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Response to Switch from Intermittent Therapy to Daily Therapy for Refractory Nodular Bronchiectatic *Mycobacterium avium* Complex Lung Disease

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Intermittent three-times-weekly antibiotic therapy is recommended for the initial treatment of patients with noncavitary nodular bronchiectatic *Mycobacterium avium* complex lung disease. Although some experts recommend switching from intermittent to daily therapy for patients whose sputum has persistent positive cultures after intermittent therapy, the clinical efficacy of these modifications is unknown. Of 20 patients whose sputum had persistent positive cultures after 12 months of intermittent antibiotic therapy, specimens from 6 patients (30%) achieved a negative culture after a change to daily therapy.

Mycobacterium avium complex lung disease (MAC-LD) is the most common form of lung disease caused by nontuberculous mycobacteria (NTM), and the prevalence of MAC-LD is increasing worldwide (1–12). MAC-LD can present as the upper lobe fibrocavitary form, which occurs primarily in men with underlying lung disease such as previous pulmonary tuberculosis, or as the nodular bronchiectatic (NB) form, which occurs primarily in women without other underlying lung disease (13–15).

Intermittent three-times-weekly therapy, which consists of a macrolide (clarithromycin [CLR] or azithromycin [AZM]), rifampin (RIF), and ethambutol (EMB), is recommended for the initial treatment of noncavitary NB MAC-LD (16). After at least 12 months of this intermittent antibiotic therapy, however, sputum culture conversion fails in about 15% to 25% of patients (17, 18). Some experts recommended modifications of the first-line therapy, such as switching from intermittent therapy to daily therapy, for these patients (19). However, there are no data in the literature regarding the clinical efficacy of these modifications in patients with refractory NB MAC-LD. The objective of the present study was to evaluate the effects of switching from intermittent therapy to daily therapy in noncavitary NB MAC-LD patients whose sputum failed culture conversion after at least 12 months of initial intermittent antibiotic therapy.

We recently reported the treatment outcomes of 118 treatment-naive patients with noncavitary NB MAC-LD who initiated standard intermittent antibiotic therapy (18). The regimen for the intermittent therapy included the following components administered three times weekly: 500 mg of AZM or 1,000 mg of CLR, EMB at 25 mg/kg of body weight, and 600 mg of RIF. Of these patients, 79 patients (67%) achieved successful sputum culture conversion and 39 patients (33%) had unfavorable outcomes, including 13 patients with early discontinuation of antibiotic therapy and 26 patients whose sputum failed to convert to negative cultures despite 12 months of intermittent antibiotic therapy (18).

Of these 26 patients, 1 patient was transferred to another hospital, and 25 patients continued antibiotic therapy in our institution; intermittent therapy continued in 4 patients (16%), and intermittent therapy was switched to daily therapy in 21 patients (84%). The modifications of antibiotic therapy in these 21 patients were at the discretion of the attending physician. The regimen for the daily therapy included the following components: 250 mg of AZM, 15 mg/kg of EMB, and 450 mg/day of RIF (for a body weight of $<$50 kg) or 600 mg/day of RIF (for a body weight of $\geq$50 kg). Drug susceptibility test results at the time of initial intermittent therapy and before the switch from intermittent to daily therapy were available for all patients, and the MAC isolates recovered from 1 patient showed development of resistance to CLR (MIC, $\geq$32 μg/ml) during intermittent antibiotic therapy. Of the 21 patients who switched to daily therapy, sputum culture conversion rates were analyzed in 20 patients, excluding 1 patient who developed CLR-resistant MAC-LD during intermittent therapy. Sputum conversion was defined as three consecutive negative cultures, with the time of conversion defined as the date of the first negative culture (18). The 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 (18).

Of the 20 patients, 10 (50%) were female. The median age was 57 years (interquartile range [IQR], 49 to 65 years), and the median body mass index was 20.6 kg/m^2 (IQR, 19.4 to 21.8 kg/m^2). None of the patients was positive for HIV infection. The etiologic agents included *Mycobacterium intracellulare* in 14 patients (70%)

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and *M. avium* in 6 patients (30%). A total of 6 patients (30%) had a positive acid-fast bacillus (AFB) smear at the time of the switch from intermittent to daily therapy.

Of 20 patients, the sputum of six patients (30%) became negative after the change to daily therapy. The median time to sputum conversion was 56 days (IQR, 28 to 109 days). However, sputum culture conversion failed in 14 patients (70%), even after switching to daily therapy that was a median of 541 days (IQR, 367 to 768 days) in duration. Of these 14 patients, 4 patients underwent pulmonary resection, comprising lobectomy ($n = 2$) or lobectomy plus wedge resection ($n = 2$), after a median of 394 days (IQR, 245 to 564 days) of daily therapy, and a negative sputum culture was achieved and maintained in 3 of these 4 patients. Follow-up drug susceptibility testing showed that the development of CLR resistance occurred in 2 (21%) of 14 patients whose sputum had CLR-susceptible MAC isolates at the time of the switch to daily therapy and who had persistent positive cultures during the daily therapy. Of these 2 patients who developed CLR-resistant MAC-LD, 1 patient achieved negative sputum culture conversion after pulmonary resection, and the sputum of the other patients remained culture positive despite prolonged antibiotic therapy.

There were no significant differences with respect to baseline characteristics, such as age, sex, body mass index, smoking history, etiologic organism, comorbidities, or positive AFB smear, at the start of daily therapy between the 6 patients whose sputum achieved negative culture conversion and the 14 patients whose sputum failed to achieve negative conversion (data not shown).

Although some experts recommend modifications of the first-line therapy, such as switching from intermittent therapy to daily therapy, for noncavitary NB MAC-LD patients whose sputum failed to achieve culture conversion after at least 12 months of initial intermittent antibiotic therapy, there are no data demonstrating the treatment efficacy of these modifications. To our knowledge, this is the first study to evaluate the clinical efficacy of these modifications in patients with persistently culture-positive NB MAC-LD who failed to respond to initial intermittent antibiotic therapy. According to our results, about 30% of patients experienced a favorable treatment outcome.

In 1997, the American Thoracic Society (ATS) guidelines recommended a daily macrolide-based multidrug regimen for the treatment of MAC-LD (20). However, this regimen is poorly tolerated and can lead to a variety of side effects, such as gastrointestinal symptoms and ocular toxicity (21–23). In 2007, revised guidelines issued by the ATS and the Infectious Diseases Society of America (IDSA) recommended intermittent, three-times-weekly therapy for the initial treatment of noncavitary NB MAC-LD (16). Such intermittent therapy has potential advantages in reducing drug side effects, treatment discontinuation, and medication costs. However, successful sputum culture conversion rates were reported to be 75% to 85% after at least 12 months of this intermittent antibiotic therapy (17, 18). Some modifications or intensification of the initial first-line therapy, such as switching from intermittent therapy to daily therapy, a change from RIF to rifabutin, or the addition of parenteral drugs (amikacin or streptomycin) may be beneficial for these patients (19). Our study found that about 30% of patients experienced a favorable treatment outcome after switching from intermittent therapy to daily therapy.

The present study has several important limitations. First, the switch from intermittent to daily therapy was based on the decision of the attending physician without an established institutional protocol. Second, there was no significant difference in the sputum culture conversion rates between the patients who continued intermittent therapy (1 of 4 patients [25%]) and those who switched to daily therapy (6 of 20 patients [30%]; $P = 1.000$), although the number of patients in each group was small. Third, the number of cases was too small to detect clinically significant findings regarding predictors of favorable or unfavorable responses to the modifications of antibiotic therapy. Forth, genotypic data were unavailable in this study. Microbiologic recurrence during antibiotic therapy or after completion of therapy is not uncommon in patients with NB MAC-LD (17, 24, 25). Therefore, we could not differentiate between persistent infection with the initial MAC strain and reinfection with a new MAC strain in these patients.

In conclusion, this report suggests that switching from intermittent to daily therapy can achieve sputum culture conversion in about 30% of patients with persistently culture-positive NB MAC-LD who fail to respond to the initial intermittent antibiotic therapy. Further studies will be needed to differentiate treatment failure from reinfection and to identify better therapeutic regimens with the addition of potentially effective drugs, such as intravenous or inhaled amikacin, inhaled liposomal amikacin, fluoroquinolones, and clofazimine, in these patients with NB MAC-LD (26–29).

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