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Original article

Treatment outcomes of refractory MAC pulmonary disease treated with drugs with unclear efficacy

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ABSTRACT

We aimed to investigate the treatment outcomes of patients with refractory *Mycobacterium avium* complex (MAC) lung disease treated with regimens containing drugs with unclear efficacy. Of all patients diagnosed with MAC lung disease between April 2004 and September 2012 at a tertiary referral center in South Korea, the outcomes of 51 patients treated with regimens containing drugs with unclear efficacy (clofazimine, moxifloxacin, rifabutin, and linezolid) because of treatment failure after receiving standard treatment were retrospectively analyzed. The mean age (standard deviation) of the 51 patients was 59.0 (10.3) years and 29 (56.9%) were male. The etiologic agent was *M. avium* in 17 patients (33.3%) and *Mycobacterium intracellulare* in 34 patients (66.7%); 42 patients (82.4%) had the fibrocavitary form of the disease. Of the 51 patients, 26, 28, 35, and 7 received clofazimine-, moxifloxacin-, rifabutin-, and linezolid-containing regimens (numbers are not mutually exclusive), with median drug administration durations of 147, 128, 209, and 88 days, respectively. Overall, 8 patients (15.7%) had a favorable response. Treatment outcomes did not differ by drug regimen or even by the combination of more than 2 drugs. The treatment outcomes of patients with refractory MAC lung disease were unsatisfactory with regimens containing possibly effective drugs such as clofazimine, moxifloxacin, rifabutin and linezolid.

1. Introduction

Because nontuberculous mycobacteria (NTM) are increasingly recognized as worldwide human pathogens, including in South Korea, NTM disease can be seen as an emerging public health threat [1,2]. The *Mycobacterium avium* complex (MAC) consists of *M. avium* and *Mycobacterium intracellulare* and is the most common etiology of NTM lung disease in South Korea [3].

The treatment of MAC with antituberculosis (TB) drugs was initially unsatisfactory, but the introduction of newer macrolides has led to improved treatment outcomes for MAC lung disease [4]. Its current treatment recommendations include macrolide (clarithromycin or azithromycin), ethambutol, and rifamycin. However, the treatment success rate for macrolide-containing regimens in the treatment of MAC lung disease is only about 40%–60% [1,5]. Nevertheless, there have been few studies of the optimal regimen for patients with refractory MAC lung disease.

The aim of the present study was to investigate the treatment outcomes of patients with refractory MAC lung disease treated with a regimen containing drugs with unclear efficacy.

2. Patients and methods

2.1. Study subjects

The study subjects were selected from all patients treated for MAC lung disease between April 2004 and September 2012 at Asan Medical Center, a 2700-bed referral hospital in Seoul, South Korea. All patients met the diagnostic criteria for NTM lung disease according to American Thoracic Society (ATS) guidelines [6]. Among

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these patients, 51 were treated with a regimen containing drugs with unclear efficacy against MAC [ie, clofazimine (CFZ), moxifloxacin (MXF), rifabutin (RFB), and linezolid (LZD)] for more than 1 month because of treatment failure after receiving standard treatment. All 51 patients had previously been treated with a macrolide (mainly clarithromycin)-containing regimen and 70.6% (36/51) had received aminoglycoside (mainly streptomycin) as recommended by ATS guidelines [6]. The patients' medical records were retrospectively reviewed. Our study protocol was approved by the Institutional Review Board of the Asan Medical Center, which waived the requirement for informed consent due to the retrospective nature of the analysis.

2.2. Assessment of treatment outcomes

Sputum conversion was defined as 3 consecutive negative cultures within 6 months. If the patients could not expectorate sputum during the treatment duration, the sputum was considered to have converted to negative. Sputum reversion was defined as 2 consecutive positive cultures after sputum conversion [7]. For those patients still on treatment, only those who received antibiotic therapy for more than 12 months were included in the outcome analysis.

Treatment success was defined as negative cultures for the infecting MAC strains for 12 months or longer after the initiation of therapy [8]. In addition to the conventional definition of treatment failure [6], treatment outcome was considered to be a failure, by reference to the revised 2013 WHO definitions of outcomes of patients with multidrug-resistant TB (MDR-TB)/extensively drug-resistant TB (XDR-TB), if treatment was terminated for any reason or a permanent regimen change of at least 2 drugs was needed [9]. Additionally, other outcome categories, such as died or lost to follow-up, were defined [9]. A favorable response was defined as either treatment success or, for those still on treatment, a culture conversion without reversion. All remaining treatment outcomes (eg, treatment failure, died, culture conversion with reversion) were defined as unfavorable responses. Moreover, the microbiologic, symptomatic and clinical responses were also separately assessed to analyze the treatment outcomes.

2.3. Statistical analysis

All analyses were performed by using SPSS software (version 12.0; SPSS, Chicago, IL). The 2 groups were compared by using a Student's *t*-test or a Mann–Whitney test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Odds ratios and multiple logistic regression analysis were used to calculate the adjusted risk. All tests of significance were two-sided; *P* values <0.05 were considered statistically significant.

3. Results

3.1. Characteristics of the study subjects

The mean age of the 51 patients was 59.0 years; 29 (56.9%) were male. The etiologic agent was *M. avium* in 17 patients (33.3%) and *M. intracellulare* in 34 patients (66.7%); 42 patients (82.4%) had the fibrocavitary form of the disease. In addition, 26 patients (51.0%) were tested for human immunodeficiency virus; all were negative.

3.2. Antibiotic treatment

Patients received 150 mg/day, 400 mg/day, and 300 mg/day of CFZ, MXF, and RFB, respectively. LZD was administered at a dose of 600 mg once daily for 4 patients. The remaining 3 patients received 600 mg/day at first for a mean duration of 105 days and subsequently the reduced dose of 300 mg/day. The median duration of drug administration was 147 days (interquartile range [IQR], 73–335 days), 128 days (IQR, 63–312 days), 209 days (IQR, 69–365 days), and 88 days (IQR, 61–232 days) for CFZ, MXF, RFB, and LZD, respectively. A median of 2 drugs (range, 0 to 4 drugs) was used simultaneously as companion drugs with these 4 drugs. Azithromycin was the most commonly prescribed companion drug (56.9%, 29/51), followed by aminoglycosides (mainly streptomycin; 52.9%, 27/51). In all patients, these oral drugs were administered on a daily basis. Patients received aminoglycoside 5 or 3 times per week depending on age, with a median duration of 150 days (IQR, 75–290 days).

3.3. Treatment outcomes

Overall, according to the definition of the present study, 8 patients (15.7%) had a favorable response (the favorable response group) and 43 patients (84.3%) had an unfavorable response (the unfavorable response group). The 2 groups were comparable in terms of baseline characteristics except for the statistically significant difference in the number of patients with a negative sputum acid-fast bacilli (AFB) smear (Table 1).

The detailed treatment outcomes of the 51 patients are shown in Table 2. Of the 8 patients who achieved a favorable response, none experienced recurrence during the median 232-day follow-up (IQR, 105–560 days). The treatment outcomes assessed by the microbiologic, symptomatic and clinical response are shown in Table 3.

The patients in the favorable group underwent a significantly longer period of total treatment (558 days vs 228 days; $P < .001$). Surgical resection of the pulmonary lesion was performed in 3 out of 51 patients (5.9%), with no difference between the 2 groups. Excepting those patients with a favorable response or who underwent surgery, surgical resection was not performed in the remaining 41 patients because of a bilateral lesion ($n = 12$), poor pulmonary function test ($n = 9$), unacceptably high operative risk

Table 1
Clinical characteristics of the 51 study subjects with refractory MAC lung disease.

	Total patients ($n = 51$)	Favorable group ($n = 8$)	Unfavorable group ($n = 43$)	*P* value
Age	59.0 ± 10.3	56.6 ± 10.3	59.5 ± 10.4	0.482
Male gender	29 (56.9%)	3 (37.5%)	26 (60.5%)	0.268
Body mass index	19.3 ± 2.9	20.4 ± 2.9	19.1 ± 2.9	0.237
Previous history of tuberculosis	39 (76.5%)	6 (75.0%)	33 (76.7%)	1.000
No. of previous MAC treatments	1 (1–3)	1 (1–2)	1 (1–3)	0.407
Negative sputum AFB smear	19 (37.3%)	6 (75.0%)	13 (30.2%)	0.040
Underlying disease				0.984
Chronic lung disease	7 (13.7%)	1 (12.5%)	6 (14.0%)	
Diabetes mellitus	7 (13.7%)	1 (12.5%)	6 (14.0%)	
Malignancy	4 (7.8%)	0	4 (9.3%)	
Other[a]	5 (9.8%)	0	5 (11.6%)	
Type of disease				0.619
Fibrocavitary	42 (82.4%)	6 (75.0%)	36 (83.7%)	
Nodular bronchiectatic	9 (17.6%)	2 (25.0%)	7 (16.3%)	
No. of involved lobes[b]	5 (1–6)	5 (2–6)	5 (1–6)	0.909
Etiology				0.703
Mycobacterium intracellulare	34 (66.7%)	6 (75.0%)	28 (65.1%)	
Mycobacterium avium	17 (33.3%)	2 (25.0%)	15 (34.9%)	

Abbreviations: MAC = *Mycobacterium avium* complex; AFB = acid-fast bacillus.
Values represent the mean (SD), number (%) or median (range).
[a] Includes hypertension ($n = 2$), cerebrovascular accident ($n = 1$), rheumatoid arthritis ($n = 1$) and Parkinson's disease ($n = 1$).
[b] A total of 6 lobes in each patient's lung (the lingular segment was considered as a separate lobe) were assessed.