ERJ Express. Published on October 18, 2018 as doi: 10.1183/13993003.01038-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

The second recurrence of MAC lung disease after successful treatment for first recurrence

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Please cite this article as: Kwon BS, Shim TS, Jo K-W. The second recurrence of MAC lung disease after successful treatment for first recurrence. *Eur Respir J* 2018; in press (https://doi.org/10.1183/13993003.01038-2018).

Research letters

Title: The second recurrence of MAC lung disease after successful treatment for first recurrence

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Take-home message

We found that approximately 60% of patients who were successfully treated for their first recurrence of MAC lung disease eventually experienced a second recurrence. Approximately half of the second recurrence patients required anti-MAC treatment.

Key words

Mycobacterium avium complex, second recurrence, treatment

To the editor:

The recurrence rate of *Mycobacterium avium* complex (MAC) lung disease (LD) after successful treatment is approximately 10%–48% [1-3]. These episodes represent true relapse from the same MAC strain or a reinfection with a new strain [1, 2, 4]. Nodular bronchiectatic (NB) type, old age, lower body mass index (BMI) and *Mycobacterium avium* isolates are related to recurrence [3, 5, 6].

However, information on the clinical course of MAC-LD after successfully treating the first recurrence is limited [7]. We therefore investigated the second recurrence in patients with MAC-LD who were successfully treated for the first recurrence, with a focus on the rate and treatment outcomes of second recurrence, and its predictors.

We categorised radiologic abnormalities into three groups: (1) cavitary NB, (2) non-cavitary NB and (3) fibrocavitary (FC), as previously defined [5, 8]. Only the patients who received treatment for ≥12 months were analysed for treatment response. Treatment outcomes were categorised as follow [9]: (1) treatment failure: no conversion to negative sputum culture even after ≥12 months of treatment; (2) treatment completion: achievement of sputum culture conversion with a treatment duration after conversion of <12 months; and (3) treatment success: achievement of sputum culture conversion with a treatment duration after conversion of ≥12 months. Recurrence was defined as two consecutive positive sputum cultures after treatment success.

Between March 2000 and August 2017, 104 patients who experienced first recurrence of MAC-LD, amongst the 372 patients who achieved treatment success for MAC-LD, were identified at the Asan Medical Center in Seoul, South Korea. Of these 104 patients, clinical symptom deteriorations were noted in 61 (58.7%) patients and radiological changes were noted in 62 (59.6%) patients. Of 104 patients, 55 (52.9%) patients received anti-MAC treatment. The most common radiological finding was the non-cavitary NB type, which was

observed in 39 (70.9%) patients. Daily therapy comprising macrolides, ethambutol, and rifamycin was the most commonly prescribed regimen. The overall success rate of treatment of the first recurrence was 61.8% (34/55).

Amongst the 34 patients who achieved treatment success after the first recurrence of MAC-LD, 20 (58.8%) experienced a second recurrence during the median follow-up of 15.2 months (interquartile range [IQR], 7.7–26.4 months). The etiologic agent was *Mycobacterium avium* in 12 patients (60.0%) and *Mycobacterium intracellulare* in 8 patients (40.0%). Amongst the 20 patients, deterioration in the radiological changes and clinical symptoms were observed in 16 (80%) and 9 (45%) patients. A drug susceptibility test was performed in 85% of the patients (17/20); no macrolide-resistant cases were detected.

Amongst the 20 patients with second recurrence, 9 (45%) patients received anti-MAC treatment. Radiological features included the non-cavitary NB type in 7 patients (77.8%), the cavitary NB type in 1 patient (11.1%) and the FC type in 1 patient (11.1%). Radiological deterioration was noted in all 9 patients, and the symptoms worsened in 5 patients. Further, 8 patients were treated with the daily therapy comprising macrolides (azithromycin for 7 patients and clarithromycin for 1 patient), ethambutol and rifamycin (rifampin or rifabutin), with or without moxifloxacin. The remaining patient received a combination of daily azithromycin, rifabutin, clofazimine and moxifloxacin due to a previous history of optic neuropathy caused by ethambutol. All 9 patients were administered streptomycin three–five times per week via intramuscular injections for a median duration of 4.8 months (IQR, 3.8–7.3 months). The treatment outcomes for the second recurrence were as follows: treatment success, 44.4% (4/9); treatment completion, 11.1% (1/9); and treatment failure, 44.4% (4/9).

An analysis of factors related to the second recurrence revealed no significant differences based on the radiological type. That is, amongst the 34 patients who achieved treatment success for the first recurrence, a second recurrence occurred in 58.6% (17/29) of the NB

type and 60.0% (3/5) of the FC type (Figure 1; $P = 0.955$). No other clinical variables were significant factors of the second recurrence.

To the best of our knowledge, this is the first study to investigate the rate of second recurrence after successful treatment of the first recurrence of MAC-LD, its predictors and treatment outcomes. Our findings reveal several important clinical implications. First, even after successful treatment of the first episode of recurrence, secondary episodes of MAC-LD recurrence were also frequent. We found that approximately 60% of patients who were successfully treated for the first recurrence eventually experienced a second recurrence, which suggests that the recurrence of MAC can occur repeatedly in a substantial proportion of patients. The most probable explanation for repetitive recurrence is reinfection caused by unavoidable exposure to environmental sources, such as water and soil [10]. This is a particular issue in subjects with host immune deficiencies, which predisposes individuals to pulmonary MAC infections [11]. Reinfection has been reported to occur more often than true relapse in MAC-LD [2, 4, 5, 7].

The second important finding is that approximately half of the patients with secondary recurrence required anti-MAC treatment, with unsuccessful outcomes; the treatment success rate was less than half, although all patients received macrolide-containing regimens that included aminoglycoside. The reason for this low treatment success rate appears unclear given that there were no cases of macrolide resistance, and only two cases displayed the cavitary form of the disease. Recently, Jhun *et al.* found that refractory MAC-LD is commonly caused by reinfection with new strains [12]. In their study, amongst 49 patients with refractory MAC-LD whose pre- and post-treatment isolates were stored, genotyping revealed that reinfection by new MAC strains occurred in 36 (73%) patients. Only 13 (27%) patients had persistent infections with their original strains. We thought that reinfection with new MAC strains could be the most plausible reason for the low treatment success rate in the

present study. In this light, the statement from the British Thoracic Society guidelines is noteworthy: 'If available, genotyping may help distinguish relapse from reinfection' [13]. We believe that this statement can be applied to any cases with first or second recurrence for identifying the cause and preparing an appropriate treatment regimen.

In addition to radiological type, previous studies have reported that older age, lower BMI, and *M. avium* isolates were associated with the first recurrence of MAC-LD [6]. However, none of these variables were related to a second recurrence in our study. This could be attributed to the small sample size, warranting further studies with a sufficient number of patients to identify factors related to the second recurrence in similar cases.

Our study has several limitations. Our study was a retrospective study performed at a single centre with small sample size. Moreover, 7 patients experienced a first recurrence but failed to follow-up. Although the number of patients lost to follow-up was small, this may have affected the results. Additionally, we did not have any apparent algorithm or criteria to determine treatment initiation for patients who experienced recurrence. Moreover, the treatment regimen was decided by the attending clinicians without a constant protocol. Finally and most importantly, we did not genotype the isolates; therefore, we could not distinguish the difference between relapse and reinfection in our cases.

In conclusion, we found that approximately 60% of patients who achieved successful treatment for the first recurrence of MAC-LD eventually experienced a second recurrence. Approximately half of the second recurrence patients required anti-MAC treatment, with unsatisfactory outcomes.

Acknowledgements

None

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FIGURE LEGEND

Figure 1. Kaplan–Meier curves of the cumulative rate of second recurrence in patients successfully treated for the first recurrence of *Mycobacterium avium* complex lung disease.

NB, nodular bronchiectasis; NC, non-cavitary; CNB, cavitary nodular bronchiectasis; FC, fibrocavitary