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Note

Efficacy and safety of intermittent maintenance therapy after successful treatment of *Mycobacterium avium* complex lung disease☆

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ABSTRACT

Background: The optimal duration of antimicrobial therapy for *Mycobacterium avium* complex lung disease (MAC-LD) is unknown, and recurrence rates are high after treatment discontinuation. Intermittent therapy is recommended for the initial treatment of non-cavitary nodular/bronchiectatic MAC-LD. We hypothesized that intermittent maintenance therapy (IMT) could effectively prevent recurrence after successful treatment of MAC-LD.

Methods: Adult patients diagnosed with MAC-LD who received IMT after successful daily therapy (DT) between January 1, 2006 and December 31, 2016 were identified from clinical databases at three institutions in Japan. Treatment outcomes were evaluated for all patients.

Results: Of 38 patients (median age, 66 years; 29 women; nodular/bronchiectatic form, 29 patients) who received IMT after successful treatment, one was excluded due to death from an unknown cause, 1 month after IMT initiation. Finally, treatment outcomes were evaluated for 37 patients. Twenty-eight (76%) patients had sustained negative culture results over a median follow-up duration of 2.7 (interquartile range [IQR], 1.9–6.0) years, while six (16%) required switching to DT because of clinical deterioration over a median follow-up duration of 2.7 (IQR, 1.6–4.1) years. Favorable clinical outcomes were achieved for all patients who exhibited clinical deterioration. All patients tolerated the antimicrobials without discontinuation, and follow-up drug susceptibility testing showed negative results for clarithromycin-resistant MAC in the patients who experienced clinical deterioration.

Conclusions: IMT after successful treatment may be a feasible option for patients with MAC-LD. Further studies should determine the population that would benefit from this strategy.

The incidence of pulmonary infection due to nontuberculous mycobacteria (NTM) is increasing worldwide [1–4]. In Japan, *Mycobacterium avium* complex lung disease (MAC-LD) is the most common form of pulmonary NTM infection [3], affecting the health-related quality of life of patients [5]. MAC-LD is also an important cause of morbidity and mortality [6]. Standard antimicrobial therapy, including macrolide-containing regimens, is recommended for MAC-LD until the patient demonstrates negative culture results for 1 year. However, recent studies have shown a high recurrence rate for MAC-LD after the discontinuation of antimicrobials, following successful treatment [7–9].

Intermittent therapy is recommended for the initial treatment of the non-cavitary nodular/bronchiectatic (NB) form of MAC-LD [10]. A historical cohort study revealed that intermittent therapy is as effective as daily therapy (DT) and is better tolerated by

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patients [11]. Therefore, we hypothesized that intermittent maintenance therapy (IMT) could effectively prevent recurrence after successful treatment. The aim of the present study was to evaluate the efficacy and safety of IMT after successful treatment of MAC-LD.

Adult patients diagnosed with MAC-LD on the basis of the ATS/IDSA 2007 statement [10] who received IMT after successful DT from January 1, 2006 to December 31, 2016 were identified at Keio University Hospital, Higashinagoya National Hospital, and Fukujuji Hospital. Data were collected from the patients' medical records. All patients were observed until their death, the date of their last visit, or the end of the study (August 31, 2017). Successful treatment was defined as no positive culture result with a stable course after the achievement of sputum conversion. Sputum conversion was defined as three consecutive negative culture results with the time to conversion defined as the date of the first negative culture [11]. Clinical deterioration was defined as two consecutive positive culture results for MAC [7] or one positive culture result plus deterioration of symptoms or CT findings. Drug susceptibility results were available for all patients. Clarithromycin (CLR) resistance was defined by a minimum inhibitory concentration of $\geq$32 μg/mL.

Table 1 shows the clinical characteristics of the 38 patients at the time of switching to IMT. The NB form (29 patients, 76%) was the most common radiographic pattern [12]. The median modified Reiff score, indicating the severity of bronchiectasis [13], was 2 (IQR, 1–4). Four patients (11%) had CLR-resistant MAC before successful treatment. The initial treatment was well tolerated by all patients except one with visual disturbance, and sputum conversion was achieved for all patients after a median DT duration of 0.3 (IQR, 0.1–1.8) years. After successful DT with a median duration of 2.4 (IQR, 2.0–3.5) years, antimicrobials were changed to follow the IMT regimen by the attending physician. IMT was administered for a median duration of 2.5 (IQR, 1.6–5.2) years after successful treatment. Almost all patients received IMT on an alternate-day basis. The regimen included CLA (100%), ethambutol (95%), rifampicin (100%), moxifloxacin (11%), and sitafloxacin (3%).

One patient died from an unknown cause 1 month after IMT initiation. The clinical deterioration rates for the remaining patients and clinical outcomes are shown in Figs. 1 and 2. There were no differences between the NB form and the other forms (log-rank test, $P = 0.483$; Fig. 1B). Of the 37 patients, 28 (76%), including four who discontinued IMT, had sustained negative culture results over a median follow-up duration of 2.7 (IQR, 1.9–6.0) years. Six patients (16%) switched to DT because of clinical deterioration over a median follow-up duration of 2.7 (IQR, 1.6–4.1) years. IMT was discontinued for the remaining three patients (8%) at 0.4, 1.8, and 6.3 years, respectively, at the request of the patients themselves. Clinical deterioration occurred in these patients at 0.8, 0.3, and 3.6 years after discontinuation of therapy, respectively. Of the nine patients with clinical deterioration, seven achieved negative conversion of sputum culture after DT, while two were kept under observation without treatment because of stable symptoms and CT findings. Of five patients with the FC form or a cavitary lesion, one patient was excluded due to death from an unknown cause, 1 month after beginning IMT; two patients exhibited clinical deterioration at 2.1 and 3.3 years, respectively. Moreover, of the four patients with CLR-resistant MAC before IMT administration, two exhibited clinical deterioration at 1.7 and 3.4 years, respectively. Importantly, these four patients achieved negative conversion of sputum culture after switching to DT. Follow-up drug susceptibility testing did not show the development of CLR-resistant MAC in

Table 1
Clinical characteristics of patients with MAC-LD at the time of switching to intermittent therapy.

Variables	Patients (n = 38)
Age, years	66 (60–72)
BMI, kg/m^2	19.1 (18.0–20.8)
Female sex	29 (76)
Smoking status: Never/Former/Current	32 (84)/4 (11)/2 (5)
Charlson comorbidity index	0 (0–1)
Underlying pulmonary disease[a]	
COPD	3 (8)
Lung cancer	2 (5)
Radiographic pattern	
NB/FC/NB + FC/Unclassified	29 (76)/1 (3)/3 (8)/5 (13)
Presence of cavitary lesion	5 (13)
Modified Reiff score	2 (1–4)
CLR-resistant MAC	4 (11)
History of pulmonary resection[b]	4 (11)
Recurrence after treatment for MAC	8 (22)
Duration until sputum conversion, years	0.3 (0.1–1.8)
Duration of daily therapy, years	2.4 (2.0–3.5)
Regimen for daily therapy	
CLR, RIF, EMB	38 (100)
Addition of MXF/STFX	5 (13)
Addition of AMK	3 (8)
Duration of intermittent therapy, years	2.5 (1.6–5.2)
Dosage interval: alternate days/three times per week	36 (95)/2 (5)
Regimen for intermittent therapy, including dosage	
CLR, 800/600 mg	37 (97)/1 (3)
EMB, 750/500 mg	9 (24)/28 (74)
RIF, 600/450/300 mg	23 (61)/13 (34)/2 (5)
MXF, 400 mg	4 (11)
STFX, 200 mg	1 (3)

Data are shown as number of patients (%) or median (interquartile range).
AMK, amikacin; BMI, body mass index; CLR, clarithromycin; COPD, chronic obstructive pulmonary disease; EMB, ethambutol; FC, fibrocavitary; NB, nodular/bronchiectatic; RIF, rifampin; MAC, *Mycobacterium avium* complex; MAC-LD, *Mycobacterium avium* complex lung disease; MXF, moxifloxacin; STFX, sitafloxacin.
[a] None of the patients had other underlying pulmonary diseases, such as pulmonary tuberculosis, asthma, or interstitial lung disease.
[b] Adjunctive resection surgery for MAC-LD.

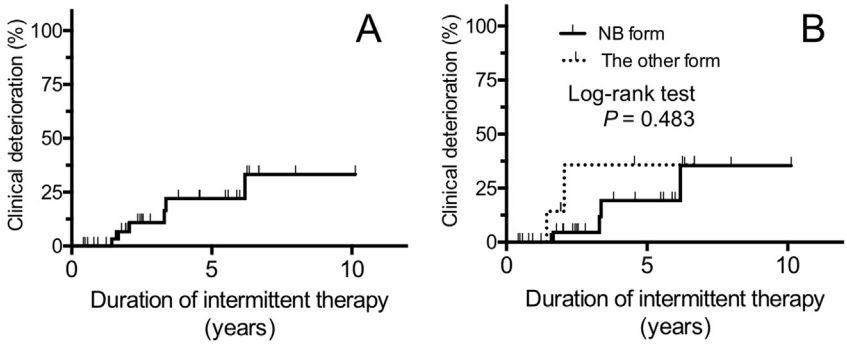

Fig. 1. (A) The rate of clinical deterioration in patients receiving intermittent maintenance therapy (IMT) after successful treatment of *Mycobacterium avium* complex lung disease. (B) Kaplan–Meier curves showing the recurrence rates for the NB form and the other forms. Tick marks represent censored data, including the date of the last visit or discontinuation of IMT without deterioration. The rate of clinical deterioration in patients who received IMT after successful treatment is 11% at 3 years, 22% at 6 years, and 33% at 10 years.

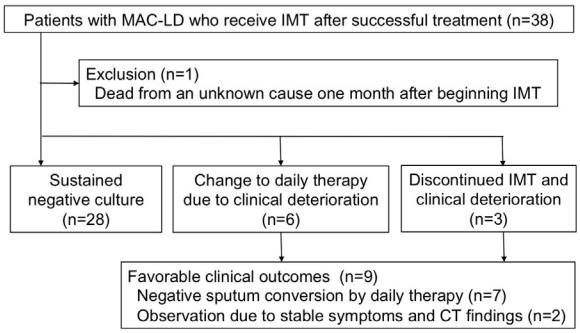

Fig. 2. A flowchart depicting the clinical outcomes of patients who received intermittent maintenance therapy (IMT) after successful treatment of *Mycobacterium avium* complex lung disease. CT, computed tomography; IMT, intermittent maintenance therapy; MAC-LD, *Mycobacterium avium* complex lung disease.

these four patients. There were no severe adverse events, such as visual disturbances, during IMT. Two patients experienced mild adverse events (grade 2 leukopenia in one and grade 1 rash in the other); however, all patients tolerated the antimicrobials without discontinuation.

In our study, which mainly included patients with the NB form of MAC-LD, 76% of patients had sustained negative culture results, whereas 24% showed clinical deterioration. A favorable outcome was eventually achieved for all patients who showed clinical deterioration. Previous studies have shown considerable variation in the recurrence rate for MAC-LD without therapy after successful treatment, because of differences in the treatment regimens, disease form, severity of CT findings, and follow-up duration. However, recent studies have indicated that the NB form of MAC-LD is associated with a higher recurrence rate [7–9]. Notably, two recent studies presenting the recurrence rates after successful treatment of MAC-LD, using Kaplan–Meier curves, revealed that the recurrence rate for the NB form was approximately 50% at 4 or 5 years after treatment. Moreover, their multivariate analyses showed that the NB form was a predictive factor for recurrence [7,8]. The recurrence rate for the NB form was lower in our study than in the two previous studies. The NB form classically occurs in female nonsmokers without any risk factors and is affected by host genetic factors [14] and exposure to these ubiquitous organisms [15]. Because these factors do not change immediately, IMT may be effective in preventing recurrence.

This study has several limitations. First, it is a retrospective study with a small sample size. Second, the decision to switch to IMT after successful treatment was based on the preference of the attending physician and patient instead of an established protocol. However, guidelines have recommended that antimicrobial therapy should be ideally administered for >1 year after negative conversion of sputum culture [10,16]. Furthermore, our study mostly included patients with the NB form, which is associated with a high recurrence rate. Third, we did not identify whether recurrence was due to reinfection or true relapse because genotype data were not available. However, previous reports indicate that recurrent MAC-LD is usually caused by reinfection [8,9]. Fourth, the appropriate duration of IMT remains unclear. In the study period, 24 of 37 patients (65%) continued IMT. Therefore, the recurrence rate after discontinuation of IMT still remains unclear. Additionally, the total drug dose could be higher for patients receiving IMT than for those receiving retreatment after recurrence. However, if MAC-LD worsens after treatment cessation, lung destruction can occur, resulting in decreased pulmonary function or impaired health-related quality of life. In the present study, we confirmed that all patients, including elderly individuals, tolerated the antimicrobials without adverse effects during long-term IMT.

In conclusion, this study demonstrates that IMT may be a safe and effective option to prevent recurrence after successful DT for MAC-LD. Further studies should determine the populations that would benefit from IMT and retreatment after recurrence, as well as the optimal duration of IMT for the prevention of recurrence.

Conflicts of interest

The authors declare that they have no competing interests.

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None.

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