Outcome of shorter treatment duration in non-cavitary nodular bronchiectatic *Mycobacterium avium* complex lung disease

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Background: The recommended treatment duration for non-cavitary nodular bronchiectatic (NC-NB) *Mycobacterium avium* complex (MAC) lung disease (LD) is at least 12 months after culture conversion, but evidence supporting this is limited. This study investigated whether treatment for less than 12 months after culture conversion is acceptable in terms of recurrence rate.

Methods: The study enrolled the patients diagnosed with NC-NB MAC LD between 2001 and 2014 at a tertiary referral center in South Korea who received the standard treatment for at least 9 months after culture conversion up to October 2018. The patients were divided into a shorter treatment group (9–11 months after culture conversion) and a standard treatment group (≥12 months).

Results: Of the 228 patients enrolled, 59 (25.9%) were treated for 9–11 months after culture conversion and 169 (74.1%) for ≥12 months. The mean treatment durations after culture conversion in the shorter and standard treatment groups were 11.1 and 13.8 months, respectively (P<0.001). During median follow-up durations after the completion of treatment of 56.5 and 55.9 months, respectively, the recurrence rates in the two groups were similar, at 39.0% (23/59) and 36.7% (62/169). There were also no significant differences between the groups in the 1-year and 3-year recurrence rates.

Conclusions: Post-conversion treatment shorter than the recommended duration may be adequate in terms of recurrence rate for patients with NC-NB MAC LD who receive the standard treatment for at least 9 months after culture conversion.

Keywords: *Mycobacterium avium* complex (MAC); recurrence; treatment duration; culture conversion

Introduction

The incidence and prevalence of nontuberculous mycobacteria (NTM) disease are increasing worldwide, including in South Korea (1,2). NTM comprise a diverse group of organisms, of which *Mycobacterium avium* complex (MAC) is the most frequently encountered in South Korea (2). Its most common clinical manifestation in adult patients is MAC lung disease (LD) (3).

Until recently, there were considered to be three radiological types of MAC LD: nodular bronchiectatic (NB), fibrocavitary (FC), and unclassifiable (4). However, Koh *et al.* found that the treatment outcomes for a cavitary form of NB

disease were similar to those for the FC type and therefore suggested that the NB type should be further divided into cavitary NB (CNB) and non-cavitary NB (NC-NB) (5). Immediate treatment is not recommended for patients with the NC-NB form because this type is often indolent and the treatment is associated with possible adverse events (6). Although the treatment outcome for NC-NB MAC LD is favorable (5), the recurrence rate after successful treatment is extremely high, at around 25–50% (5,7-9).

The guidelines for MAC LD treatment recommend that a macrolide-based regimen should be continued for at least 12 months after the sputum culture converts to negative (4,10,11). However, supporting evidence for this recommendation is limited (12). The goal of treatment for so long after culture conversion is to achieve a relapse-free cure. Nevertheless, substantial numbers of patients with NC-NB MAC LD experience recurrence after successful treatment, and it is therefore possible that a shorter treatment period than the recommended 12 months would result in a similar recurrence rate. As yet, this has not been investigated. The aim of this study, therefore, was to investigate whether treatment for <12 months after culture conversion is acceptable in terms of recurrence rate for patients with the NC-NB form of MAC LD.

Methods

Patients

This retrospective study examined data for patients at Asan Medical Center, a 2,700-bed referral hospital in Seoul, South Korea, who met the American Thoracic Society (ATS) criteria for MAC LD between 2001 and 2014. Of these, the 451 patients who were treated with any type of antibiotic for ≥9 months (i.e., 270 days) after culture conversion up to October 2018 were selected for the analysis. The 9 months cut-off criterion was arbitrary, chosen because we thought that at least 9 months of treatment after culture conversion would be required to keep recurrence after cure within an acceptable range. Patients were excluded if their treatment was other than by the standard regimen, they had radiological types of MAC LD other than the NC-NB form, the follow-up data were insufficient, or their MAC isolates were resistant to clarithromycin. The medical records of the remaining patients were analyzed in November 2018 (*Figure 1*).

The study protocol was approved by the Institutional Review Board (RFB) of Asan Medical Center (IRB No. 2018-0986), which waived the requirement for informed consent because of the retrospective nature of the analysis.

Patient groups

The included patients were classified into two groups on the basis of treatment duration: the shorter duration group, who received treatment for ≥9 and <12 months after culture conversion, and the standard duration group, who received treatment for the standard duration of ≥12 months after culture conversion. Culture conversion was defined as at least three consecutive negative mycobacterial cultures of respiratory samples, each collected at intervals of at least 4 weeks, with the date of the first negative culture defined as the date of culture conversion (13).

Treatment regimen and treatment outcome analysis

The inclusion and exclusion criteria selected only patients who received the standard regimen; thus, the included patients received the same macrolide-based regimen of clarithromycin or azithromycin along with rifampin and ethambutol, prescribed according to the patient's weight (4). In some patients, the treatment regimen was changed after initiation because of an adverse reaction to rifampin or ethambutol. In such cases, we regarded the treatment regimen as standard if both rifampin and ethambutol were prescribed for ≥80% of the total duration of the treatment (14). The treatment could be reinforced with parenteral drugs, such as streptomycin or amikacin, as decided by the attending physician.

Previous studies of the treatment outcomes of MAC LD analyzed treatment success rates (5,15). However, the aim of the present study was to compare the recurrence rates between the two groups (shorter *vs.* standard duration), so we did not compare the treatment success rates. Instead, we assessed whether the recurrence rate in the shorter duration group was acceptable during the follow-up period after the completion of treatment. We also compared the 1- and 3-year recurrence rates between the two groups.

Redevelopment was defined as a subsequent diagnosis of NTM LD after completion of the initial treatment, irrespective of the causative NTM organism (5). Recurrence was defined as redevelopment in which two or more positive cultures were obtained for the same MAC species (*M. avium* or *M. intracellulare*) as that treated in the initial LD (5,15,16).

Radiologic evaluation and microbiological examination

Radiographic abnormalities on chest computed tomography

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at the time of diagnosis were categorized as FC, CNB, NC-NB, or unclassifiable, as previously defined (5,17). The extent of the disease was assessed according to how many of the six lung lobes were involved, considering the lingular segment to be a separate lobe (9).

Expectorated sputum or samples obtained from bronchoscopy were cultured in both solid medium (Ogawa medium; Korean Institute of Tuberculosis, South Korea) and liquid medium (BACTEC 960 Mycobacterial Growth Indicator Tube; Becton Dickinson, Sparks, MD, USA). Acid-fast bacilli (AFB) smears were prepared by Ziehl-Neelsen staining. Positive liquid cultures and colonies on the solid medium were subjected to polymerase chain reaction assays using Seeplex TB detection (Seegen, Seoul, Korea) to differentiate between a *M. tuberculosis* complex and NTM. The species of NTM isolates were identified by polymerase chain reaction and restriction fragment length polymorphism methods based on the *rpoB* gene, or by reverse blot hybridization assays of *rpoB* (18,19). The MAC isolates were identified as one of two species: *M. avium* or *M. intracellulare*.

Statistical analysis

The data are presented as means (± standard deviations) or medians with interquartile ranges (IQRs) for continuous variables, and numbers (%) for categorical variables. The data were compared by Student's *t*-tests or Mann-Whitney *U* tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables. All the tests were two-sided and P values less than 0.05 were considered statistically significant. The recurrence rates after treatment completion were compared between the two groups by the Kaplan-Meier method. Multivariate logistic analyses were used to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the 1- and 3-year recurrence rates. The variables used in the multivariate logistic analyses were selected as those with a statistical significance level of <0.1 in the univariate analysis, together with treatment duration. The statistical analysis was performed using SPSS software (version 24.0; IBM Corp., Armonk, NY, USA).

Results

Study subjects

The eligibility screening identified 228 patients with macrolide-susceptible NC-NB MAC LD that had been treated with the standard regimen for ≥9 months after sputum culture conversion. The mean age of the patients was 60.3 years, and 68.9% were female. Daily therapy was administered to almost all the patients (97.4%, 222/228). Of the 228 patients, 59 (25.9%) received treatment for 9–11 months after culture conversion (the shorter duration group), and the remaining 169 (74.1%) received treatment for ≥12 months (the standard duration group; *Figure 1*). The mean treatment durations after culture conversion in the two groups were 11.1±0.8 months and 13.8±1.7 months, respectively (P<0.001). The main reasons for stopping treatment earlier than the recommended 12 months were the attending physician's decision (n=55, 93.2%), and adverse drug events (n=4, 6.8%). The two groups were comparable except that the shorter duration group was significantly more likely to have chronic liver disease as a comorbidity (*Table 1*).

Recurrence rates after the completion of treatment

The median (IQR) follow-up durations after the completion of treatment were 56.1 (31.3–78.1) months overall and 56.5 (31.8–83.6) and 55.9 (31.2–75.9) months for the shorter and standard duration groups, respectively (P=0.583) (*Table 1*). Of the 228 patients, 111 (48.7%) experienced the redevelopment of NTM LD during follow-up, of which 85 (37.3%) were recurrences. The recurrence rates in the two groups were similar: 39.0% (23/59) in the shorter duration group and 36.7% (62/169) in the standard duration group (P=0.753). The cumulative rates of recurrence in the two treatment groups based on the Kaplan-Meier method are shown in *Figure 2*; this showed no significant difference (P=0.713). *Table 2* presents a comparison of clinical characteristics between the patients who experienced recurrence during the follow-up and those who did not. A similar proportion of each were in the shorter duration group (27.1% *vs.* 25.2%; P=0.753; *Table 2*).

1- and 3-year recurrence rates

Of the 228 patients, 210 (92.1%) were followed up for at least a year after the completion of treatment. Of these, 53 received the shorter duration of treatment and 157 received the standard duration. Recurrence occurred in 17.0% (9/53) of the shorter duration patients and 12.7% (20/157) of the standard duration patients (P=0.439). *Table 3* compares the characteristics of the patients according to whether they experienced recurrence in the first year. A significantly
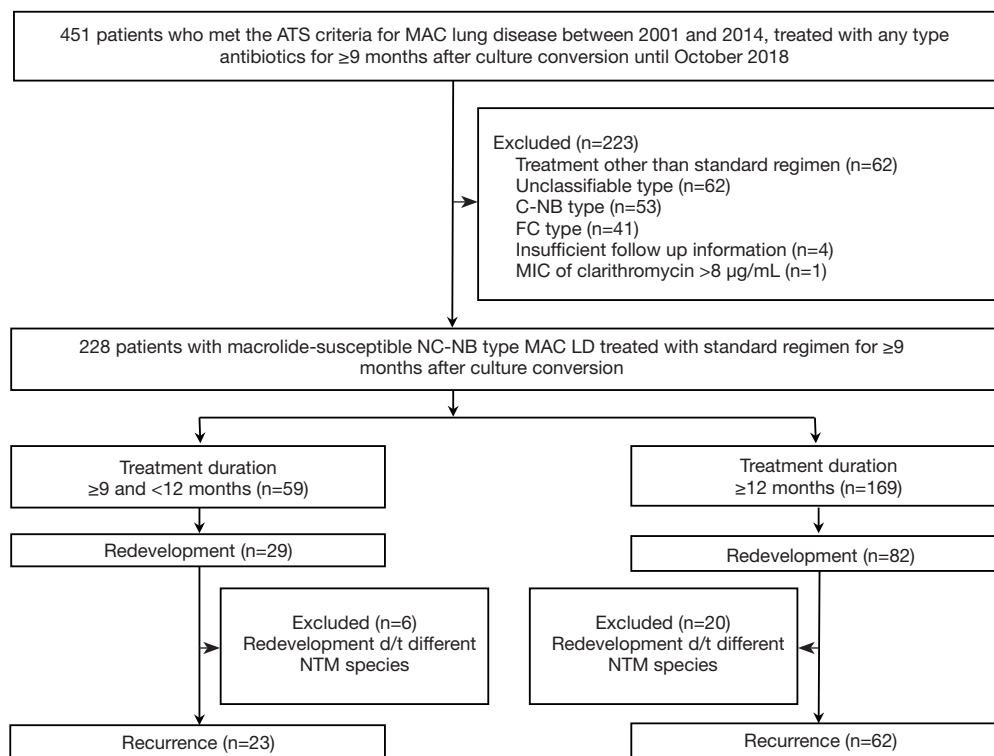
Figure 1 Study flow chart. ATS, American Thoracic Society; MAC, *Mycobacterium avium* complex; CNB, cavitary nodular bronchiectatic; FC, fibrocavitary; MIC, minimum inhibitory concentration; NC-NB, non-cavitary nodular bronchiectatic; MAC LD, *Mycobacterium avium* complex lung disease; NTM, nontuberculous mycobacteria.

higher proportion of those with 1-year recurrence were aged ≥60 years.

Of the 163 patients followed up for at least three years after the end of treatment, 43 were in the shorter duration group and 120 in the standard duration group. Recurrence occurred in 41.9% (18/43) and 36.7% (44/120) of these groups, respectively (P=0.547). *Table 4* compares the characteristics of the patients who experienced recurrence during the three years and those who did not. Most clinical characteristics, including treatment duration after culture conversion, were comparable in the two groups, although there were significant differences in the proportions of those aged ≥60 years and with a previous history of NTM treatment, and in the number of involved lobes.

Multivariate analysis

Table 5 summarizes the results of the multivariate analysis, which revealed that age ≥60 years was the only significant risk factor for 1- and 3-year recurrence after treatment completion (1-year recurrence: adjusted OR, 2.565; 95%

CI, 1.020–6.450; P=0.045; 3-year recurrence: adjusted OR, 2.511; 95% CI, 1.256–5.019; P=0.009). Neither the 1-year nor the 3-year recurrence rates were significantly associated with the length of treatment after culture conversion in the multivariate analyses.

Discussion

Although the guidelines recommend that macrolide-based regimens for treating MAC LD should be administered for at least 12 months after sputum culture conversion (4,10,11), the supporting evidence for this is limited (12,20). A substantial proportion of patients with the NC-NB form of MAC LD eventually experience recurrence after successful treatment; this suggested that a shorter duration of treatment might yield similar results in terms of recurrence rate. To the best of our knowledge this is the first study to investigate whether this was the case. The study was conducted in a single tertiary referral center in South Korea through a retrospective analysis of consecutive patients with MAC LD, and its most important finding was that

Table 1 Baseline characteristics and treatment outcomes of 228 patients with macrolide-susceptible non-cavitary nodular bronchiectatic *Mycobacterium avium* complex lung disease, compared between those with shorter treatment duration (9–11 months) and standard duration (≥12 months)

Characteristic/outcome	Total (n=228)	Shorter duration (n=59)	Standard duration (n=169)	P
Age (y)	60.3±10.7	61.8±10.4	59.8±10.8	0.218
Age ≥60 years	123 (53.9)	35 (59.3)	88 (52.1)	0.336
Female	157 (68.9)	39 (66.1)	118 (69.8)	0.595
BMI (kg/m^2)	20.6±2.6	20.7±2.8	20.6±2.6	0.919
Current or past smoker	43 (18.9)	16 (27.1)	27 (16.0)	0.060
Previous history of TB treatment	75 (32.9)	22 (37.3)	53 (31.4)	0.404
Previous history of NTM treatment	14 (6.1)	6 (10.2)	8 (4.7)	0.134
Comorbidity				
COPD	26 (11.4)	9 (15.3)	17 (10.1)	0.280
Diabetes mellitus	17 (7.5)	4 (6.8)	13 (7.7)	>0.999
Chronic liver disease	17 (7.5)	8 (13.6)	9 (5.3)	0.038
Malignancy	43 (18.9)	11 (18.6)	32 (18.9)	0.961
Etiology				0.410
Mycobacterium avium	111 (48.7)	26 (44.1)	85 (50.3)	
Mycobacterium intracellulare	117 (51.3)	33 (55.9)	84 (49.7)	
Positive AFB smear at treatment initiation	77 (33.8)	24 (40.7)	53 (31.4)	0.193
Number of involved lobes	3.5±1.3	3.5±1.3	3.4±1.4	0.380
Use of injectable aminoglycosides	87 (38.2)	21 (35.6)	66 (39.1)	0.638
Daily therapy	222 (97.4)	58 (98.3)	164 (97.0)	>0.999
Surgical resection	5 (2.2)	2 (3.4)	3 (1.8)	0.606
Time to initiate treatment after diagnosis (months)	5.2 (1.7–12.0)	3.9 (1.2–10.7)	5.3 (1.8–13.8)	0.353
Treatment duration after culture conversion (months)	13.1±2.0	11.1±0.8	13.8±1.7	<0.001
Follow-up duration after treatment completion (months)	56.1 (31.3–78.1)	56.5 (31.8–83.6)	55.9 (31.2–75.9)	0.583
Recurrence	85 (37.3)	23 (39.0)	62 (36.7)	0.753

BMI, body mass index; TB, tuberculosis; NTM, nontuberculous mycobacteria; COPD, chronic obstructive lung disease; AFB, acid-fast bacilli. Data are presented as mean (± standard deviation), median (interquartile range), or number (%).

the recurrence rate after treatment completion was similar between the shorter treatment group and the standard treatment group. Thus, treatment for a shorter period than the recommended 12 months after culture conversion may be acceptable for patients with NC-NB MAC LD who have received the standard treatment for at least 9 months after culture conversion.

The recommendation to maintain treatment for at least 12 months after culture conversion in MAC LD is based on only limited evidence (12,20). In one study (12), Wallace *et al.* reported intermediate results for 50 patients with

MAC LD treated with clarithromycin regimens between January 1992 and October 1994, concluding that "patients should be treated until culture-negative 10 to 12 months." This was based on their finding that none of the 23 patients who had maintained culture negativity for a mean of 12.0 months while receiving therapy experienced recurrence during a mean of 19.1 months follow-up after treatment completion. In 2002, another study reported that new positive sputum cultures after culture negativity for 10 to 12 months treatment were usually due to reinfection rather than disease relapse, supporting the recommendation for
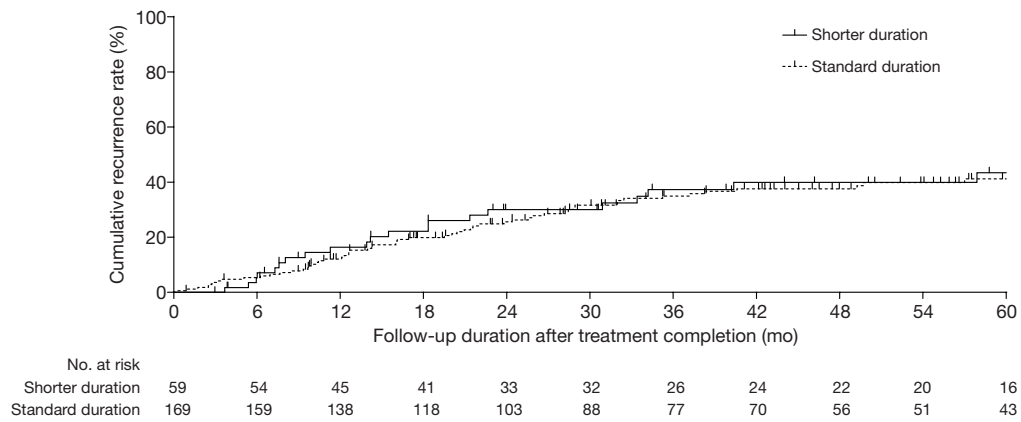
No. at risk										
Shorter duration	59	54	45	41	33	32	26	24	22	20	16
Standard duration	169	159	138	118	103	88	77	70	56	51	43

Figure 2 Kaplan-Meier estimates of the cumulative recurrence rates after treatment completion according to the duration of treatment after culture conversion: shorter duration (9–11 months) or standard duration (≥12 months). The recurrence rates in the two groups were similar (P=0.713 by the Gehan-Breslow test).

Table 2 Clinical characteristics of the 228 patients, compared according to whether there was recurrence during follow-up

Characteristic	Total (n=228)	Recurrence (n=85)	No recurrence (n=143)	P
Age (y)	60.3±10.7	61.2±10.1	59.7±11.0	0.329
Age ≥60 years	123 (53.9)	53 (62.4)	70 (49.0)	0.050
Female	157 (68.9)	56 (65.9)	101 (70.6)	0.454
BMI (kg/m^2)	20.6±2.6	20.7±2.3	20.6±2.8	0.784
Current or past smoker	43 (18.9)	15 (17.6)	28 (19.6)	0.718
Previous history of TB treatment	75 (32.9)	33 (38.8)	42 (29.4)	0.142
Previous history of NTM treatment	14 (6.1)	9 (10.6)	5 (3.5)	0.031
Comorbidity				
COPD	26 (11.4)	10 (11.8)	16 (11.2)	0.895
Diabetes mellitus	17 (7.5)	10 (11.8)	7 (4.9)	0.056
Chronic liver disease	17 (7.5)	6 (7.1)	11 (7.7)	0.860
Malignancy	43 (18.9)	18 (21.2)	25 (17.5)	0.491
Etiology				0.705
Mycobacterium avium	111 (48.7)	40 (47.1)	71 (49.7)	
Mycobacterium intracellulare	117 (51.3)	45 (52.9)	72 (50.3)	
Positive AFB smear at treatment initiation	77 (33.8)	30 (35.3)	47 (32.9)	0.708
Number of involved lobes	3.5±1.3	3.7±1.3	3.4±1.3	0.079
Use of injectable aminoglycosides	87 (38.2)	28 (32.9)	59 (41.3)	0.211
Daily therapy	222 (97.4)	85 (100.0)	137 (95.8)	0.087
Surgical resection	5 (2.2)	3 (3.5)	2 (1.4)	0.364
Shorter treatment duration (9–11 months)	59 (25.9)	23 (27.1)	36 (25.2)	0.753
Time to initiate treatment after diagnosis (months)	5.2 (1.7–12.0)	4.4 (1.1–11.9)	5.3 (1.9–13.3)	0.414
Follow-up duration after treatment completion (months)	56.1 (31.3–78.1)	68.5 (46.5–91.1)	45.0 (23.7–70.8)	<0.001

BMI, body mass index; TB, tuberculosis; NTM, nontuberculous mycobacteria; COPD, chronic obstructive lung disease; AFB, acid-fast bacilli. Data are presented as mean (± standard deviation), median (interquartile range), or number (%).

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Table 3 Clinical characteristics of the 210 patients followed up for at least 1 year, compared according to whether or not they experienced recurrence

Characteristic	Total (n=210)	1-y recurrence (n=29)	No 1-y recurrence (n=181)	P
Age (y)	60.4±10.7	62.0±10.6	60.1±10.8	0.370
Age ≥60 years	115 (54.8)	21 (72.4)	94 (51.9)	0.040
Female	143 (68.1)	20 (69.0)	123 (68.0)	0.914
BMI (kg/m^2)	20.6±2.5	20.7±2.3	20.6±2.6	0.832
Current or past smoker	40 (19.0)	4 (13.8)	36 (19.9)	0.611
Previous history of TB treatment	69 (32.9)	12 (41.4)	57 (31.5)	0.293
Previous history of NTM treatment	13 (6.2)	4 (13.8)	9 (5.0)	0.086
Comorbidity				
COPD	23 (11.0)	1 (3.4)	22 (12.2)	0.213
Diabetes mellitus	17 (8.1)	5 (17.2)	12 (6.6)	0.066
Chronic liver disease	14 (6.7)	3 (10.3)	11 (6.1)	0.417
Malignancy	39 (18.6)	6 (20.7)	33 (18.2)	0.752
Etiology				0.756
Mycobacterium avium	103 (49.0)	15 (51.7)	88 (48.6)	
Mycobacterium intracellulare	107 (51.0)	14 (48.3)	93 (51.4)	
Positive AFB smear at treatment initiation	69 (32.9)	9 (31.0)	60 (33.1)	0.822
Number of involved lobes	3.5±1.3	3.6±1.2	3.5±1.3	0.618
Use of injectable aminoglycosides	78 (37.1)	10 (34.5)	68 (37.6)	0.749
Daily therapy	206 (98.1)	29 (100.0)	177 (97.8)	>0.999
Surgical resection	4 (1.9)	2 (6.9)	2 (1.1)	0.093
Shorter treatment duration (9–11 months)	53 (25.2)	9 (31.0)	44 (24.3)	0.439
Time to initiate treatment after diagnosis (months)	4.8 (1.6–10.9)	6.9 (1.0–13.4)	4.8 (1.8–10.8)	0.882
Follow-up duration after treatment completion (months)	59.2 (38.3–81.3)	66.6 (44.5–88.3)	57.3 (37.7–79.6)	0.106

BMI, body mass index; TB, tuberculosis; NTM, nontuberculous mycobacteria; COPD, chronic obstructive lung disease; AFB, acid-fast bacilli. Data are presented as mean (± standard deviation), median (interquartile range), or number (%).

12 months treatment after culture conversion (20). These studies have provided the evidence base for guidelines including those of the ATS in 2007 (4) and of the British Thoracic Society guidelines in 2017 (10), as well as for expert opinion (1,11,21). However, no further study since these guidelines were published has investigated whether the duration of MAC LD therapy should be 12 months beyond sputum culture conversion. In the present study we showed that, at least for the NC-NB form of MAC LD, a treatment duration shorter than the recommended 12 months after culture conversion may be adequate.

In our study, the mean duration of the treatment of the shorter treatment group was nearly 3 months shorter than that of the standard group. Although the mean treatment duration for the shorter treatment group was 11.1 months, which may appear to differ only to a small extent from the recommended "at least 12 months" of treatment, in practice many attending physicians treat patients for far longer than 12 months as a result of the words "at least". Treatment durations after culture conversion of around 16–18 months have been reported in previous studies (5,9,16,22). In the present study, the mean treatment duration in the standard

Table 4 Clinical characteristics of the 163 patients followed up for at least 3 years, compared according to whether or not they experienced recurrence

Characteristic	Total (n=163)	3-y recurrence (n=62)	No 3-y recurrence (n=101)	P
Age (y)	59.9±10.2	62.3±9.8	58.4±10.2	0.019
Age ≥60 years	87 (53.4)	43 (69.4)	44 (43.6)	0.001
Female	115 (70.6)	40 (64.5)	75 (74.3)	0.185
BMI (kg/m^2)	20.7±2.4	20.7±2.2	20.6±2.6	0.798
Current or past smoker	29 (17.8)	10 (16.1)	19 (18.8)	0.664
Previous history of TB treatment	56 (34.4)	24 (38.7)	32 (31.7)	0.359
Previous history of NTM treatment	8 (4.9)	7 (11.3)	1 (1.0)	0.005
Comorbidity				
COPD	20 (12.3)	7 (11.3)	13 (12.9)	0.765
Diabetes mellitus	15 (9.2)	6 (9.7)	9 (8.9)	0.869
Chronic liver disease	13 (8.0)	5 (8.1)	8 (7.9)	>0.999
Malignancy	33 (20.2)	13 (21.0)	20 (19.8)	0.857
Etiology				0.701
Mycobacterium avium	82 (50.3)	30 (48.4)	52 (51.5)	
Mycobacterium intracellulare	81 (49.7)	32 (51.6)	49 (48.5)	
Positive AFB smear at treatment initiation	45 (27.6)	19 (30.6)	26 (25.7)	0.497
Number of involved lobes	3.4±1.3	3.7±1.4	3.3±1.2	0.043
Use of injectable aminoglycosides	58 (35.6)	19 (30.6)	39 (38.6)	0.302
Daily therapy	163 (100.0)	62 (100.0)	101 (100.0)	–
Surgical resection	4 (2.5)	3 (4.8)	1 (1.0)	0.154
Shorter treatment duration (9–11 months)	43 (26.4)	18 (29.0)	25 (24.8)	0.547
Time to initiate treatment after diagnosis (months)	4.2 (1.6–10.7)	4.1 (1.1–11.8)	4.3 (1.8–10.4)	0.783
Follow-up duration after treatment completion (months)	68.5 (52.4–89.6)	67.6 (52.5–83.7)	69.1 (51.5–90.7)	0.828

BMI, body mass index; TB, tuberculosis; NTM, nontuberculous mycobacteria; COPD, chronic obstructive lung disease; AFB, acid-fast bacilli. Data are presented as mean (± standard deviation), median (interquartile range), or number (%).

Table 5 Analyses of factors affecting recurrence in non-cavitary nodular bronchiectatic *Mycobacterium avium* complex lung disease

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	aOR (95% CI)	P
1-y recurrence				
Shorter treatment duration (9–11 months)	1.401 (0.595–3.301)	0.440	1.190 (0.484–2.929)	0.705
Age ≥60 years	2.430 (1.023–5.770)	0.044	2.565 (1.020–6.450)	0.045
Previous history of NTM treatment	3.058 (0.876–10.676)	0.080	2.769 (0.735–10.438)	0.132
Diabetes mellitus	2.934 (0.950–9.060)	0.061	1.960 (0.586–6.560)	0.275
Surgical resection	6.630 (0.896–49.050)	0.064	8.100 (0.976–67.194)	0.053
3-y recurrence				
Shorter treatment duration (9–11 months)	1.244 (0.611–2.531)	0.548	1.047 (0.487–2.250)	0.907
Age ≥60 years	2.932 (1.503–5.718)	0.002	2.511 (1.256–5.019)	0.009
Previous history of NTM treatment	12.727 (1.526–106.135)	0.019	8.598 (0.997–74.189)	0.051
Number of involved lobes	1.299 (1.006–1.677)	0.045	1.207 (0.919–1.586)	0.176

OR, odds ratio; CI, confidence interval; aOR, adjusted OR; NTM, nontuberculous mycobacteria lung disease.

treatment group was approximately 14 months. Given the relatively long treatment period after culture conversion in clinical practice, reducing the treatment duration to 11 months would be a meaningful difference. Considering the well-known adverse events associated with long-term antimycobacterial treatments (23) and the costs associated with the treatment, we believe that a shorter treatment duration might be acceptable, at least for a subset of patients. It should be emphasized that we do not believe treatment for a shorter duration would be applicable to all patients with the NC-NB form of MAC LD. Stopping treatment earlier than recommended can potentially lead to the incomplete eradication of the causative organism, resulting in the eventual recurrence of the original strain. This treatment strategy should therefore be employed with caution for selected patients, such as those with an initially low mycobacterial burden who experience adverse drug events and whose treatment duration was close to the recommended length. A prospective randomized trial is needed to establish which patients could be treated for a shorter duration.

Recurrence after successful treatment can be the result of a relapse of the same MAC strain or reinfection with a new strain. The period between the end of treatment and recurrence is shorter with a relapse than with reinfection: a true relapse generally occurs within 1 year, whereas reinfection typically occurs after 1–2 years (5,9,16,22). Reinfection after treatment success is due to exposure to an environmental source, such as water or soil (24); household tap water tends to be the main source of *M. avium* pulmonary infection, whereas *M. intracellulare* pulmonary infections are generally acquired from soil (25). This is a particular issue for individuals with immune deficiencies, which predispose them to pulmonary MAC infections (26). In our study, the 1-year recurrence rate was slightly higher in the shorter duration group, although the difference was not statistically significant. Considering that recurrence in the first year is more likely to be due to a relapse, the residual mycobacterial burden of the initial strain could be responsible for this slight difference in recurrence rate in the shorter treatment group. However, the difference in recurrence rate between the two groups seemed to disappear with longer follow-up, as shown in *Figure 2*. The 3-year recurrence rates, which are more likely to reflect reinfection by a different strain, were similar. These findings suggest that the shorter treatment duration eventually resulted in a similar recurrence rate to that with the standard duration, with a possible slight increase in relapse rate soon after the end of treatment, but ultimately a similar reinfection rate as

time elapsed. However, we did not genotype the isolates, so we were not able to determine whether these recurrences were due to relapse or reinfection.

Current guidelines recommend the same treatment duration after culture conversion for all subtypes of MAC LD irrespective of the presence of cavitation (i.e., FC or CNB *vs.* NC-NB). Cavitation is the classic hallmark of a very high mycobacterial burden in mycobacterial LD (27). Thus, there are more bacilli in the lungs in cavitary MAC LD. In addition, the destruction of the vascular architecture of the cavity limits drug supply and penetration into the cavitary lesion (28), so a longer duration of total treatment might be needed in cavitary MAC LD. It is also possible that the remnant mycobacterial burden after culture conversion is higher in MAC LD with cavitation, requiring a longer treatment duration after microbiologic conversion to eradicate the remnant organisms. This could be another reason for considering shorter treatments for the NC-NB form of MAC LD than for the FC or CNB forms.

In the present study, age ≥60 years was a statistically significant risk factor for both 1- and 3-year recurrence. There are several plausible explanations for this. First, there are various host immune responses to MAC infection, such as the secretion of interferon gamma, tumor necrosis factor alpha, interleukin-6, interleukin-12, and TH1 immunity triggered through Toll-like receptors (29). Waning immunity with age could be one reason why older patients might be more susceptible with reinfection with a MAC organism after the successful eradication of the initial infection. Second, approximately 90% of South Koreans have received the bacillus Calmette-Guérin (BCG) vaccination, which is mandatory because of the high incidence of tuberculosis in South Korea (30). In addition, before 1997, those with the negative tuberculin skin test at age 12 years were revaccinated with BCG. The BCG vaccination is known to be protective against infection with *M. avium* (31). However, a recent study has reported that the vaccine effectiveness of BCG seemed to wane beyond 20 years after vaccination (32). Thus, the decreased effectiveness of the BCG vaccination may be another reason for the higher recurrence rate due to reinfection of a MAC organism among the patients aged ≥60 years, whose BCG vaccination was administered at least 40 years previously.

Our study had several limitations. Most significantly, our analysis was conducted at a single referral center, with a non-randomized retrospective design. In addition, the decision about treatment duration was mainly made by the attending physician, so it is likely to have been determined

by unmeasured factors that affected the patients' compliance with treatment. We were unable to identify the exact reason for the decision for a shorter treatment duration for most of the 59 patients. It is uncertain whether the results of this study can be applied to those undergoing intermittent therapy, as most of our patients received daily therapy. Finally, we did not genotype the isolates, so we were unable to distinguish between relapse and reinfection.

In conclusion, during a median follow-up of approximately 5 years, the recurrence rate in patients with NC-NB MAC LD who received the standard treatment for 9–11 months after achieving culture conversion was similar to that of patients who received treatment for the recommended ≥12 months. This finding suggests that post-conversion treatment that is shorter than the recommended duration may be applicable for selected patients with NC-NB MAC LD.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the Institutional Review Board (RFB) of Asan Medical Center (IRB No. 2018-0986), which waived the requirement for informed consent because of the retrospective nature of the analysis.

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