapy group), 11 (26%) redeveloped NTM lung during the median follow-up period of 16.6 months (IQR, 5.1 to 32.2 months) up to June 30, 2017. This rate was not different between the daily therapy group (6/21, 29%) and the intermittent therapy group (5/22, 23%, P = 0.736). In these 11 patients, MAC lung disease from the same species recurred in six

TABLE 4 Treatment outcomes

Treatment outcome[a]	No. (%) or median (IQR)[b]			
	Total (n = 53)	Daily therapy (n = 26)	Intermittent therapy (n = 27)	P
Symptomatic response				0.416
Improved	47 (88)	24 (92)	23 (85)	
Unchanged	3 (6)	2 (8)	1 (4)	
Worsened	3 (6)	0 (0)	3 (11)	
Radiographic response on HRCT				0.608
Improved	37 (70)	18 (69)	19 (70)	
Unchanged	12 (22)	7 (27)	5 (19)	
Worsened	4 (8)	1 (4)	3 (11)	
Sputum culture conversion	43 (81)	21 (81)	22 (82)	0.999
Time to culture conversion (months)	1.4 (1.0–8.4)	1.6 (1.1–5.0)	1.3 (1.0–10.1)	0.920
Development of macrolide resistance	2 (4)	2 (8)	0 (0)	0.236
Redevelopment of NTM lung disease	11/43 (26)	6/21 (29)	5/22 (23)	0.736
Caused by same species	6/43 (14)	2/21 (10)	4/22 (18)	
M. avium → *M. avium*	4	1	3	
M. intracellulare → *M. intracellulare*	2	1	1	
Caused by different species	5/43 (12)	4/21 (19)	1/22 (5)	
M. avium → *M. intracellulare*	1	1	0	
M. avium → *M. kansasii*	1	1	0	
M. avium → *M. avium/M. massiliense*	1	1	0	
M. intracellulare → *M. abscessus*	2	1	1	

[a]Abbreviations: HRCT, high-resolution computed tomography; NTM, nontuberculous mycobacteria.
[b]Data are presented as numbers (%) or as medians (interquartile ranges).

TABLE 5 Crude and adjusted proportions and odds ratios for culture conversion[a]

Variable	Crude or adjusted % proportion (95% CI) of culture conversion		% differences of proportion[b] (95% CI)	OR[c] (95% CI)	*P*
	Daily therapy	Intermittent therapy			
Crude state	80.8 (51.5–94.3)	81.5 (52.6–94.6)	−0.7 (−21.8–20.4)	1.048 (0.265–4.148)	0.947
Adjusted state[d]	93.9 (62.9–99.3)	91.0 (52.5–98.9)	2.9 (−11.3–17.2)	0.652 (0.071–5.967)	0.689

[a]Abbreviations: OR, odds ratio; CI, confidence interval.
[b]Calculated as the proportion of culture conversion in patients with daily therapy − the proportion of culture conversion in patients with intermittent therapy. Therefore, positive values mean that daily therapy was more effective than intermittent therapy, and negative values mean the opposite.
[c]Calculated using ratio of odds of culture conversion in daily therapy to those in intermittent therapy. Therefore, values greater than 1 mean that daily therapy was more effective than intermittent therapy, and values less than 1 mean the opposite.
[d]Adjusted for age, sex, body mass index, smoking, etiologic organism (*M. avium* versus *M. intracellulare*), sputum smear positivity, forced expiratory volume in 1 s, and choice of macrolide (clarithromycin vs. azithromycin).

(55%) cases (four cases of *M. avium* and two cases of *M. intracellulare*), and NTM lung disease from a different NTM species developed in five (45%) cases (Table 4).

Genotyping of paired isolates. As described previously, recurrent MAC lung disease was caused by the same species in 38 patients among the 53 patients in the study. Among these 38 patients, paired MAC isolates from the time of the previous initial treatment episode and the time of diagnosis of recurrent MAC lung disease were available for genotype analysis in 14 (37%) patients (eight patients infected with *M. avium* and six patients infected with *M. intracellulare*). A total of 30 isolates from 14 patients were examined, including two isolates from two patients who developed a second recurrence of MAC lung disease caused by the same species after treatment for recurrent MAC lung disease. The morphotype of each single colony was classified macroscopically as smooth or rough. If the isolates included colonies of both morphotypes, single colonies of each type were analyzed separately. Finally, 98 single colonies were sampled from these isolates, and the median number of single colonies per patients was seven (range, 4 to 15). All initial and recurrent isolates were susceptible to clarithromycin and had no *rrl* mutations (see Table S1 in the supplemental material).

Among the 14 patients, most cases were caused by reinfections with new MAC genotypes different from the initial MAC genotypes (12/14, 86%); only two cases of relapse were caused by the same MAC genotypes that caused the original disease (2/14, 14%) (see Fig. S1 in the supplemental material). In addition, two patients with a second recurrence were reinfected with additional new MAC genotypes that differed from the genotypes of both the initial infection and the first recurrence (see Table S1 and Fig. S1 in the supplemental material).

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the clinical efficacy of intermittent antibiotic therapy for recurrent noncavitary NB MAC lung disease. One of the most important findings in our study was that patients who received intermittent therapy had similar treatment response rates compared to patients in the daily therapy group with respect to symptomatic improvement, HRCT improvement, culture conversion and maintenance, and time to culture conversion. In addition, the proportion of culture conversion was not different between daily and intermittent therapy groups. This constitutes important information that could aid in determining the most appropriate treatment strategy for recurrent MAC lung disease.

The treatment success rate for patients with previous treatment history for MAC lung disease is significantly lower (38 to 69%) than that for newly treated MAC patients (68 to 91%) for both daily antibiotic therapy (18, 19) and intermittent antibiotic therapy (20–23). Based on these results, current guidelines recommend very aggressive therapy composed of three oral drugs daily plus parenteral injection of streptomycin or amikacin in patients who have been treated previously, regardless of clinical phenotype, although intermittent therapy is recommended as the initial therapy for noncavitary NB MAC lung disease (4). In all these previous studies, however, a substantial proportion (more than 50% in some studies) of enrolled patients had fibrocavitary MAC

lung disease, and some patients even had macrolide-resistant MAC lung disease (18–23). In the present study, which focused on patients with recurrent noncavitary NB MAC lung disease, sputum culture conversion rates were higher than 80% in both intermittent therapy and daily therapy groups, comparable to those obtained in patients with newly treated NB MAC lung disease (10, 15, 24).

Previous studies found that 22 to 50% of patients with MAC lung disease experience recurrence of MAC lung disease after successful treatment (10–15). The majority of these recurrences were reported to be due to reinfection rather than true relapse, especially in patients with NB MAC lung disease (10, 11, 15). Wallace et al. found that patients with NB MAC lung disease frequently suffer from multiple or repeated infections, whereas patients with fibrocavitary MAC lung disease are frequently infected with a single strain (16). In their subsequent study, they analyzed the genotypes of isolates in patients with NB MAC lung disease and showed that most infections were from new MAC strains after completing initial therapy (10, 17). In our recent study, which included 481 MAC patients, we found that the proportion of reinfections was higher in patients with NB MAC disease (82%) than in those with fibrocavitary MAC disease (40%) (15).

In the present study, more than one-fourth (15/53, 28%) of patients with recurrent NB MAC lung disease experienced recurrence due to infection with a MAC species different from the MAC organism present at the initial treatment, and genotype analysis performed in cases with recurrence caused by the same MAC species demonstrated that most of the analyzed cases were due to reinfections with new MAC genotypes (12/14, 86%), although the genotype analysis results were available for only one-third (14/38, 37%) of these patients. All of these findings suggest that a large proportion of our recurrent cases was likely caused by new MAC genotypes rather than true relapse caused by the same MAC genotypes.

Given the high reinfection rate by new genotypes in recurrent NB MAC lung disease, universal aggressive daily therapy with oral and parenteral agents might not be warranted for managing patients with recurrent noncavitary NB MAC lung disease. The results of our study strongly suggest that intermittent oral antibiotic therapy without parenteral drug administration, rather than more toxic daily oral therapy plus parenteral drug administration, might be more appropriate for these patients.

The present study had several limitations. First, this study was conducted at a single referral center with specialized NTM clinics. Second, we did not use a prospective randomized controlled design to compare the clinical efficacy of daily versus intermittent therapy. Thus, there is a possibility that not enough patients were included to confirm the noninferiority of intermittent therapy compared to the daily therapy. Third, since patients were treated with daily therapy or intermittent therapy during different time periods, according to our treatment protocols, there could be selection bias between the groups in this retrospective study. Fourth, genotyping data were not available for a significant proportion of patients with recurrent disease caused by the same MAC species. Thus, we could not differentiate between persistent infection with the initial MAC strain and reinfection with a new MAC strain in these patients. Fifth, *M. chimaera*, new species closely related to *M. intracellulare*, was not differentiated in this study. However, *M. chimaera* is relatively rare in South Korea (25–27).

Lastly, the follow-up duration after treatment of recurrent disease was relatively short. In conclusion, the majority of recurrent noncavitary NB MAC lung disease cases were caused by reinfection by either a different MAC species or the same MAC species with a different genotype. Considering that distinguishing between relapse and reinfection in recurrent cases requires molecular typing methods that are not routinely available in clinical practice in most countries, intermittent three-times-weekly oral antibiotic therapy could be a reasonable treatment strategy for recurrent noncavitary NB MAC lung disease. In light of our findings, current treatment guidelines may need to be reevaluated, although further clinical studies are recommended.

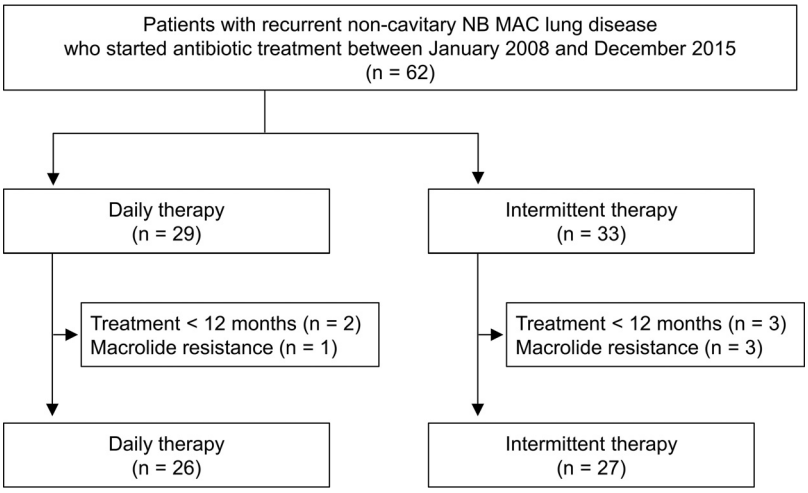

FIG 1 Study population. NB, nodular bronchiectatic form; MAC, *M. avium* complex.

MATERIALS AND METHODS

Study population. Consecutive patients who had a history of previous treatment of MAC lung disease and for whom antibiotic treatment for recurrent noncavitary NB MAC lung disease was initiated between January 2008 and December 2015 were identified using the database of the NTM Registry of Samsung Medical Center (a 1,979-bed referral hospital in Seoul, South Korea). All patients met the diagnostic criteria for NTM lung disease (4). Data were from an ongoing institutional review board-approved prospective observational cohort study to investigate NTM lung disease, and written informed consent was obtained from all participants (clinicaltrials.gov identifier NCT00970801) (15, 24).

Radiologic phenotypes were classified according to the main features on chest X-ray and HRCT. HRCT scans were available for all patients at the time of initiation of treatment for recurrent noncavitary NB MAC lung disease. All patients had characteristic chest X-ray and HRCT findings, such as the presence of multifocal bronchiectasis, clusters of small nodules, and absence of cavities on chest HRCT (8, 9).

During the study period, 99 patients with recurrent MAC lung disease started antibiotic treatment. After excluding 17 patients with fibrocavitary form, 14 patients with cavitary NB form, and six patients with unclassifiable form of MAC lung disease, 62 patients with recurrent noncavitary NB MAC lung disease who initiated antibiotic therapy were identified. All patients had persistent respiratory symptoms and radiographic progression associated with MAC lung disease. In our institution, intermittent therapy was introduced for initial treatment of all patients with noncavitary NB MAC lung disease in January 2011 (24), and intermittent therapy was also applied in patients with recurrent noncavitary NB MAC lung disease beginning in January 2012. Of 62 patients, 29 (47%) received daily therapy and 33 (53%) patients received intermittent therapy for recurrent disease during the study period. After excluding patients who received less than 12 months of antibiotic treatment ($n = 5$) and patients with macrolide-resistant MAC lung disease ($n = 4$), 53 patients with recurrent noncavitary NB MAC lung disease were included in the final study, comprising 26 patients with daily therapy and 27 patients with intermittent therapy (Fig. 1).

Antibiotic treatment. All patients received standardized combination antibiotic treatment, which consisted of an oral macrolide (CLR or AZM), EMB, and RIF (4). The daily therapy regimen included an oral macrolide (1,000 mg CLR or 250 mg AZM), 15 mg/kg EMB, and 450 mg RIF (body weight $<$ 50 kg) or 600 mg RIF (body weight $\geq$ 50 kg). Streptomycin or kanamycin was administered intramuscularly at 10 to 15 mg/kg (500 to 1,000 mg) three times a week in the daily therapy group for the first several months, at the discretion of the attending physician, especially in patients with acid-fast bacilli smear-positive sputum (24). The regimen for intermittent therapy included an oral macrolide (1,000 mg CLR or 500 mg AZM), 25 mg/kg EMB, and 600 mg RIF three times weekly. Patients were generally treated until culture negative for 12 months (24).

Treatment outcomes. After 12 months of treatment, we evaluated improvement in symptoms, HRCT findings, and conversion of a sputum culture. Symptomatic responses were determined by the attending physician, and radiographic responses were evaluated based on the radiologists' interpretation of HRCT scans (24). HRCT scans were available in all patients after 12 months of treatment. Sputum examinations were performed at 1, 3, and 6 months after initiation of antibiotic treatment and then at 2- to 3-month intervals during treatment. Sputum culture conversion was defined as three consecutive negative cultures, and the time to culture conversion was defined as the date of the first negative culture (24). The clinical efficacy of antibiotic therapy was determined based on the sputum negative sputum culture conversion and maintenance of negative cultures for more than 12 months (4).

Microbiological examinations. Clinical isolates were identified using PCR-restriction fragment length polymorphism analysis of the *rpoB* gene or reverse-blot hybridization assay of the *rpoB* gene (24, 28). Drug susceptibility testing was performed using the broth microdilution method (29). Isolates with a MIC of 32 μg/ml or greater for clarithromycin were considered resistant to macrolides (29).

Mutations in the 23S rRNA gene (*rrl*) were detected by PCR sequencing as described previously (30). Mycobacterial genotyping was performed using repetitive sequence-based PCR (rep-PCR), which was standardized according to the DiversiLab Mycobacterium kit protocol (bioMérieux, Marcy l'Étoile, France) (31). Reports of rep-PCR were generated based on the Kullback-Leibler method, and isolates with identical profiles or >97% similarity were regarded as indistinguishable (32). In patients with recurrent MAC lung disease for whom initial and recurrent MAC isolates were stored, we distinguished between "relapse" with the same MAC genotype and "reinfection" with a new MAC genotype.

Statistical analyses. All data are presented as numbers (percentages) for categorical variables and medians (interquartile ranges [IQRs]) for continuous variables. Data were compared using Pearson χ^2 tests or Fisher exact tests for categorical variables and Mann-Whitney U tests for continuous variables. To compare the outcomes of daily therapy versus intermittent therapy, an adjustment for confounding factors, including age, sex, body mass index, smoking, etiologic organism (*M. avium* versus *M. intracellulare*), sputum smear positivity, forced expiratory volume in 1 s, and choice of macrolide (clarithromycin versus azithromycin), was conducted. The crude and adjusted proportion of patients with culture conversion was calculated by logistic regression analysis. All statistical analyses were performed using PASW (version 18.0; SPSS Inc., Chicago, IL), and a two-sided $P < 0.05$ was considered significant.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.01812-17.

SUPPLEMENTAL FILE 1, PDF file, 0.9 MB.

ACKNOWLEDGMENTS

We thank Soohyun Ahn, a statistician in Samsung Medical Center, for help with the statistical analysis.

C.L.D. received grants from Insmed, Inc., not associated with the submitted work. Otherwise, we have no conflicts of interest to declare.

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT, and Future Planning (NRF-2015R1A2A1A01003959) and by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, Republic of Korea (HI15C2778). The sponsor had no role in the design of the study, collection, and analysis of the data, or preparation of the manuscript.

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